THE ACIDIC HYDROLYSIS OF SOME HYDROXYANILIDES

by

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A thesis submitted for the Degree of Doctor of Philosophy of the University of Glasgow.

September 1972

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CONTENTS

SUMMARY

Available evidence concerning the mechanism of acid catalysed amide hydrolysis and the roles played by intramolecular hydroxyl groups are briefly reviewed. Methods of treating kinetic and equilibrium data obtained from studies of reactions in moderately concentrated mineral acids are summarized.

The rate enhancements observed upon the inclusion of a γ or δ hydroxyl group in alkyl anilides are thought to be the result of a greater availability of a nucleophilic species at the reaction centre.

The possible significance which can be given to the results of hydration parameter and linear free energy treatments of rate data from moderately concentrated acids is discussed. These parameters at least indicate that water performs another function besides that of nucleophile in acid catalysed amide hydrolysis.

All kinetic parameters derived indicate that the intramolecular and intermolecular reactions proceed by similar mechanisms.

A study was carried out of the acid catalysed lactonization of some bicyclic and olefinic hydroxy anilides in which the reactive groups are held in constant close proximity.

Abnormal absorbance changes over normal anilide acid catalysed hydrolysis indicate that the reactions being monitored have changed in some way. It is suggested that the rate determining step in the reaction has altered. Two mechanisms for the reaction are proposed.

ACKNOWLEDGEMENTS

I would like to express my gratitude to Dr. B. Capon, my supervisor, for his invaluable advice and encouragement throughout the course of this work.

I am also indebted to the technical staff of the Chemistry department for the services they have provided. I am sincerely grateful to my wife for the typing of this thesis and for her moral support throughout. Finally, I would like to thank the Science Research Council for financial support.

September 1972

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to Patricia

INTRODUCTION

The concept of participation of a suitably disposed, intramolecular hydroxyl group in the hydrolysis of alkyl anilides in aqueous and moderately concentrated mineral acid solutions is studied in this work.

Accordingly, as an introduction, intramolecular participation in amide hydrolysis, relevant treatments of kinetic data obtained in moderately concentrated mineral acids and the general characteristics of acid catalysed amide hydrolysis are briefly reviewed.

INTRAMOLECULAR PARTICIPATION IN ACID HYDROLYSIS.

The Hydroxyl Group.

Hydroxyl groups are present as substituents in many organic molecules and, although their normal electronic substituent effects are not often of great importance, they, in their role as intramolecular catalysts, can have profound effects on organic reactions.

The manner in which, and the extent to which the hydroxyl group fulfils the role of intramolecular catalyst depends upon the nature of the reaction in which it participates and its disposition to the centre of reaction.

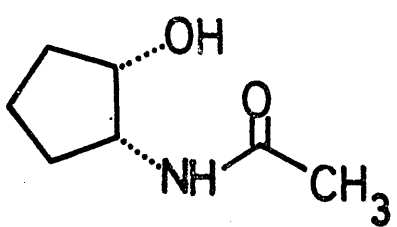
Thus, in the acid catalysed dehydration of 1,4 dihydroxy 4-methyl n-pentane to 1-hydroxy, 4-methyl, 4-pentene the hydroxyl group can be viewed[1,2] as an internal general base, facilitating the formation, by abnormal dehydration, of the terminal olefin.

In the alkaline hydrolysis of steroidal alicyclic 1,3 diaxial hydroxy acetates, facilitation of the hydrolysis with respect to the acetate and the 1,3 diaxial methoxy acetate of the same steroid has been attributed[3] to general acid catalysis by the alcoholic group to either the alkyl or acyl oxygen of the ester group, which in turn activates the ester group to attack by nucleophiles.

Thus, although the intramolecular hydroxyl group can

participate as a general acid-base catalyst, it may, in favourable circumstances, also participate as an intramolecular nucleophilic catalyst. Nucleophilic participation by intramolecular hydroxyl groups has been particularly in evidence in the hydrolysis reactions of suitable hydroxy amides where large numbers of N→O acyl migrations have been observed [4,5].

The probable steric requirements of certain N→O transfer reactions were demonstrated by Van Tamelen[6] in an investigation of cis(1) and trans(2) 1,2-acylaminocyclopentanols. Under acidic conditions the trans isomer would not react whereas the cis isomer readily underwent the transfer reaction at room temperature. The trans isomer was found to rearrange to produce the inverted cis product upon refluxing for 24 hours in acidic conditions.



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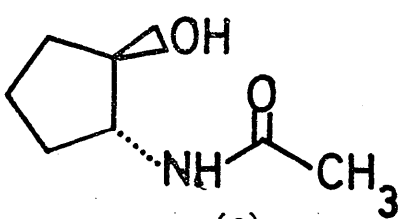
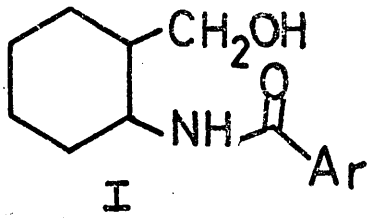


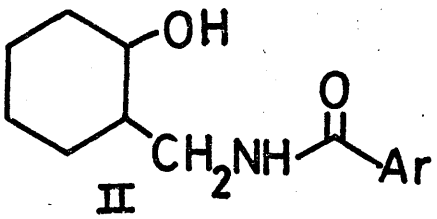
(2)

Further insight into the steric, electronic and energetic requirements of acid catalysed N→O acyl migration reactions was provided by Benrath et al,[8] who studied the cis and trans isomers of (3) and (4) and the corresponding series of cyclopentanes.



I

(3)



II

(4)

Benrath et al observed that, in general, the transfer rates in compounds of the type I were a factor of 2-3 greater than the rates of acyl transfer in compounds of the type II.

In the cyclohexane series the trans isomers were found to react faster than the cis isomers whereas in the cyclopentane series the reverse was found, the rate of reaction of the trans isomer only becoming measurable by the authors at 130°C.

Also, electron releasing substituents in the para position in the aromatic ring were found to increase the transfer rate whereas electron withdrawing substituents decreased the rate.

Nucleophilic participation by intramolecular, aliphatic hydroxyl group in the acid catalysed hydrolysis of amides was firmly established when Zurn[9] found the rates of hydrolysis of ω-hydroxy γ-butyramide and δ-valeramides in IN HCl to be factors of 18 and 45 respectively, greater than the rates of hydrolysis of the corresponding n-alkylcarboamides.

Intramolecular nucleophilic attack by an aliphatic hydroxyl group had previously been postulated[10] to account for the rapid hydrolysis of allohydroxylysyl-glycinamide in strong acid after being first suggested to explain the observed hydrolysis of aldonamides[11].

Bruice and Marquardt[12] compared the rates of hydrolysis of acetamide and 4-hydroxybutyramide over the pH range 5-10 at 100°C. Using the results of Zurn[9] they observed that the pH rate profile of 4-hydroxybutyramide has three distinct regions. In two of these regions, common to the pH rate profile of acetamide, in moderately strong acid and base solutions, the pseudo first order rate constant was observed to be dependent upon the oxonium ion concentration and the hydroxide ion concentrations respectively. The rate enhancements of 15-20 observed in these regions for the hydrolysis of 4-hydroxybutyramide compared to the hydrolysis of n-butyramide, were concluded to be due to intramolecular participation of the hydroxyl group. A plateau near neutrality in the pH rate profile of 4-hydroxybutyramide was shown to

indicate the presence of an efficient spontaneous unimolecular solvolysis due to the presence of the hydroxyl group with resultant rate enhancement over the rate of solvolysis of n-butyramide at neutral pH of 800. Thus these authors concluded that 4-hydroxybutyramide hydrolysis occurs via the formation of intermediate γ-butyrolactone at all pH values and they present the following scheme to represent hydrolysis at all pH values.

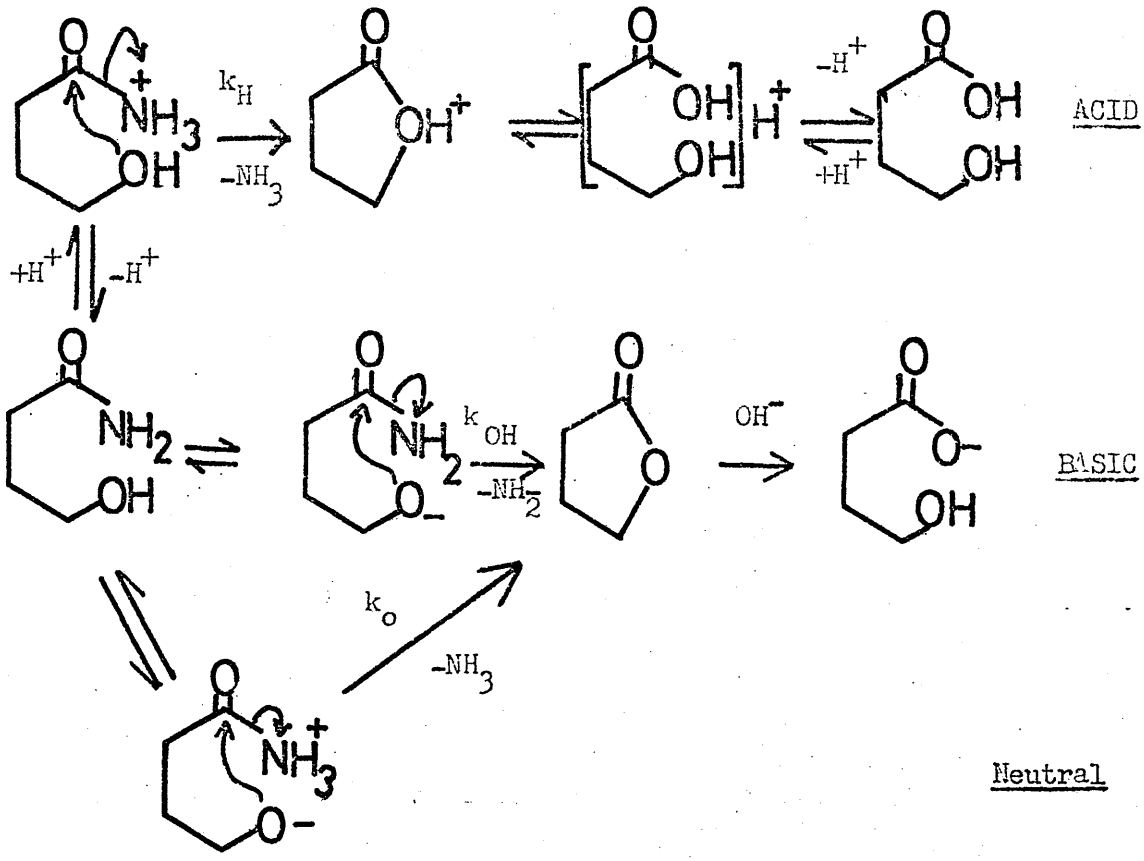


Fig. I

Thus the observed rate for the neutral and alkaline regions is described by equation (1).

$$\frac{-d\,[\text{amide}]}{dt} = (\,k_{OH^-}[OH^-] + k_o\,)\,[\text{amide}]. \qquad (1)$$

Witkop[13] discussed the results of Zurn[9] and suggested that the acid catalysed hydrolysis of 4-hydroxybutyramide proceeds by nucleophilic attack of hydroxy oxygen on the carbonyl carbon of the protonated amide with direct transfer of hydroxy hydrogen to nitrogen.

Martin, Hendrick and Parcell[14] extended the study of the hydrolysis of 4-hydroxybutyramide into the strong acid region. They observed the hydrolysis rates over a series of temperatures and over a series of concentrations of perchloric acid up to 8.75 molar. By using a kinetically determined acid dissociation constant for the amide, Bunnett[46] correlations of the observed rate constant, corrected for the fraction protonation, with the water activity gave ω values of 0.37, 0.55 and 0.30 for temperatures 15°, 25° and 35°C respectively

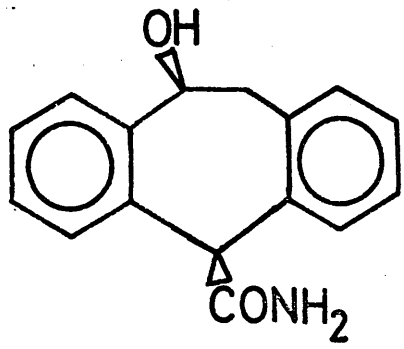
Determinations of k_1 ,the first order rate constant for hydrolysis of the protonated amide led to a value of 14.6 K cal/mol for the activation energy, of -28e.u. for the activation entropy and a value for the pre-exponential factor, log A, of 7.2.

Based on these results, and upon literature values for activation parameters of straight chain amides,these authors

observed that this hydrolysis reaction was characterized by comparatively low activation energy and pre-exponential factor and by a more negative entropy of activation. They concluded that the pronounced lowering of the activation energy more than offsets unfavourable changes in log A and ΔS^* and leads to an enhanced rate. The more negative activation entropy for the hydrolysis of 4 - hydroxybutyramide compared with straight chain amides is considered indicative of nucleophilic attack by the hydroxyl function at the amide carbonyl to form a cyclic lactone intermediate.

In this work, the rate - acidity plot shows the normal[32] maximum observed in amide hydrolysis at $H_o = -1.7$ at 25°C, and thus leads the authors, on the basis of the accepted explanation of the existance of the rate maximum[67] to conclude, although the derived ω value according to Bunnett's[46] criterion is unclassifiable, that water is involved in the rate determining step. It is suggested that determined value is low by 3-5 units due to a heavily hydrated hydroxyl group since similar observed[46] anomalies in ω values for the lactonization of 4-hydroxybutyric acid are explained in this manner. It is finally concluded that the true ω value should fall well within the range >3.3 which would be in agreement with their hypothesis that water is involved as a proton transfer agent in the rate determining step.

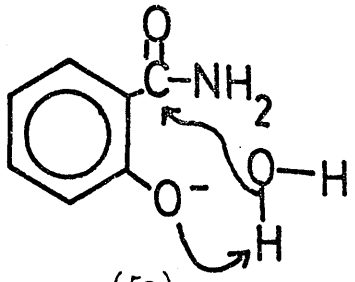
Transannular participation was suggested to account for the instability in the solid state and in solution of 10, 11 dihydro, syn 11-hydroxy, syn 5-carboxyamido, 5H, dibenzo a, d cycloheptene[15] (5).



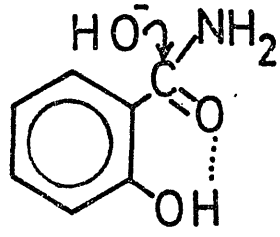
(5)

The corresponding lactone was found to form with the evolution of ammonia in this compound, whereas the corresponding anti 11-hydroxy and the 11 unsubstituted compound were found to be stable.

Based upon predictions of electronic effects of salicyl substituents on the rates of alkaline hydrolysis of 5-nitro-salicylamide and salicylamide in the event of either intramolecular general acid (5b) or general base catalysis (5a) predominating, Bruice and Tanner[16] concluded that the 18 fold rate decrease observed, when considering the observed rate at the plateau region of the sigmoid pH-rate profile, upon the introduction of the 5-nitro substituent could best be explained by the mechanism (5a) involving an intramolecular general-base-catalysed reaction of the ionized amide.



(5a)

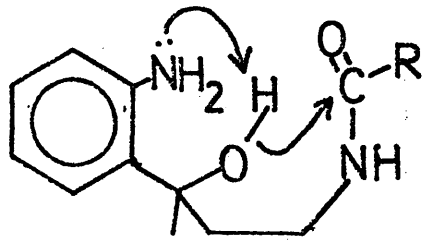


(5b)

This conclusion was based on the argument that the general-acid-catalysed mechanism would be inconsistant with the observed rate decrease since nitro substitution would have an acid strengthening effect on the phenolic group and would also make the amide group more susceptible to nucleophilic attack.

In a re-analysis of the data, Capon and Ghosh[112] concluded that the observed substituent effects do not allow an unambiguous assignment of mechanism to be made. On the basis of the expected effect of the known phenolic dissociation constant ratio on the consequent relative rate requirements for the alkaline hydrolysis of the two benzamides, and also upon the concentration of the postulated reactive form for intramolecular general acid catalysis, these authors reasoned that the general acid catalysis mechanism could not be ruled out and thus no unambiguous assignment of mechanism could be made.

Concerted intramolecular general-base nucleophilic catalysis has been suggested[17] to account for the hydrolysis of the amide function in compounds of the type (6).



(6)

The hydrolysis of 4-hydroxybutyranilide at pH 9.0 was found by Cunningham and Schmir[18] to be catalysed specifically by phosphate and bicarbonate buffers. From their results they concluded that, in the absence of phosphate or bicarbonate ion, the reaction involved intramolecular nucleophilic participation by the hydroxyl function to form a tetrahedral intermediate which breaks down to products in a rate limiting step. Although considerable rate acceleration was achieved and was thought to result from the availability of a mechanism involving the breakdown of a neutral or zwitter ionic intermediate, the advantage of spacial proximity of the reacting groups was thought to be largely offset by an unfavourable partitioning ratio for the anionic carbinolamine predicted as an intermediate in the proposed reaction mechanism (Fig II). In the hydrolysis in neutral or alkaline solution of 2-phenyliminotetrahydrofuran,[172,175] it is thought that rate determining hydration also leads to this type of intermediate, capable of yielding aniline and butyrolactone or 4-hydroxybutyranilide at acid or alkaline pH respectively. Also, at fixed pH, the presence of phosphate or bicarbonate buffers causes increased yields of aniline but not of reaction rate because intermediate formation is the rate determining step in this case. In the 4- hydroxybutyranilide hydrolysis at fixed

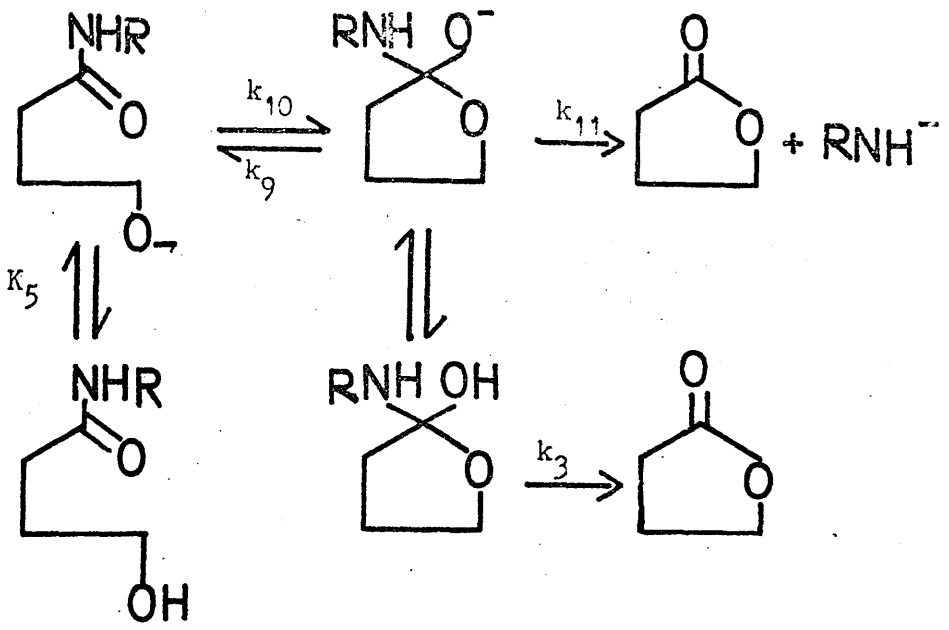
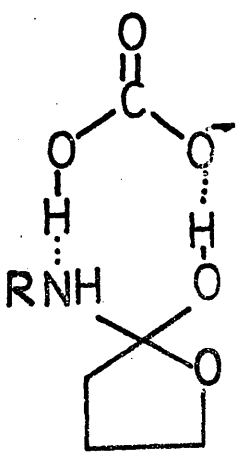
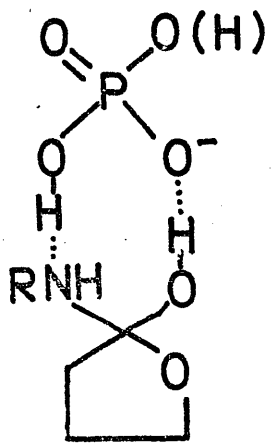


Fig. II

pH, the phosphate or bicarbonate catalysts are thought to change the rate limiting step to that of cyclization by specifically bifunctionally catalysing the breakdown of the proposed neutral carbinolamine intermediate to products via cyclic transition states (7) and (8).



(7)



(8)

Consistant with these proposals, it was observed that a steady value of rate was achieved as catalyst concentration was increased.

Belke, Su and Shafer[19] studied the hydrolysis of N-phenyl and N-benzyl 2-hydroxymethylbenzamide. They found that acids and bases enhanced the hydrolysis rate by catalysing the lactonization of the hydroxy amides to phthalide.

Kinetic evidence indicated that the lactonization of the amide is a multistep process with a change in the rate-controlling step occurring at approximately pH 8.

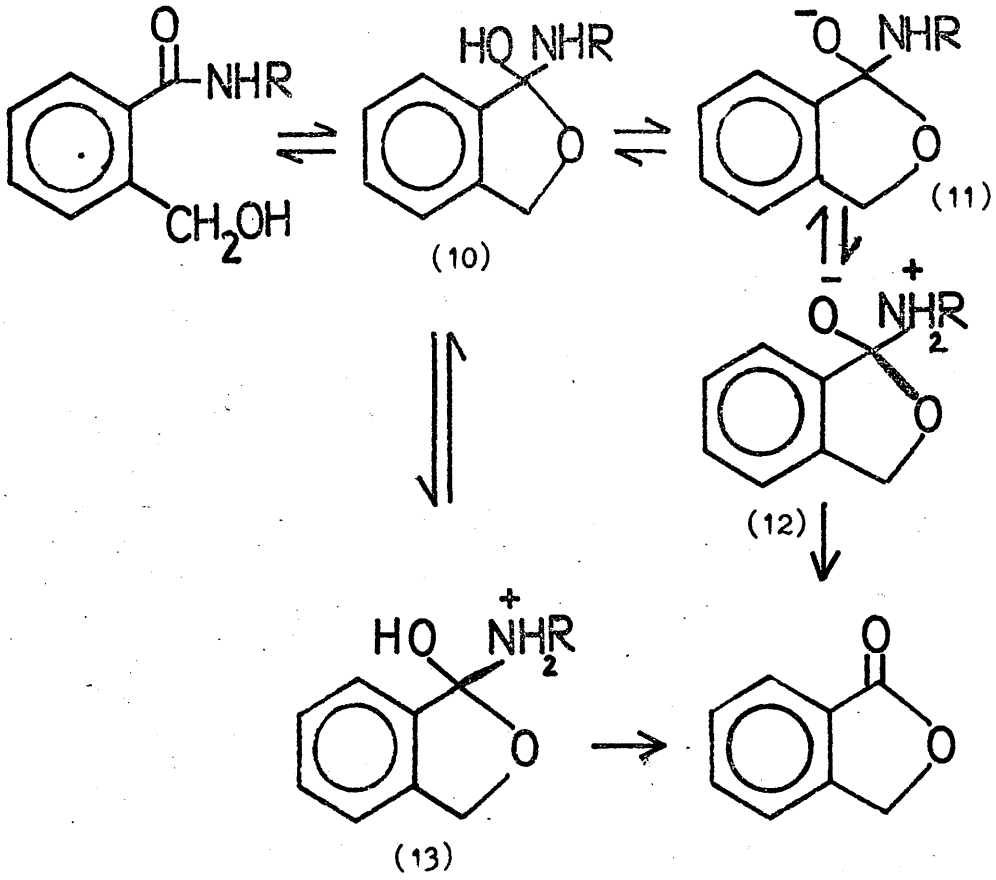
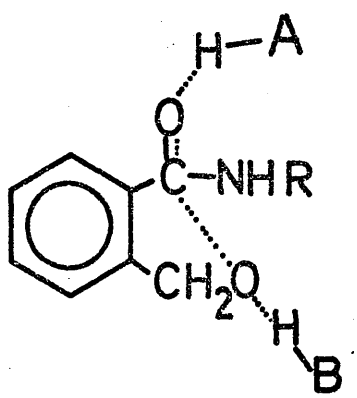


Fig. III.

The dependence of the catalytic efficiency of bases upon the pKa of their conjugate acids suggests that, below pH 8, the rate determining step for base catalysed lactonizations was diffusion controlled proton transfer between catalyst and intermediates (11) and (12). Their results also suggested that the rate determining step for the observed acid catalysed reaction below pH 8 involves the catalysis of the elimination of the amine from the intermediate (13) by the conjugate base of the catalyst.

Above pH 8, cyclization to the carbinolamine (10) was considered to be rate determining and general base catalysis of the lactonization was observed.

The following structure (14) was thought to be a possible representation of transition states for the acid and base catalysed transition from (9) to (10).



In this structure A or B is a proton acceptor other than H_2O or $\bar{O}H$. Acid catalysis would be observed when the remaining group (B or A) was H_2O, and base catalysis would be observed when the remaining group was $\bar{O}H$.

Efficient catalysis by imidazole is observed in this amide hydrolysis and is thought to demonstrate the feasibility of an imidazole facilitated attack of a hydroxyl group on an amido group as a model for the acylation of a serine proteinase by its substrate.

The mechanistic conclusions drawn by these authors are contrary to the findings of Schmir et al in their studies of 4-hydroxybutyranilide lactonization and of 2-phenyliminotetrahydrofuran hydrolysis. Recently Schmir et al[174] studied the hydrolysis of 1-benzyl-imino 1,3 dihydroisobenzofuran in accordance with the possibility that the hydrolysis intermediate would be similar or identical to that produced in the lactonization of N-benzyl 2-hydroxymethylbenzamide if the amide hydrolysis proceeds through an O-protonated form by hydroxyl group nucleophilic attack. It was demonstrated that the reaction products were pH dependent in the same way as were the reaction products of 2-phenyliminotetrahydrofuran hydrolysis. Overall the behavior of the compound parallels that of iminolactones and imidate esters previously studied. These authors concluded that the lactonization of N-benzyl 2-hydroxymethylbenzamide proceeds via a mechanism qualitatively similar to that previously suggested for 4-hydroxybutyranilide in which the rate limiting step is intermediate formation or intermediate breakdown at acid or alkaline pH respectively.

INTRAMOLECULAR PARTICIPATION OF OTHER FUNCTIONAL GROUPS IN AMIDE HYDROLYSIS.

Examples of intramolecular participation of a variety of functional groups in the reactions of carboxylic acid derivitives are legion[4,5]. The majority of studies of intramolecular participation of this type have had esters as the subject of investigation and significantly less work has been done on the seemingly analogous hydrolysis of amides.

Of the intramolecular functional groups which have been investigated as possible participants in amide hydrolysis, the principle subjects of study have been the hydroxyl group [4-19] and the carboxyl[4] group. The first recognized instance of intramolecular participation was recorded by Leach and Lindley[20] who recognized that the hydrolysis of L-leucyl-L-asparagnine was dependent upon the mole fraction of the intramolecular carboxylate group in the undissociated form. A mechanism involving participation of the undissociated carboxyl function was then suggested.

The respective requirement for carboxyl and carboxylate anion in amide and ester hydrolysis was recognised by Bender et al[21] for the hydrolysis of the mono amide and mono methyl ester of phthalic acid.

Nitrogen participation in the form of imidazole[22], pyridine[23], pyridine N-oxide[24], aromatic amine[25] and amide[4,5] has been

implicated in the intramolecularly catalysed hydrolysis of amides. In the case of imidazole participation in amide hydrolysis, the rate enhancements although not as large as in ester hydrolysis are sufficiently large to suggest nucleophilic catalysis[26]. The most significant feature in this case is that it is the protonated imidazole which is implicated as the catalytic species[4].

Intramolecular amide groups can have a profound effect as nucleophilic catalysts. The amide anion is an ambident nucleophile and a variety of mechanisms are seen which proceed through intermediates such as oxazolones, oxazolenes, benzoylanthril and imides[27].

Sulphur participation has been demonstrated for thioamides, thioureas and dithiocarbamates[26].

COMPARISON OF INTERMOLECULAR AND INTRAMOLECULAR CATALYSIS

Although the same chemical principles govern both intramolecular and intermolecular reactions, stringent stereochemical requirements are often present in the former which can cause the intramolecular reaction to proceed by a different route than the bimolecular reaction. The proximity of the catalyst to the reaction centre leads to the predominance of nucleophilic over general acid-base catalysis in intramolecular reactions.

Comparison of the first order intramolecular reaction with the second-order intermolecular reactions is possible for similar reactions proceeding by the same type of mechanism[28]. This comparison is achieved by calculating the effective concentration of intermolecular catalyst required for equivalence of the rates of intra- and intermolecular reactions. On a mole fraction basis, if this figure is less than unity then it is feasible that the simple local concentration effect is sufficient to cause the observed rate enhancement. The maximum in this calculation occurs where the derived mole fraction is unity, this corresponding to the reactant being completely surrounded by catalyst molecules. However, the large rate enhancements observed for some intramolecularly catalysed reactions exceed this maximum and it therefore necessary to invoke other factors to explain these large rate increases.

It is stated[45] that the intramolecular reactions should be

favoured over simple bimolecular processes since, in the latter, a considerable loss of translational entropy must accompany the bringing together of reactants to form a transition state. Also, favourable orientation of the catalytic group with respect to the reaction site in an intramolecular reaction has been suggested to lead to additional entropy advantage over the bimolecular reaction.[4]

Although examples of comparable intramolecular and intermolecular reactions have been recorded in which the observed rate enhancement can be attributed to a more favourable activation entropy[29], the activation enthalpies being approximately equal, other examples, have been recorded in which the enhanced rate of the intramolecular reaction is due to a more favourable activation enthalpy in the presence of an unfavourable activation entropy, or, in which an enhanced rate is observed in the presence of unfavourable enthalpies and entropies of activation[31].

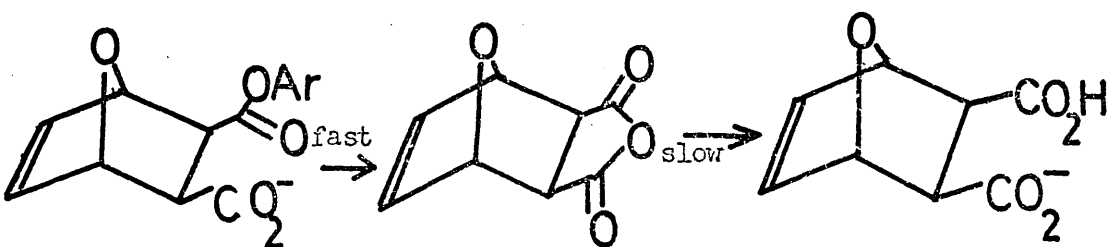
Thus, if the initial premise is correct, other entropy and enthalpy factors, which can be of sufficient magnitude to overcome any favourable changes incurred in the transition from intermolecular to intramolecular reaction, must have been neglected.

Large entropy barriers to reaction can arise from a requirement for the orientation and electrostriction of a number of surrounding solvent molecules. Ring closure reactions of flexible chain molecules, which invariably occur in intramolecular nucleophilic catalysis, generally have unfavourable entropies because of the

loss of internal rotation upon ring formation. Similar unfavourable entropies are thus expected for the formation of transition states which require a similar loss of freedom of rotation[28].

It is almost certain that such processes as desolvation, dispersion, solvent interaction and the associated free energies have to be taken into account in intra- as well as inter-molecular reactions[28].

Jenks[28] has suggested that the rate of ring closure in the



(15)

ester (15) is facilitated by the carboxylate group not being solvated by water on the side which attacks the ester and hence does not require to undergo a desolvation process at this site.

Other considerations which have to be taken into account in a comparison of intramolecular reactions should include conformational, electrostatic and steric effects in the two types of transition states[32].

Although there are a few reactions in which significant

additional rate acceleration could be expected from favourable orientation or rotomer distribution of the reactants in an intramolecular reaction in which the catalytic group and the reactive centre are in fixed reactive position, the view is held that, for the great majority of reactions, it is unlikely that orientational requirements are so strict that induction of a favourable orientation will lead to a large rate acceleration and that the very large rate accelerations which are observed in some intramolecular reactions are too large to be explained in these terms[28].

COMPARISON OF INTRAMOLECULAR AND ENZYMIC CATALYSIS.

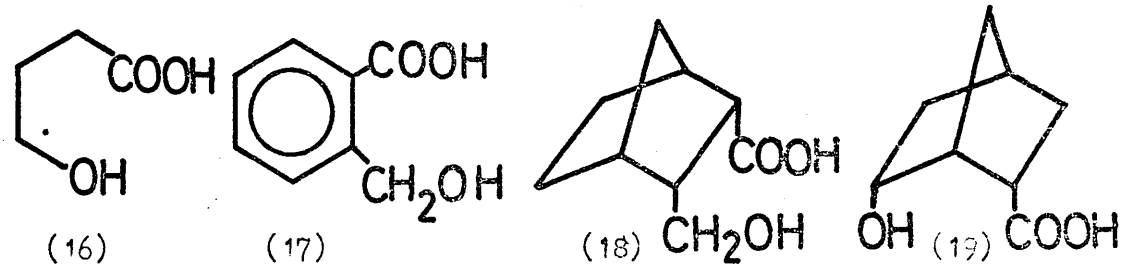
In recent years considerable advances in intramolecular catalysis have been made, stimulated in large part by the hypothesis that intramolecular catalysis can serve as a simple model of the intracomplex catalysis exhibited by enzymes, and fostered by the hope that modes of catalysis postulated for enzymic systems, but not observable in intermolecular systems, would appear in intramolecular systems.

The view has thus been expressed that the very large rate enhancements observed in some intramolecular reactions are too large to be expressed in terms of local concentration effects, favourable orientation and rotamer distribution[28], yet there exists factors as large as 10^{12} between the rates of enzymic and intramolecular reactions[33].

Effects to explain the large catalytic activity of enzymes have involved the concept of simultaneous concerted involvement of two or more catalytic groups[32]. The suggestion that this mechanism is involved in certain reactions has been criticized[34] and it has been suggested that electronic coupling is a prerequisite for multifunctional catalysis and that most quoted examples are merely examples of tautomeric catalysis[35].

Changes in reactivity induced by structural variation in intramolecular lactonization of hydroxy acids have induced Storm and Koshland[36] to propose 'orbital steering' as the factor which

causes large rate enhancements in intramolecular and enzymic catalysis.[110,111] These authors suggest that proximity combined with a highly sensitive orientation factor for reaction related to the shape of the atomic orbitals should provide factors large enough to bridge the gap between the observed rates of intramolecular and enzymic catalysis. This suggestion was tested by consideration of the rates of lactonization of the series of hydroxy acids, structures (16) to (19) and their corresponding thiolacids.



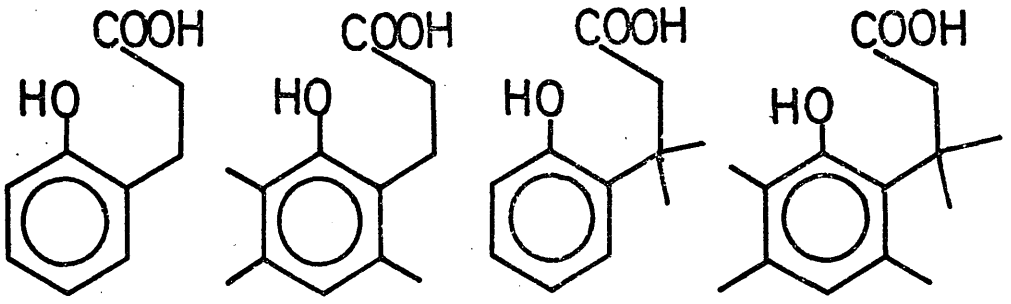
(16) (17) (18) (19)

Correction factors applied to the observed rates gave second order rate constants of which k_2^{19} was approximately 46 times greater than k_2^{16}

The concept of 'orbital steering' has been critized[37-40]. It has been suggested that the magnitude of the applied corrections was inadequate and that it is premature to invoke this new concept since the observed difference in rates could arise solely from the differences in the increases in strain and losses of rotational freedom in going to the transition state[37].

Milstein and Cohen[41] found that as a result of alkyl

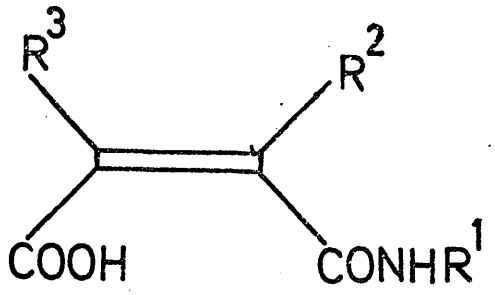
substitution in the aromatic ring and side chain of hydrocoumaric acid to give compounds (20) to (23) increased in the rate constants in the lactonization at pH 7 by factors up to 10^{11} were observed.



(20) (21) (22) (23)

This effect was attributed to a unique interlocking of methyl groups producing a severe conformational restriction of the side chain and increasing greatly the population of the most productive conformer. This suggested narrowing of the distribution of conformational population by eliminating non productive isomers was termed "stereopopulation control" by these authors and was suggested as a model for conformational restraint imposed by an enzyme on a substrate which would have a close-fitting multipoint attachment.

Similar large rate increases were observed in a system of fixed conformation (24) [42].



(24)

By varying the R groups, rate increases over 10 powers of 10 were observed, the introduction of a second R^3 alkyl group into a system with R^1 and R^2 alkyl groups having disproportionately large effects. The large changes in rate were found to reflect exclusively activation enthalpy changes, the activation entropies being actually less favourable for the more reactive compounds. The authors conclude that a simple buttressing effect of the four coplanar substituents forces the reactive groups into closer proximity and raises the energy of the initial state relative to the transition state for cyclization.

It has been pointed out[39] that it can be established that translational and overall rotational motions provide the important entropic driving force for enzymic and intramolecular rate accelerations. Internal rotations and unusually severe orientational requirements are considered to be of secondary importance. It is estimated that the loss of translational and overall rotational entropy in going from second to first order reaction in solutions is approximately 45 e.u. (standard state 1 M at 25°). Although this large loss of entropy can be partially compensated for by low frequency motions in the

products and transition state, effective concentrations approaching 10^{8}M can be accounted for without the introduction of new concepts[36,41] or terms.

ACIDITY FUNCTIONS AND THEIR APPLICATIONS TO AMIDES.

In dilute aqueous solution of strong acids the proton donating power of the medium is acceptably defined as the concentration of oxonium ion. In concentrated solutions of acids the solvent is essentially no longer water and the proton donating power of the medium cannot be expressed so simply.

Attempts to define this and related powers for a variety of systems, and to apply the interpretations of these attempts to the thermodynamic and kinetic behaviour of organic solutes in concentrated solutions of acids and bases have led to the evolution of the broad subject of acidity functions. The subject has been recently thoroughly reviewed[43] and the following discussion deals briefly with the salient features which can be related to a study of amide hydrolysis in concentrated acid solutions.

The original acidity function concept was proposed by Hammett and Deyrup[44] who suggested that the proton donating power of strongly acidic solutions could be referred to a thermodynamic standard state in water by the stepwise application of progressively less basic indicators in progressively stronger acid solutions.

For the proteolytic equilibrium of the indicator In, a neutral Brönsted base;

$$HIn^{+} \rightleftharpoons In + H^{+} \qquad (2)$$

the thermodynamic equilibrium constant can be written

$$K = \frac{a_{H^+} \cdot f_{In}}{f_{HIn^+}} \cdot \frac{[In]}{[HIn^+]} \qquad (3)$$

where activities, activity coefficients and concentrations are symbolized by a, f and [] respectively. Considering the ratio ($a_{H^+} \cdot f_{In} / f_{HIn^+}$), although the component terms are separately indeterminable, the term as a whole can be experimentally determined and is of the type to offer physical meaning.

This ratio is defined as

$$h_o = \frac{a_{H^+} \cdot f_{In}}{f_{HIn^+}} \qquad (4)$$

and thus equation (3) can be expressed as

$$-\log h_o = H_o = pK + \log \frac{[In]}{[HIn^+]} \qquad (5)$$

The Ho scale is referred to a standard state of infinite dilution in water where activity coefficients become unity so that equation (5) becomes

$$pH = pK + \log \left([In] / [H\,In^+] \right) \qquad (6).$$

The Ho scale may thus be viewed as an extension of the pH scale into strong acid.

However, for the general base B in proteolytic equilibrium

$$BH^+ \rightleftharpoons B + H^+ \qquad (7)$$

the thermodynamic dissociation constant can be expressed

$$K_{BH^+} = \frac{a_{H^+} \cdot f_B}{f_{BH^+}} \cdot \frac{[B]}{[BH^+]} \qquad (8)$$

but sustituting for a_{H^+} from equation (4) in equation (8) gives

$$K_{BH^+} = h_o \cdot \frac{[B]}{[BH^+]} \cdot \frac{f_B \, f_{HIn^+}}{f_{BH^+} \cdot f_{In}} \qquad (9)$$

Thus the construction of an acidity scale based upon a series of progressively weaker bases depends upon the assumption that the activity coefficients of all the indicators respond in the same way to changes in acidity, and the general applicability of these scales depends upon the ratios of activity coefficients being independent of the structure of the base, so that the ratio $(f_B \cdot f_{HIn^+} / f_{BH^+} \cdot f_{In})$ is equal to unity and a plot of the equation

$$H_o = pK_{BH^+} + \log ([B] / [BH^+]) \qquad (10)$$

is linear with unit slope.

Those organic solutes, which do have similar activity coefficient behaviour to the series of primary anilines used to establish the H_o scale, will obey these conditions, and the derived pK_{BH^+} values for such compounds, referred to as Hammett bases, will be the thermodynamic equilibrium constants referred to the standard state free energy of ionization.

Those compounds which do not fit equation (10) must be regarded as following a different acidity function and the pK_{BH^+} values derived from a plot of equation (10) would be the H_o value for the solution in which they are half converted to their conjugate acids. This type has among its numbers aryl olefins, aliphatic ethers, phenols and, notably, amides. It has thus been observed that groups of bases with different structures and basic sites of ten show significant deviations in acidity function behaviour from that of Hammett bases.

Hammett and Deyrup[44] noted that the H_o acidity function could correlate the rates of certain reactions. Thus the observed rate constants, k, were found to be consistant with equation (11)

$$\log k + H_o = \text{constant.} \qquad (11)$$

The rates of other reactions were found to correlate with the acid concentration.

Zucker and Hammett[45] proposed that this distinction was associated with precise differences in mechanism. On the basis of equations (12) and (13), respectively depicting generalized A1 and A2 mechanisms for the hydrolysis of an organic solute S in acid solution,

$$S + H^+ \overset{\text{fast}}{\rightleftharpoons} SH^+ \underset{k_o}{\overset{\text{slow}}{\longrightarrow}} A^* \longrightarrow \text{products} \qquad (12)$$

$$S + H^+ \overset{\text{fast}}{\rightleftharpoons} SH^+ + H_2O \underset{k_o}{\overset{\text{slow}}{\longrightarrow}} A^* \longrightarrow \text{products} \qquad (13)$$

Zucker and Hammett[45] proposed two general systems to account for the effects of highly acidic media on the rates of oxonium ion catalysed reactions. Well documented derivations produce two general equations for the observed rate constants of A1 reactions

$$k_1 = \frac{[S]}{[S] + [SH^+]} \cdot \frac{k_o}{K_{SH^+}} \cdot h_o \cdot \frac{f_S \cdot f_{BH^+}}{f_B \cdot f^*} \qquad (14)$$

(where k_1 is the observed first order rate constant, k_o is the rate constant for the slow step, f^* is the **activity coefficient** for the transition state A^* for the slow step) and for the observed rate constant for the A2 mechanism.

$$k_1 = \frac{[S]}{[S] + [SH^+]} \cdot \frac{k_2}{K_{SH^+}} \cdot [H^+] \cdot \frac{f_S \cdot f_{H^+} \cdot a_w}{f^*} \qquad (15)$$

(where k_2 is the rate constant for the rate of loss of the sum of equilibrium concentrations of S and SH^+ for the bimolecular rate determining step).

These equations include the activity coefficient ratios ($f_S.f_{BH^+}/f_B.f^*$) and ($f_S.f_{H^+}.a_w/f^*$). The Zucker-Hammett hypothesis, in requiring $\log_{10} k_1$, the logarithm of the pseudo first order rate constant, to be linear with unit slope in $-H_o$ or $\log_{10} [H^+]$, requires at least one of the activity coefficient terms to be constant over the range of acid studied. This is analagous to requirements inherent in the original acidity function concept

which have not been found to be generally observed. Thus, the now established fact that changes in base structure can lead to the need for significantly different acidity functions leaves no doubt that the Zucker-Hammett hypothesis based on H_o will not be generally applicable.

Bunnett[46] noted that plots of ($\log k_{obs} + H_o$) and of ($\log k_{obs} - \log [HX]$), or appropriate other functions for more basic substrates, were often linear, or approximately so, in $\log a_w$ and that their slopes defined parameters (ω and ω^* respectively) useful for classification of reactions. The parameters ω and ω^* were associated with the manner of involvement of water in the rate determining steps of reactions of established mechanism thus developing an empirical criterion of mechanism.

Theoretical significance[46] was added to this empirical treatment by a consideration of the generalised equation for the acid catalysed reaction of the organic substrate S in which each species is considered as fully hydrated.

$$S(H_2O)_s + H(H_2O)_n^+ \rightleftharpoons SH(H_2O)_p^+ + (s+n-p)\ H_2O \qquad (16)$$

$$SH(H_2O)_p^+ + (t-p)H_2O \longrightarrow A^*(H_2O)_t^+ \longrightarrow \text{products} \qquad (17)$$

The rate law stemming from these equations is

$$\text{Rate} = k_{obs}\left[S\right]_{st} = \frac{k}{K_{SH^+}}\left[S(H_2O)_s\right]\left[H(H_2O)_n^+\right] a_{H_2O}^{(t-s-n)} \frac{f_{S(H_2O)_s} \cdot f_{H(H_2O)_n^+}}{f^*_{(H_2O)_t^+}} \qquad (18)$$

In the case where $\left[SH^+\right] \ll \left[S\right]$, $\left[S\right]_{st} = \left[S\right]$. Thus when logarithms are taken the following equation is obtained:

$$\log k_{obs} - \log \left[H(H_2O)_n^+\right] = (t-s-n) \log a_w + \log \frac{k}{K_{SH^+}} + \log f_{S(H_2O)_S} + \log \left(f_{H(H_2O)^+}/f^*_{(H_2O)_t^+}\right). \quad (19)$$

Thus if the activity coefficient terms are medium independent $\log k_{obs} - \log \left[H_3O^+\right]$ will be linear in $\log a_{H_2O}$ with slope ω^* approximately equal to (t-s-n).

Considering the protonation equilibrium of a Hammett base in which all species are fully hydrated

$$B(H_2O)_b + H(H_2O)_n^+ \rightleftharpoons BH(H_2O)_a^+ + (b+n-a)\ H_2O \quad (20)$$

leads to the definition of the acidity function

$$h_o = \frac{\left[H(H_2O)_n^+\right]}{a_w^{b+n-a}} \cdot \frac{f_{B(H_2O)_b} f_{H(H_2O)_n^+}}{f_{BH(H_2O)_a^+}} \quad (21)$$

From this equation (21), an expression for $\left[H(H_2O)_n^+\right]$ may be obtained which when substituted in equation (18) yields, upon taking logarithms and rearranging,

$$\log k_{obs} + H_o = (t-s+b-a) \log a_w + \log(k/K_{SH^+}) + \log \frac{f_{S(H_2O)_S} f_{BH(H_2O)_a^+}}{f_{B(H_2O)_b} f^*_{(H_2O)_t^+}} \quad (22)$$

Again, if all the assumptions concerning the activity coefficients in the construction of the acidity function h_o and concerning the generality of application of the function to other bases of different structural types are applied then $(\log k_{obs} + H_o)$ should be expected to be linear in $\log a_w$ with slope ω equal to $\left[(t-s) - (a-b)\right]$. Thus this hydration hypothesis in its extreme form relates ω to the hydration of the transition state less substrate in the protonation of an indicator base. Since these assumptions have been shown to be not generally correct, this hydration parameter treatment suffers from the same types of limitations as described for the Zucker-Hammett treatment[45].

It had been noted that although log I for uracils[47] and many primary, secondary and tertiary benzamide and napthamide derivatives (where $I = \frac{[SH^+]}{[S]}$) was a linear function of $-H_o$ the slopes were often appreciably less than unity[48-51]. Edward and Wang[52], in noting that propionamide was not a Hammett base, suggested that the difference in ionization behaviour of amides was due to a difference in the cationic hydration, in that the amides were more hydrated. Thus the appreciable difference between the ionization behaviour of amines and amides and the significant difference in the resulting activity coefficient behaviour led Yates et al[53] to define a new acidity coefficient, H_A, based upon measurements of the extent of the protonation of a series of primary amides in concentrated acid solutions. No amide, however, was found to link the weakly basic

amides in concentrated acid solutions with standard state pure water and so 4-nitroanilide [which was found to overlap with the strongest amide base used, 2-pyrrole carboxamide] was employed for this purpose.

The H_A scales for various concentrated acids have been determined and it has been observed that H_A is not a unique function of water activity for HCl and H_2SO_4 since generally $(H_A-H_o)_{H_2SO_4} > (H_A-H_o)_{HCl}$. Discussions of this deviation between H_o and H_A have considered individual activity coefficient variation or variation in hydration requirements between protonated amides and amines[54] ; this leads to the conclusion that protonated amides are H-bonded to more solvating water molecules than are primary anilinium ions. A simple picture of the solvated amide has been produced[50,53] . Consistant with the fact that, in H_2SO_4, $H_A > H_o$ is the finding that f_{AH^+} increases faster than f_{BH^+} (where AH^+ = anilinium ion and BH^+ = benzamide cation).

Yates and Stevens[55] criticised the application of Bunnett's relationship to amides and to other bases which have been shown not to follow H_o. They suggested that a modified hydration parameter treatment incorporating the h_A acidity function would be more appropriate. The theoretical derivation of this treatment is similar to that described above except that the general indicator base B refers to the amides used to construct the H_A acidity function[53] . Thus, this derivation, when considering a weakly

basic substrate, gives the following relationship for the first order rate constant k_{obs}:

$$k_{obs} = \frac{k}{K_{SH^+}} \cdot h_A \cdot \frac{f_{S(H_2O)_S}\, f_{BH(H_2O)_a^+}}{f^*_{(H_2O)_t}\, f_{B(H_2O)_b}} \cdot a_w^{r+(b-a)-(s-p)} \qquad (23)$$

based on equation (16) and the representation for the slow step in the general acid-catalysed reaction

$$SH(H_2O)_p^+ + r(H_2O) \xrightarrow{k} A^*(H_2O)_t^+ \longrightarrow \text{products} \qquad (25)$$

Equation (23) closely approximates to

$$k_{obs} = \frac{k}{K_{SH^+}}\, h_A\, a_w^{\,r} \qquad (26)$$

since $f_{S(H_2O)_S}$ and $f_{B(H_2O)_b}$ refer to the same type of species and it is a much less extreme assumption than that used in the Bunnett hydration parameter treatment[46] to suggest that these terms will approximately cancel. For the same reason the term (b-a)-(s-p) will be effectively zero. Taking logarithms and rearranging leads to

$$\log k_{obs} + H_A = r \log a_w + \log k/K_{SH^+} \qquad (27)$$

For more basic substrates protonated to an appreciable extent the corresponding equation can be shown to be

$$\log k_{obs} - \log (h_A/K_{SH^+} + h_A) = r \log a_w + \log k/K_{SH^+} \qquad (28)$$

Thus r can be more directly related to the number of water molecules required to convert the protonated substrate to the transition state.

Bunnett and Olsen[56,57] observed that, for diverse reactions in solutions of the same mineral acid, linear relationships existed between log Q and/or log k_2, where Q, the equilibrium quotient for substrate S is defined as $[SH^+] / [S][H^+]$ and k_2 the second order rate coefficient as $k_{obs} / [H^+]$.

In the absence of a suitable reaction for which rate or equilibrium date was available over a broad concentration range, Bunnett and Olsen chose to correlate experimental equilibrium or rate data against the equilibrium protonation of a hypothetical aromatic primary amine, B, of pK_{BH^+} zero, for which a plot of log I versus H_o has slope 1.00.

Thus, this protonation obeys the relationship

$$H_o = pK_{BH^+} + \log [B] / [BH^+] \qquad (28)$$

and thus $$\log Q_B = -H_o - \log [H^+] \qquad (29)$$

Assuming that the equilibrium quotient and the second order rate coefficient for the protonation and reaction of substrate S follow the equations

$$\log \frac{[SH^+]}{[S]} + H_o = \phi_e (H_o + \log [H^+]) + pK_{SH^+} \qquad (30)$$

$$\log k_r = \phi_r (H_o + \log [H^+]) + \log k_r^o \qquad (31)$$

where ϕ_e is a parameter which expresses the response of equilibrium to changing acid concentration,

pK_{SH^+} is the thermodynamic pK for the base S referred to infinite dilution in water,

$\log k_r$ is the phenomenological rate coefficient for the step

$SH^+ \log k_r$ is the phenomenological rate coefficient for the step

$\log SH^+ + H_2O \longrightarrow$ Transition state

in $\log k_r^o$ is the second order rate coefficient at infinite dilution

ϕ_r is a parameter which characterises the kinetic effect of changing the reaction medium.

Since the overall reaction rate can be expressed as $k_{obs} [S]_{stoic.}$ and $k_r [SH^+]$,

$$\log k_r = \log k_{obs} - \log \frac{[SH^+]}{[S] + [SH^+]} \qquad (32)$$

When the sign and magnitude of these parameters is considered it can be seen that they represent the relative rates of change of the factors under consideration and the equilibrium quotient of the hypothetical base. Bunnett and Olsen show that these parameters are proportionality constants between the logarithms of activity coefficient ratios.

$$\log \frac{f_B \cdot f_S}{f_{SH^+} \cdot f_B} = \phi_e \log \frac{f_{BH^+}}{f_B \cdot f_{H^+}} \qquad (33)$$

$$\log \frac{f_{SH^+}}{f^*} = \phi_r \log \frac{f_{BH^+}}{f_B \cdot f_{H^+}} \qquad (34)$$

where all terms have their usual significance.

Medium effects on rates and equilibria have been interpreted in terms of hydration change. Although Bunnett and Olsen recognise

this hypothesis as extreme, in the absence of any indication of the extent of this factor on medium effects, they discuss the magnitude of ϕ values in these terms. Considering the protonations and reactions of substrate S and hypothetical base B (equations 16,17 and 20) the following relations are derived:-

$$\phi_e = \frac{(p-s)-(a-b)}{(b+n-a)} \quad ; \quad \phi_r = \frac{(t-p)}{(b+n-a)} \qquad (35)$$

On this basis, for 3.5 -7M mineral acid, (b+n-a) is approximately 4.5 and average hydration changes can be expressed as 4.5ϕ or ω'.

Three mechanistic categories of ϕ have been envisaged and are listed in table 1.

Equations (30) and (31) can be added to obtain the approximate expression suitable for very weak bases

$$\log k_{obs} + H_o = \phi(H_o + \log [H^+]) + \log \frac{k_r^o}{K_{SH^+}} \qquad (36)$$

from which $\phi = (\phi_e + \phi_r)$ is noted. (37)

Kresge et al[58] have suggested an approach to the study of mechanisms in concentrated acid solutions. This approach, which does not rely upon the use of H_o, considers the equilibrium formation of a protonated intermediate and its conversion to products. The basic concept lies in the ability to represent the activity coefficient of the transition state, f^*, by the equation

$$f^* = (f_S \cdot f_{H^+})^{1-\alpha} f_{SH^+}^{\alpha} \qquad (38)$$

where α represents the extent to which the transition state resembles the protonated intermediate

From the generalized mechanism

$$S + H^+ \rightleftharpoons SH^+ \overset{k}{\rightleftharpoons} \text{products} \qquad (39)$$

the experimental rate constant k_{obs} will be

$$k_{obs} = \frac{k}{K_{SH^+}} [H^+] \frac{f_{H^+} f_S}{f^{\ddagger}} \qquad (40)$$

which leads to the equation, where I is the ionization ratio $\frac{[SH^+]}{[S]}$

$$\log_{10} \frac{k_{obs}}{[H^+]} = \alpha \log_{10} (I/[H^+]) + \log_{10} (k \; K_{SH^+}^{\alpha-1}) \qquad (41)$$

from which the parameter α can be determined. By comparison with the l.f.e.r. equations it can be shown that α is related to the parameters ϕ and ϕ_e by the equation

$$\alpha = (\phi - 1) / (\phi_e - 1) \qquad (42)$$

This test of mechanism was first applied to hydrogen exchange reactions in trihydroxy- and trimethoxybenzene.

However, this parameter would appear to be limited to cases where the transition state lies between substrate and protonated substrate[57].

THE HYDROLYSIS OF AMIDES

The subject of amide hydrolysis has recently been reviewed[59] and it has been pointed out that, although the mechanism of alkaline hydrolysis of amides has been determined, doubts about the precise mechanism of acid hydrolysis still remain[59,60] and the existance of a mechanism general to amides of varying structures has been questioned.[94]

Thus the following discussion deals briefly with evidence for, and conclusions concerning the mechanism of acid catalysed hydrolysis of amides since this is a subject under consideration in this work.

Acid - Catalysed Amide Hydrolysis.

The reactions of carboxylic acid derivatives have been the subject of continued investigation over a long period and the topic has been reviewed [32]. In many cases, general and subsidiary mechanisms have been proposed and identified. The hydrolysis of simple esters, for example, has been shown to proceed by an $A_{Ac}2$ mechanism in aqueous acid, whereas sterically hindered aromatic esters have been shown to proceed by an $A_{Ac}1$ mechanism [32]. The base catalysed hydrolysis of amides has proved to be relatively straightforward [59], as have the mechanisms of hydrolysis of acid halides and anhydrides [32], but, although extensive studies have been carried out [59] the nature of the general mechanism of acid-catalysed hydrolysis of amides has not yet been unambiguously established [59,60].

The experimental rate constants for the hydrolysis, in concentrated aqueous HCl solutions, of a diverse series of amides have been shown to be approximately proportional to the HCl concentration [61].

The acid catalysed hydrolysis of amides were studied by Reid [62] who showed that, in reasonably dilute acid solutions, the rate of hydrolysis was first order in both total amide and total hydrogen ion concentrations.

The most notable feature of the kinetics of acid catalysed hydrolysis of amides is, however, the existance of a maximum in

the plot of rate against acid concentration. This was first observed by Benrath[63] and has been found to occur generally in the hydrolysis of a number of aliphatic and aromatic amides in strong acids[64-67]. The position of this maximum has been shown to vary depending upon the structure of the amide and upon the nature of the acid, but generally occurs at acidities numerically greater than the pK_A of the amide[32].

Examinations of the effects of substituents on the hydrolysis of aliphatic and aromatic amides have been carried out. In benzamides meta or para electron attracting substituents on the benzene nucleus were found to accelerate and electron releasing substituents found to decelerate the hydrolysis rates[68], whereas ortho substituents, independent of their polar effects[69,70], retard the reaction through steric hinderance[62].

In aliphatic amides the rate of hydrolysis was found to be governed by a combination of steric,[69,71,72], polar and conjugative substituent effects of which steric effects were most important. Thus the rate of hydrolysis of n-butyramide is twice as slow as that of n-propionamide[69].

Studies of the deuterium isotope effect on the acid catalysed hydrolysis of acetamide[66,74] and benzamide[73] in HCl showed that in both cases the effect of the change from H_2O to D_2O as solvent was to shift the entire profile so that the maximum occurred at lower acid concentration. The hydrolysis of these amides are found

to proceed more rapidly in D_2O at low acid concentrations and more rapidly in H_2O at high acid concentrations. Since, on the basis of a fivefold smaller autoprotolysis constant, D_2O is believed to be less basic than H_2O,[74,75] these observations can be explained in terms of the following reaction scheme[74].

$$S + H^+ \rightleftharpoons SH^+$$
$$SH^+ + H_2O \rightleftharpoons A^* \longrightarrow \text{products} \qquad (43)$$

In the less basic solvent, D_2O, the substrate will be able to compete more favourably for the deuteron than for the proton in H_2O. Thus the concentration of the conjugate acid will achieve a maximum more quickly in D_2O than in H_2O, provided the second step does not show an inverse effect. Thus in low acid concentrations the pre-equilibrium controls the isotope effect and the reaction is more rapid in D_2O than in H_2O. At high acid concentrations the amide is largely in the form of the conjugate acid in either solvent. The displacement on the conjugate acid would be expected to be slower for D_2O than for H_2O since the former is the weaker base.

Thus, on the basis of kinetic and substituent effect evidence, the acid catalysed hydrolysis can be discussed in terms of a pre-equilibrium protonation followed by nucleophilic attack of water on the conjugate acid [59], but it has been recognised that the inverse solvent isotope effect observed at low acidities does not rule out rate determining proton transfer if it were accompanied

by other covalency changes [76].

Arrhenius parameter results are also in accord with the bimolecular mechanism[61b,77,78,79,80].

Bender [32] summarized the data obtained and noted that the hypothesis of nucleophilic attack by solvent water on the protonated amide intermediate as the rate determining step effectively accounted for all the experimental facts, and represented the proposed mechanism as follows

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NHR^1 + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[R\text{-}\overset{OH}{\overset{\|}{C}}\text{-}NHR^1\right] \xrightarrow[H_2O]{+k_3} \text{hydrolysis products} \quad (44)$$

slow

To account for the appearance of a maximum in the hydrolysis rate versus acid concentration plot, hypotheses involving complete ionization and subsequent salt formation,[63] a changing mechanism as acid concentration is increased [65] were discarded in favour of the suggestion that the decrease in rate at intermediate acid concentrations was due to decreasing water activity [67]. It was suggested that the maximum occurred at the point at which the increasing acid concentration had a proportionately smaller effect in enhancing the acidity than in decreasing the water activity.

This hypothesis was found to account quantitatively for the changes in the rate of hydrolysis with acid concentration[61c]. Thus the experimental rate constant, k_{obs}, can be related to

the second order rate constant, k_2, by the expression

$$k_{obs} = k_2 K_{AH^+} [H_3O^+]/(K_{AH^+} + h_o) \quad (45)$$

where K_{AH^+} is the equilibrium constant for the dissociation of the protonated amide and h_o is the Hammett [44] acidity function. In the light of the earlier discussion[53], h_A should perhaps be used here instead of h_o.

Generally for weak bases or at low acidities, $K \gg h_o$ and equation (45) simplifies to the following expression

$$k_{obs} = k_2 [H_3O^+] \quad (46)$$

Thus a linear dependence of the experimental first order rate constant on the concentration of the hydronium ion is predicted and is found in dilute acid solution[61c].

However in strong acid solution, when $K \ll h_o$, equation (46) simplifies to

$$k_{obs} = k_2 . K [H_3O^+]/h_o \quad (47)$$

Since h_o increases with acid concentration much more rapidly than $[H_3O^+]$, k_{obs} decreases in high concentrations of acids. When $K \ll h_o$ protonation of the amide will be substantially complete ; the decrease in the rate of hydrolysis can thus be regarded as a consequence of the decreasing availability of water.

Other forms of the equation (45) have been applied to the hydrolysis of o-nitroacetanilide in H_2SO_4[77] .

In substituted benzamides, the effect of a sustituent could be manifested in either the pre-equilibrium step, in the subsequent rate determining step or in both steps. The Hammett ρ constants[81] would bear the theoretical relationship to one another.

$$\rho \text{ overall} = \rho_1 + \rho_2 \qquad (48)$$

where 1 and 2 refer to the pre-equilibrium and rate determining steps respectively. It is possible to determine all three ρ constants independently and it was found that the above relationship was closely approximated by the experimental data[68] thus corroborating the proposed mechanism.

Attempts to determine the unique or predominant centre of protonation in the conjugate acid of amides in acidic media has led to the collection of a large number of experimental observations obtained by a large variety of physical and chemical methods. These observations have been reviewed[59,82] and the conclusion was reached that, although protonation of amides occurs in both of the possible positions , O-protonation predominates and N-protonation occurs to only a small degree. Perhaps the strongest evidence for these conclusions comes from proton n.m.r. work on acetamide, N, N dimethyl acetamide , formamide and N, N

dimethyl formamide[83]. At low temperatures, where solvent exchange was slow, resonances were assigned to $C=\overset{+}{O}H$. Also, resonances assigned to the methyl groups of N, N dimethyl formamide, in different environments as a result of partial double bond character of $OC-NMe_2$, remained unchanged in strong aqueous acids, thus suggesting that the O-protonated form predominates.

Observations of the loss of both cis and trans coupling of C-bound and N-bound protons of formamides at a low degree of protonation led Liler[84,85] to assert that this is consistant only with N-protonation.

Also, low activation energies for exchange of the two N-H sites of $[N^{15}]$ in concentrated acids are accounted for by Liler in terms of a tautomerism of the O and N protonated cations with the N-protonated species increasing in concentration on proceeding to dilute acids

However Martin[122] pointed out that, in formamide, since both N-bound protons undergo acid-catalysed exchange at comparable rates, simultaneous collapse of both cis and trans couplings of the C- and N- bound protons would be expected and that no conclusion concerning the site of protonation can be reached from this result. By considering proton exchange rates in formamides at acidities where the amide is only fractionally protonated, Martin provides quantitative estimates of the molar ratio of O- to N- protonated amide in dilute acid solutions. He shows that for N-Methyl acetamide this ratio is of the order of 3×10^6.

The virtual absence of oxygen exchange in the acid catalysed hydrolysis of amides, demonstrated in dilute acids[170] and recently confirmed in both dilute and 8.4M HCl[73] cannot be reconciled with an O-protonated intermediate. Also, on the assumption that the predominant cation in aqueous acids is the O-protonated form, it has not proved possible to justify a simple $A_{AC}2$ mechanism or, to formulate another suitable mechanism of acid-catalysed amide hydrolysis[32,59].

The general existance of a maximum in the plot of rate against acid concentration considerably complicates tests of acidity function behaviour as a criterion of mechanism[43].

For the postulated $A_{AC}2$ mechanism, the Zucker-Hammett hypothesis, when tested, is found to break down in even moderately concentrated acids when applied to amide hydrolysis.

In applying the empirical hydration parameter treatment to acid-catalysed amide hydrolysis, Bunnett[46] initially used K_{SH^+} values of uncertain validity. The ω values thus determined for the hydrolysis of benzamide and 4-nitrobenzamide, acetamide, propionamide and acetyglycine were redetermined by Bunnett and Olsen using more reliable, spectrophotometrically determined K_{SH^+}values for the equilibrium protonation of amides. The results are displayed in table (1). Where plots to determine ω show a degree of curvature, it was usually found that ω^* plots were close to linearity. Curvature was

attributed to a decreasing number of water molecules in the transition state with increasing acid concentration.

Since comparison of the ionization behaviour of amines and amides clearly shows that amides do not follow the Ho function, the ω values cannot be simply related to hydration changes in the rate determining step.

The modified hydration parameter treatment for amides, by using the amide acidity function, H_A, avoids the necessity of assuming the activity coefficient behaviour and the solvation requirements of the reactants and the transition state parallel the activity coefficient behaviour and the solvation requirements of the primary aniline bases and their cations used in the construction of the acidity function H_o. Initially, when applied over a restricted acidity range, good straight lines for a series of amides were obtained.[55] Values of r determined for the hydrolysis of benzamide and 4-nitrobenzamide in aqueous H_2SO_4 were 2.6 and 2.7 respectively.

These values agree fairly well with the values of the parameter b , the number of water molecules, in addition to the hydration sheath of the protonated amide needed to form the activated complex.[49] Thus, a value of 3.3 was obtained for this parameter over a relatively short concentration range in H_2SO_4.

Thus both authors came to the same conclusion as to the nature of the transition state (fig.IV)

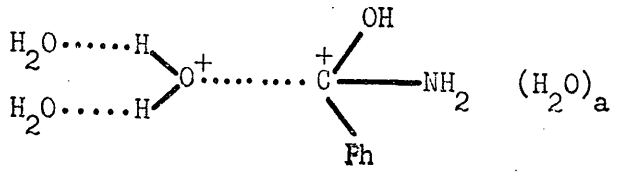


Fig.(IV)

Application of the linear free energy relationship (l.f.e.r.) treatment for reaction rates proposed by Bunnett and Olsen[57] gave typical values as in table (1). This treatment, however, was found in several cases to give non-linear plots[60,73,87]. This non-linearity in the l.f.e.r. treatment of kinetic data was discussed by Bunnett and Olsen[56] in terms of a mechanism involving two pathways occurring simultaneously.

Several authors[61c,69,88,89] had previously suggested that acid catalysed hydrolysis of amides could go via two mechanisms involving distinct intermediates and transition states depending upon whether the oxygen or the nitrogen of the amide had been protonated.

The failure of the hydration parameter, the modified hydration parameter and the linear free energy relationships to give linear plots for the hydrolysis of benzamide N-methyl benzamide and N, N-dimethyl benzamide in HCl led Bunton et al[73] to further suggest the existance of two distinct mechanistic paths, with transition states I and II in figure (V).

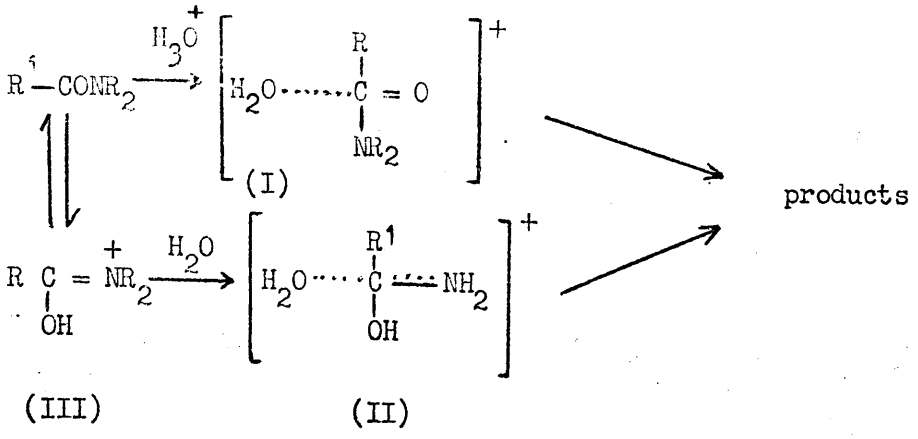


Fig. (V)

Assuming the activity coefficients of the free amides and the activity coefficients of ions of like charge to be essentially medium independent, an assumption which has been described as unrealistic,[87] an application of the Bronsted-Bjerrum rate equation gave equation (49)

$$k_{obs} C_A = (K_1 C_A C_{H^+} + K_2 C_{III}) a_w \qquad (49)$$

where C_A is the stoichiometric concentration of amide. If α is the amount of protonated amide III, equation (49) becomes

$$\frac{k_{obs}}{a_w \cdot \alpha} = \frac{k_1 C_H (1-\alpha) + k_2}{\alpha} \qquad (50)$$

This treatment was found to correlate the observed data.

Smith and Yates[60] suggest that the problem of curvature in r-type plots cannot easily be explained by postulating

dual competitive mechanisms since this would require, for the structurally different amides studied, the improbable equality of the enthalpies of activation for each pathway. The requirement that this equality should remain, over a large range of acid concentration , since the enthalpy of activation for the protonated species is observed to be medium invariant over this range, is also improbable. These authors conclude that curvature of r -type plots is likely to be due to the medium variation of the ratio of the activity coefficients of the protonated species and the transition state. The non-coincidence of r -type plots for amide hydrolysis in $HClO_4$ and H_2SO_4 has been reported as invalidating evidence for the assumed medium independence of the activity coefficient ratio by Moodie et al[87] who observe that the activity coefficient ratio clearly varies with the nature and the concentration of the strong acid and that derived r values are not reliable for this reason.

Yates and Smith[60] conclude that the absence of curvature in r -type plots for other substrates, such as esters, suggest that, on the basis of Hammond's postulate,[90] the conjugate acids of these species should resemble their transition states to a much greater degree than the amide conjugate acid resembles its conjugate acid.

Yates and Smith[60] observe that values of hydration parameters

in general will be materially affected if a_w values and observed rate constants do not refer to the same temperature.

They demonstrate that reported variations of the enthalpy of activation, ΔH^* of amide hydrolysis with medium concentration are largely due to the incorporation of a temperature of a_w into ΔH^*.

Thus plots of log k_p^T versus log a_w^{25}, where k_p^T is the specific rate constant at varying temperatures and a_w^{25} is the water activity of a particular medium at 25°C, will result in a set of non-parallel r-type plots as T is varied.

The conclusion is reached that, since ΔH^* can be shown to be medium independent when the temperature variation of a_w is taken into account, and since the shape of the r-type plots is constant, as determined by the factor log $(k/K_A).(f_{SH^+}/f^*)$ derivable from equation (25), the curvature of the r-type plots must be due to the manner in which the entropy of the reaction varies with the medium.

A suggestion that amides hydrolyse only by way of a much less predominant N-protonated amide as the reactive conjugate acid has been used by Yates and Smith[60] to explain the slowness of amide hydrolysis, the non-observation of O^{18} exchange concurrent with acid-catalysed hydrolysis[73]. The curvature of r-type plots can also be explained on this model since, if the reaction were to proceed by a minor conjugate acid form

with significantly different pK and acidity function dependence, the correction term for substrate protonation would follow a complex, changing acidity function.

These suggestions are stated to be independent of any activity coefficient behaviour.

A suggestion that the rate maximum in the plot of rate against acid concentration corresponds to a maximum in the concentration of the N-protonated form in a medium dependent tautomeric equilibrium of the two forms has been forwarded [92] but has been criticized[85].

Amides containing highly electron withdrawing N-substituents have been shown to undergo unimolecular hydrolysis in concentrated H_2SO_4 by fission of the N protonated form [93].

O'Conner et al [94] recently reported that, by a survey of correlations of acid catalysed amide hydrolysis by the hydration parameter treatments, the l.f.e.r. treatment and the empirical two-term mechanism, a classification according to structure became obvious. Aromatic amides were found to correlate poorly with hydration parameter and l.f.e.r. treatments but correlated well with the empirical two term mechanism, whereas, for aliphatic and pseudo-aliphatic amides (anilides), the reverse situation applied. They thus suggested that the mechanism for acid catalysed hydrolysis of aromatic amides involves complications which are not present in the hydrolysis of aliphatic amides.

If amide hydrolysis proceeds to an intermediate by attack of water on an O-protonated conjugate acid, it has been suggested[61c] that the tetrahedral intermediate generated in the hydrolysis of a suitable imidate ester would be a good model for that intermediate.

Based on this suggestion, Yates et al[116] studied the acidic hydrolysis of series of related N substituted benzamides and methyl benzimidates. A change in benzimidate hydrolysis product from ester/acid to amide at high acid concentration, and variances in ΔH^{*} values with increases in acid concentration suggested that a change in rate determining step was occurring. If the two reactions proceed via similar intermediates, the O^{18} exchange which would now be expected in concentrated acid solutions in amide hydrolysis was not observed. The sharp contrast between the amides and imidates in the effect of successive N substitutions on respective ΔH^{*} values, and the effects of these substitutions upon relative rates suggested to these authors that it is unlikely that each amide considered hydrolyses by a mechanism similar to that occurring in imidate hydrolysis.

Thus it was concluded that reaction, in amide hydrolysis, via a minor N-protonated form, or changes of mechanism with substitution would account for the observed results.

EXPERIMENTAL SECTION

PREPARATIVE EXPERIMENTAL.

All starting materials were commercial samples and were generally of an analytical reagent grade. They were purified by recrystallization or distillation before use.

Melting points were measured on a Kofler-Reichert hot stage melting point apparatus and are uncorrected.

I.r. spectra were recorded using Perkin-Elmer 237 and Pye Unicam SP1000 spectrophotometers and were calibrated by polystyrene-film spectral bands. The following abreviations are used:- s : strong; m : medium; w : weak (intensities) def : deformation; str : stretch; skel : skeletal; assym : assymmetric; sym : symmetric.

N.m.r. spectra were recorded as approximately 10% solutions by 60 MHz Varian T-60 and 100 MHz Varian HA-100 spectrometers. Chemical shifts were measured downfield from internal T.M.S. and are quoted in parts per million. The chemical shift quoted for multiplets is normally the centre of that multiplet. The integration value of each peak and its multiplicity are given in

parenthesis and where, upon shaking the solution with D_2O, exchange of any proton(s) produces a change in the spectrum, the change is recorded in parenthesis.

Elemental analysis were determined by the analytical staff, The University of Glasgow and are quoted as percentages.

All analytical and preparative thin layer chromatography (t.l.c.) was carried out on Kieselgel 'G', as the stationary phase, of thicknesses 0.25 mm and 1.0mm respectively.

Routes to N - Aryl γ and δ Hydroxy Amides

The majority of the 4 - hydroxy butyranilides and 5 - hydroxy valeranilides were prepared by the adaptation of a general route to the aryl esters of 4 - hydroxy butyric acid and 5 - hydroxy valeric acid[95,96].

This adapted route involves the protection of the hydroxyl of the hydroxy acid with the benzyl residue, which can be easily removed by hydrogenolysis under mild conditions.[97]

The benzyloxy acids, prepared from the corresponding lactones[95], can be condensed with an aniline in the presence of N - ethoxy carbonyl, 2 - ethoxy, 1,2 - dihydroquinoline[98] (EEDQ) to form the benzyloxy anilide.

Hydrogenolysis under mild conditions[97] yields the corresponding hydroxy anilide.

This route was used in all cases except where there was a group more susceptible to hydrogenation than the ether linkage in the molecule or where the hydroxy anilide could be formed directly from the anilide and lactone.

Preparation of 4 - Benzyloxy Butyric Acid

Anhydrous toluene (75ml) is brought to reflux in a 2 litre, three-necked flask fitted with a condenser, a dropping funnel and a mechanical stirrer. Finely ground potassium hydroxide (35g, 0.625 mol) is added to the stirred solution. 4 - butyrolactone (22g, 0.25mol) is added dropwise over 40 minutes. Dry, redistilled benzyl chloride (95g, 0.75mol) is added dropwise over 40 minutes. This mixture is refluxed for 40 hours.

The toluene is removed by vacuum distillation and the residue is refluxed in potassium hydroxide solution (1 litre, 2molar; 5hours).

The aqueous solution is cooled, extracted with ether (3x150mls) and acidified with concentrated HCl. The acidified solution was extracted with ether (3x200mls) and the ether layer was washed with brine and dried over anhydrous magnesium sulphate. The ether is removed by vacuum distillation to yield crude 4 - benzyloxy butyric acid (23.3g, 0.12mol; 48%). Distillation of the product oil under reduced pressure gave a clear oil, b.pt. 150-154°C/ 0.95mm Hg (lit. b.pt. 140-144°C/ 1.0mm Hg [95,100]).

N.m.r. ($CDCl_3$): δ 2.08 (m,2), 2.56 (m,2), 3.62 (t,2), 4.58 (s,2), 7.38 (s,5), 10.18 (s,1); i.r. (neat) ν : 3300-2400 (m), [H bonded O-H str.] , 1705 (s)[C=O str.] , 1580, 1490 (m) [Aromatic C=C str.] , 1450 (m), 1375 (m) [assym. and sym. C-H def.] , 1030 (m) [C-O str.] , 890, 740, 700 (m) [Aromatic C-H out-of-plane bend] .

Preparation of 5-Benzyloxy Valeric Acid

Using the procedure outlined above, 5-valerolactone (25g, 0.25 mol) yielded 5-benzyloxy valeric acid (28.0g, 0.146 mol; 58.1%); b.pt. of product oil 152-153 C / 0.95mm Hg [95].

N.m.r. ($CDCl_3$) δ : 1.68 (m,4), 3.48 (t,2), 4.50 (s,2), 7.33 (s,5), 9.06 (s,1); i.r.(neat) ν : 3350-2400 (m), 1700 (m), 1595 (m), 1485 (m), 1450 (m), 1380 (m), 1040 (m), 890 (m), 730 (m), 690 (m)cm^{-1}.

Preparation of N - Aryl 4 - Benzyloxybutyramides.

Several N - aryl 4 - benzyloxybutyramides were prepared from 4 - benzyloxy butyric acid and an aniline by the method of Belleau and Malek [98]. This synthesis involved the addition, in approximately 7% excess, of the condensing agent EEDQ (N - ethoxycarbonyl, 2 - ethoxy 1,2 dihydroquinoline) to an equimolar solution of the acid and the aniline in dry benzene. This solution was left overnight at room temperature. The benzene was removed by distillation under reduced pressure yielding an oil which was crystallized at 0°C from ethyl acetate / pet - ether (b.pt. 40-60°) giving in each case, a white, crystalline solid. Recrystallization from the same solvent system yielded the pure anilide in 80 - 90% yield. The infra - red spectra of these compounds showed bands in the following ranges with the corresponding assignations :-
3480 - 3260 (m) and 3370 - 3180 (w) [N-H str.], 3050 -3030 (w) [Aromatic C-H str.], 2960 - 2930 (s) and 2890 - 2860 (s) [C-H str.] 1705 - 1645 (m) [Amide I, C=O str.], 1575 - 1535 (m) [Amide II, N-H bend], 1610 -1585 (m) and 1505 - 1460 (m) [Aromatic C=Cstr.], 1475 -1455 (m) and 1385 - 1370 (m) [assym. and sym. C-H def], 1085 -1025 (m) [C-O str] 915 - 665 (m, several bands) [Aromatic C-H out - of - plane bend].

The following compounds were prepared by this method

N - Phenyl 4 - Benzyloxybutyramide

m.pt. 46-47°C. (Found: C, 75.95; H, 7.11; N, 4.93. $C_{17}H_{19}NO_2$ requires C, 75.81; H, 7.11; N, 5.20%); n.m.r. ($CDCl_3$): δ 2.10 (q,2), 2.48 (d,2), 3.63 (t,2), 4.56 (s,2), 7.36 (s,10), 7.85 (s,1); i.r. (nujol) ν :3320 (m), 3260 (w), 3030 (w), 2930 (s), 2860 (s), 1655 (m), 1532 (m), 1598 (m), 1460 (m), 1445 (m), 1378 (m), 1085 (m), 910 (m), 763 (m), 750 (m), 698 (m) cm^{-1}.

N - (p - Tolyl) 4 - Benzyloxybutyramide

m.pt. 64-65°C. (Found: C, 75.71; H, 7.28; N, 5.16. $C_{18}H_{21}NO_2$ requires C, 76.30; H, 7.47; N, 4.94%); n.m.r. ($CDCl_3$): δ 2.00 (d,2), 2.23 (s,3), 2.35 (d,2), 3.54 (t,2), 4.48 (s, 2), 7.09 (d,2), 7.21 (d,2), 7.30 (s,5), 7.64 (s,1); i.r. (nujol) ν : 3280 (m), 3180 (w), 3030 (w), 2940 (s), 2860 (s), 1645 (m), 1540 (m), 1460 (m), 1455 (m), 1375 (m), 1075 (m), 825 (m), 750 (m), 700 (m), cm^{-1}.

N - (m - Tolyl) 4 - Benzyloxybutyramide

m.pt. 59-60°C (Found: C,75.56; H, 7.31; N, 5.16. $C_{18}H_{21}NO_2$ requires C, 76.30; H, 7.47; N, 4.94%); n.m.r.($CDCl_3$): δ 2.10 (d,2), 2.48 (d,2), 3.65 (t,2), 3.80 (s,3), 4.56 (s,2), 6.90 (m,4), 7.39 (s,5), 7.70 (s,1); i.r. (nujol) ν : 3250 (m), 3150 (w), 3040 (w), 2960 (s), 2890 (s), 1660 (m), 1550 (m), 1610 (m), 1490 (m), 1460 (m), 1380 (m), 1080 (m), 890 (m), 800 (m), 750 cm^{-1}.

N - (p - Methoxyphenyl) 4 - Benzyloxybutyramide

m. pt. 70-71°C. (Found: C, 7256; H, 7.31; N, 5.16. $C_{18}H_{21}NO_3$ requires C, 72.22; H, 7.07; N, 4.68%); n.m.r. ($CDCl_3$): δ 2.02 (d,2), 2.40 (d,2), 3.51 (t,2), 3.71 (s,3), 5.53 (s,2), 6.91 (d,2), 7.20 (d,2), 7.29 (s,5), 7.75 (s,1); i.r. (nujol) ν : 3320 (m), 1525 (m), 1600 (m), 1500 (m), 1460 (m), 1375 (m), 1035 (m), 830 (m), 750 (m), 700 (m), cm^{-1}.

N - (m - Methoxyphenyl) 4 - Benzyloxybutyramide

m.pt. 60-61°C (Found: C, 72.05; H, 7.06; N, 4.72. $C_{18}H_{21}NO_3$ requires C, 72.22; H, 7.07; N 4.68%); n.m.r. ($CDCl_3$): δ 2.11 (d,2), 2.49 (d,2), 3.60 (t,2), 3.80 (s,3), 4.53 (s,2), 6.90 (m,4), 7.36 (s,5), 7.76 (s,1); i.r. (nujol) ν : 3310 (m), 3040 (w), 2950 (s), 2850 (s), 1658 (m), 1540 (m), 1605 (m), 1500 (m), 1470 (m), 1380 (m), 1045 (m), 880 (m),805 (m), 795 (m), 760 (m), 740 (m), 710 (m), 695 (m) cm^{-1}.

N - (p - Chlorophenyl) 4 - Benzyloxybutyramide

m.pt. 68-69°C. (Found: C, 67.20; H, 5.92; N, 4.40. $C_{17}H_{18}NO_2Cl$ requires C, 67.40; H, 5.98; N, 4.62%); n.m.r. ($CDCl_3$): δ 2.13 (m,2), 2.54 (t,2), 3.69 (t,2), 4.61 (s,2), 7.31 (s,4), 7.41 (s,5), 8.08 (s,1); i.r. (nujol) ν : 3310 (m), 3190 (w), 3040 (w), 2940(s), 2870 (s), 1653 (m), 1535 (m), 1590 (m), 1490 (m), 1465 (m), 1380 (m), 1080 (m), 915 (m), 860 (m), 825 (m), 750 (m), 675 (m)cm^{-1}.

N - (m - Chlorophenyl) 4 - Benzyloxybutyramide

m.pt. 60-61°C. (Found; C,67.60 ; H,5.85 ; N, 4.91.
$C_{17}H_{18}NO_2Cl$ requires C, 67.40; H, 5.98; N, 4.62%);
n.m.r. ($CDCl_3$): δ 1.98 (t,2), 2.47 (t,2), 3.57 (t,2), 4.50 (s,2),
6.20 (m,4), 7.30 (s,5), 8.15 (s,1); i.r. (nujol) ν: 3260 (m),
3180 (w), 3040 (w), 2940 (s), 2860 (s), 1665 (m), 1540 (m),
1590 (m), 1465 (m), 1455(m), 1382 (m), 1084 (m), 835 (m),
825 (m), 760 (m), 725 (m), 710 (m) cm^{-1}.

N - (p - Bromophenyl) 4 - Benzyloxybutyramide

m.pt. 77-78°C. (Found: C, 58.44; H, 5.16; N, 3.84.
$C_{17}H_{18}NO_2Br$ requires C,58.60; H,5.19; N,4.02%);
n.m.r. ($CDCl_3$): δ 2.00 (t,2), 2.50 (t,2), 3.60 (t,2),
4.55 (s,2), 7.26 (s,4), 7.34 (s,5), 8.00 (s,1); i.r. (nujol) ν :
3350 (m), 3290 (w), 3040 (w), 2960 (s), 2890 (s), 1650 (m), 1535 (m),
1590 (m), 1490 (m), 1470 (m), 1370 (m), 1080 (m), 835 (m), 825 (m),
760 (m), 725 (m), 710 (m), cm^{-1}.

N - (m - Bromophenyl) 4 - Benzyloxybutyramide

m.pt. 50-51°C (Found C, 58.71; H, 5.20; N, 4.07.
$C_{17}H_{18}NO_2$ requires C, 58.60; H, 5.19; N, 4.02%);
n.m.r. ($CDCl_3$): δ 1.99 (t,2), 2.48 (t,2), 3.60 (t,2),
4.52 (s,2), 7.35 (m,4), 7.20 (s,5), 8.10 (s,1); i.r. (nujol) ν :
3300 (m), 3200 (w), 3050 (w), 2940 (s), 2870 (s), 1660 (m),
1535 (m), 1590 (m), 1485 (m), 1460 (m), 1380 (m), 1085 (m), 800 (m),
765 (m), 730 (m), 710 (m), cm^{-1}.

Preparation of N - Aryl 5 - Benzyloxyvaleramides

Several aryl - substituted N aryl 5 - benzyloxyvaleramides were prepared from 5 - benzyloxy valeric acid and the corresponding aniline by the method of Belleau and Malek[98]. The preparative and purification method employed was the same as that described for the synthesis of the 4 - benzyloxybutyranilides.

The following compounds were prepared by this method:

N - (p - Methoxyphenyl) 5 - Benzyloxyvaleramide

m.pt. 82-83°C (Found C, 72.07; H, 7.28; N, 4.47. $C_{18}H_{23}NO_3$ requires C, 72.82; H, 7.40; N, 4.47%);
n.m.r. ($CDCl_3$): δ 1.70 (m,4), 2.30 (t,2), 3.50 (t,2), 3.72 (s,3), 4.48 (s,2), 6.75 (d,2), 7.35 (d,2), 7.36 (s,5), 7.89 (s,1);
i.r. (nujol) ν : 3320 (m), 3250 (w), 3050 (w), 2920 (s), 2850 (s), 1655 (m), 1535 (m), 1598 (m), 1510 (m), 1450 (m), 1370 (m), 1035 (m), 820 (m), 800 (m), 730 (m), 690 (m) cm^{-1}.

N - (p - Bromophenyl) 5 - Benzyloxyvaleramide

m.pt. 108-109°C. (Found C,59.78; H, 5.75; N, 3.95. $C_{18}H_{20}NO_2Br$ requires C, 59.70; H, 5.56; N, 3.87%);
n.m.r. ($CDCl_3$): δ 1.71 (m,4), 2.36 (t,2), 3.52 (t,2), 4.46 (s,2), 7.28 (s,4), 7.30 (s,5), 7.70 (s,1); i.r. (nujol) ν : 3320 (m), 3180 (w), 3030 (w), 2920 (s), 2850 (s), 1660 (m), 1520 (m), 1587 (m), 1485 (m), 1450 (m), 1370 (m), 1065 (m), 815 (m), 745 (m), 695 (m) cm^{-1}.

N - (p - Chlorophenyl) 5 - Benzyloxyvaleramide

m.pt. 96-97°C. (Found C, 68.19; H, 6.60; N, 4.40. $C_{18}H_{20}NO_2Cl$ requires C, 68.03; H, 6.34; N, 4.40%); n.m.r. ($CDCl_3$): δ 1.72 (m,4), 2.35 (t,2), 4.48 (s,2), 7.23 (s,4), 7.31 (s,5), 7.83 (s,1); i.r. (nujol) ν : 3330 (m), 3200 (w), 3050 (w), 2940 (s), 2870 (s), 1660 (m), 1530 (m), 1595 (m), 1495 (m), 1465 (m), 1380 (m), 1085 (m), 820 (m), 750 (m), 700 (m), 670 (m) cm^{-1}.

N - (m - Chlorophenyl) 5 - Benzyloxyvaleramide

m. pt. 59-60°C. (Found C, 68.28; H, 6.58; N, 5.41. $C_{19}H_{20}NO_2Cl$ requires C, 68.03; H, 6.34; N, 4.40%); n.m.r. ($CDCl_3$): δ 1.72 (m,4), 2.37 (t,2), 3.52 (t,2), 4.48 (s,2), 7.20 (m,4), 7.34 (s,5), 8.04 (s,1); i.r. (nujol) ν : 3330 (m), 3280 (w), 3040 (w), 2940 (s), 2870 (s), 1673 (m), 1538 (m), 1595 (m), 1465 (m), 1430 (m), 1380 (m), 1080 (m), 875 (m), 785 (m), 750 (m), 740 (m), 700 (m) cm^{-1}.

Preparation of γ and δ Hydroxy Anilides

Depending upon the susceptibility of the aromatic substituent in the benzyloxy anilides to hydrogenation, either of two standard[97] methods of benzyloxy ether hydrogenolysis was used.

For those compounds in which only the ether linkage was susceptible to hydrogenation the following method was used:-

a) To the benzyloxy anilide (5×10^{-3} mol) dissolved in ethanol (50ml) to form an approximately 10^{-3} molar solution, 10% by weight of 10% Palladium on charcoal is added. This solution is then stirred in an atmosphere of hydrogen until analytical t.l.c. shows that all the starting material has been hydrogenolysed. The catalyst is filtered off, the solvent removed by distillation under reduced pressure and the product, generally a white solid, is recrystallized from ether acetate/pet-ether (b.pt. 40-60°C.) to constant melting point.

The following compounds were prepared by this method:-

N - Phenyl 4 - Hydroxybutyramide

m.pt. 80-81 C. (lit. m.pt. 74-75° [99] ,83-84° [101], 78-79° [102].)
(Found: C,66.90; H,7.25; N,7.60. Calc. for $C_{10}H_{13}NO_2$. C,67.02; H,7.28; N,7.77%); n.m.r. ($CDCl_3$) δ : 1.95 (t,2), 2.42 (s,1; D_2O exchange), 3.73 (t,2), 7.35 (m,5), 7.67 (s,1), i.r. (nujol) ν : 3320 (m), 3245 (w), 3190 (w), 3040 (w), 2920 (s), 2850 (m), 1670 (m), 1545 (m), 1600 (m), 1498 (m), 1370 (m), 1050 (m), 905 (m), 750 (m), 690 (m) cm^{-1}.

N - (p - Tolyl) 4 - Hydroxybutyramide

m.pt. 104-5 C. (Found: C, 68.31; H, 7.71; N, 7.02. $C_{11}H_{15}NO_2$ requires C, 68.37; H,7.82; N, 7.25%); n.m.r. ($CDCl_3$): δ 1.93 (t,2), 2.32 (s,3), 2.50 (t,2), 2.68(s,1; D_2O exchange), 3.70 (t,2), 7.07 (d,2), 7.33 (d,2), 7.65 (s,1); i.r. (nujol) ν : 3330 (m), 3190 (w), 3280 (w), 3040 (w), 2930 (s), 2860 (s), 1665 (m), 1548 (m), 1600 (m), 1515 (m), 1450 (m), 1380 (m), 1055 (m), 918 (m), 820 (m), 730 (m) cm^{-1}.

N - (m - Tolyl) 4 - Hydroxybutyramide

m.pt. 87-88 C. (Found: C, 68.52; H, 7.96; N, 7.16. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%); n.m.r. ($CDCl_3$): δ 1.95 (t,2), 2.32 (s,3), 2.51 (t,2), 2.60 (s,1; D_2O exchange), 3.75 (t,2), 7.20 (m,4), 7.55 (s,1); i.r. (nujol) ν : 3335 (m), 3300 (w), 3190 (w), 3040 (w), 2930 (s), 2860 (s), 1665 (m), 1550 (m), 1610 (m), 1498 (m), 1450 (m), 1360 (m), 1080 (m), 900 (m), 790 (m), 745 (m), 705 (m) cm^{-1}.

N (p - Methoxyphenyl) 4 - Hydroxybutyramide

m.pt. 97.5-98.5°C. (Found C, 62.94; H, 7.11; N, 6.62. $C_{11}H_{15}NO_3$ requires C, 63.13; H, 7.27; N, 6.69%); n.m.r. ($CDCl_3$): δ 1.88 (t,2), 2.87 (s,1; D_2O exchange), 3.62 (t,2), 3.69 (s,3), 6.71 (d,2), 7.29 (d,2), 7.80 (s,1), i.r. (nujol) ν : 3310 (m), 3290 (w), 3200 (w), 3040 (w), 2940 (s), 2870 (s), 1650 (m), 1550 (m), 1602 (m), 1502 (m), 1460 (m), 1380 (m), 1040 (m), 920 (m), 835 (m), 705 (m) cm^{-1}.

N (m - Methoxyphenyl) 4 - Hydroxybutyramide

m.pt. 98-99°C. (Found C, 62.94; H, 7.11; N, 6.62.
$C_{11}H_{15}NO_3$ requires C, 63.13; H, 7.27; N, 6.69%);
n.m.r. ($CDCl_3$): δ 1.95 (t,2), 2.30 (s,1; D_2O exchange);
2.55 (t,2), 3.75 (t,2), 3.79 (s,3), 7.28 (m,5), 7.55 (s,1);
i.r. (nujol) ν : 3370 (m), 3250 (w), 3190 (w), 3056 (w), 2920 (s),
2850 (s), 1660 (m), 1545 (m), 1600 (m), 1480 (m), 1440 (m), 1370 (m),
1045 (m), 905 (m), 765 (m), 680 (m) cm^{-1}.

N - (p - Methoxyphenyl) 5 - Hydroxyvaleramide

m.pt. 97-98°C. (Found C, 64.54; H, 7.64; N, 6.26.
$C_{12}H_{16}NO_{13}$ requires C, 64.55; H, 7.67; N, 6.27%);
n.m.r. ($CDCl_3$): δ 1.68 (m,4), 1.99 (s,1; D_2O exchange);
2.37 (t,2), 3.65 (t,2), 3.77 (s,3), 6.80 (d,2), 7.32 (m,3);
i.r. (nujol) ν : 3400 (m), 3305 (w), 3190 (w), 3040 (w), 2920 (s),
2860 (s), 1650 (m), 1535 (m), 1600 (m), 1510 (m), 1460 (m), 1370 (m),
1060 (m), 820 (m), 710 (m), 690 (m) cm^{-1}.

For those compounds which contained another residue which was susceptible to hydrogenolysis under the conditions of method (a) the following procedure was used:-

(b) To a solution of the benzyloxy anilide ($5x10^{-4}$mol) in ethyl acetate (25 ml) approximately 10% by weight of 10% Platinum on charcoal catalyst was added. The solution was stirred and hydrogen, dried by passage over anhydrous calcium chloride, was bubbled through. The reaction was followed to completion by analytic t.l.c. (approximately 48 hours). The catalyst was

filtered off, the solvent removed under reduced pressure and the resultant white crystalline product recrystallised from ethyl acetate to constant melting point. Yields were generally in excess of 80% for procedure and the products showed the usual spectral characteristics. The following compounds were prepared by this method:-

N - (p - Bromophenyl) 4 - Hydroxybutyramide

m.pt. 116.5-117.5°C. (Found C, 46.54; H, 4.60; N, 5.32. $C_{10}H_{12}NO_{12}Br$. requires C, 46.70; H, 4.68; N, 5.43%); n.m.r. ($CDCl_3$): δ 1.60 (s,1; D_2O exchange); 1.94 (t,2), 2.50 (t,2), 3.72 (t,2), 7.40 (s,4), 7.42 (s,1); i.r. (nujol) ν : 3350 (m), 3300 (m), 3120 (m), 3040 (w), 2940 (s), 2870 (s), 1648 (m), 1590 (m), 1490 (m), 1440 (m), 1370 (m), 1060 (m), 925 (m), 850 (m), 825 (m), 750 (m), 700 (m) cm^{-1}.

N - (m - Bromophenyl) 4 - Hydroxybutyramide

m.pt. 116°C. (Found C, 46.51; H, 4.78; N, 5.21. $C_{10}H_{12}NO_2Br$ requires C, 46.52; H, 4.69; N, 5.43%); n.m.r. ($CDCl_3$): δ 2.09 (m,2), 2.62 (s,1; D_2O exchange); 2.69 (t,2), 3.83 (t,2), 7.56 (m,4), 7.99 (s,1); i.r. (nujol) ν : 3340 (m), 3290 (w), 3170 (w), 3080 (w), 2920 (s), 2850 (s), 1670 (m), 1540 (m), 1585 (m), 1470 (m), 1480 (m), 1370 (m), 1050 (m), 900 (m), 875 (m), 775 (m) cm^{-1}.

N - (p - Chlorophenyl) 4 - Hydroxybutyramide

m.pt. 96-98°C. (Found C, 56.6; H, 5.68; N, 6.62.
$C_{10}H_{12}NO_2Cl$ requires C, 56.20; H, 5.71; N, 6.56%);
n.m.r. ($CDCl_3$): δ 1.86 (s,1 D_2O exchange) 1.96 (t,2), 2.53 (t,2), 3.74 (t,2), 7.20 (d,2), 7.45 (d,2), 7.80 (s,1); i.r. (nujol) ν : 3290 (m), 3240 (w), 3180 (w), 3060 (w), 2920 (s), 2850 (s), 1663 (m), 1540 (m), 1370 (m), 1055 (m), 900 (m), 820 (m) cm^{-1}.

N - (m - Chlorophenyl) 4 - Hydroxybutyramide

m.pt. 96-97°C. (Found C, 56.11; H, 5.50; N, 6.61.
$C_{10}H_{12}NO_2Cl$ requires C, 56.19; H, 5.61; N, 6.56%);
n.m.r. ($CDCl_3$); δ 2.00 (q,2), 2.51 (t,2), 2.67 (s,2; D_2O exchange); 3.71 (t,2), 7.27 (m,4), 7.73 (s,1); i.r. (nujol) ν : 3345 (m), 3290 (w), 3245 (w), 3080 (w), 2920 (s), 2850 (s), 1675 (m), 1597 (m), 1590 (m), 1980 (m), 1460 (m), 1370 (m), 1052 (m), 900 (m), 875 (m), 780 (m) cm^{-1}.

N - (p - Bromophenyl) 5 - Hydroxyvaleramide

m.pt. 122-124°C. (Found C, 48.34; H, 5.13; N, 5.11.
$C_{11}H_{14}NO_2Br$ requires C, 48.53; H, 5.18; N, 5.14%);
n.m.r. ($CDCl_3$): δ 2.08 (q,2), 2.50 (t,2), 7.46 (s,4), 8.26 (s,1);
i.r. (nujol) ν : 3390 (m), 3300 (w), 3180 (w), 3030 (w), 2920 (s), 2850 (s), 1655 (m), 1590 (m), 1485 (m), 1455 (m), 1370 (m), 1048 (m), 875 (m), 720 (m) cm^{-1}.

N - (p - Chlorophenyl) 5 - Hydroxyvaleramide

m.pt. 116-117°C. (Found C, 57.95; H, 6.00; N, 6.28.
$C_{11}H_{14}NO_2Cl$ requires C, 58.01; H, 6.19; N, 6.15%);
n.m.r. ($CDCl_3$): δ 1.66 (m,5), 2.36 (t,2), 2.65 (t,2), 7.33 (m,5);
i.r. (nujol) ν : 3370 (m), 3290 (w), 3180 (w), 3040 (w), 2920 (s),
2850 (s), 1655 (m), 1535 (m), 1590 (m), 1490 (m), 1460 (m), 1370 (m),
1045 (m), 820 (m), 720 (m) cm^{-1}.

N - (m - Chlorophenyl) 5 - Hydroxyvaleramide

m.pt. 65-67°C. (Found C, 57.62; H, 6.18; N, 6.16.
$C_{11}H_{14}NO_2Cl$ requires C, 57.99; H, 6.19; N, 6.15%);
n.m.r. ($CDCl_3$): δ 1.70 (m,4), 2.36 (t,2), 2.85 (s,1; D_2O exchange);
3.61 (t,2), 7.23 (m,4), 7.68 (s,1); i.r. (nujol) ν : 3340 (m), 3300 (w),
3200 (w), 3040 (w), 2940 (s), 2860 (s), 1658 (m), 1540 (m), 1590 (m),
1480 (m), 1465 (m), 1380 (m), 1045 (m), 900 (m),810 (m),
700 (m) cm^{-1}.

Preparation of some 5 - Hydroxyvaleranilides from Valerolactone.

This method of direct formation of 5 hydroxyvaleranilides from valerolactone and an aniline was carried out as described by Knobler et al [99].

Redistilled δ-valerolactone (0.025 mol) and the redistilled aniline (0.125 mol) were heated under reflux for 2 hours. The excess aniline was removed by distillation at low temperature (approximately 70°C) under oil pump vacuum.

The residue was taken up in ethyl acetate and the solution was clarified with charcoal. The product was precipitated as a solid by addition of pet-ether and cooling to -10°C. in each case except that of N (m - Methoxyphenyl) 5-hydroxy valeranilide where initial purification by preparative t.l.c. was required (20% ethyl acetate/chloroform; band at R_f 0.16) before crystallization would occur. The solid was crystallized in each case from ethylacetate/benzene. The spectral characteristics of these compounds prepared by other routes were identical.

The following compounds were prepared by this method:-

N - Phenyl, 5 - Hydroxyvaleramide

m. pt. 66-67°C. (lit m.pt. 68-70°C. [99]). (Found C, 68.06; H, 7.82; N, 7.10. Calc. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%); n.m.r. ($CDCl_3$): 1.65 (m,4), 2.34 (t,2), 2.95 (s,1; D_2O exchange), 3.61 (t,2), 7.33 (m,5),8.18 (s,1); i.r. (nujol) : 3450 (sh,w), 3400 (w), 3280 (w), 3040 (w), 2930 (s), 2860 (s), 1670 (m), 1550 (m), 1605 (m), 1480 (m), 1460 (m), 1380 (m), 1075 (m), 890 (m), 820 (m), 725 (m) cm^{-1}.

N - (p - Tolyl) 5 - Hydroxyvaleramide

m.pt. 102-103°C. (lit. m.pt. 115°C.[99]) (Found C,69.44; H, 8.13; N, 6.55. Calc. for $C_{12}H_{16}NO_2$ C, 69.54; H, 8.27; N, 6.76%); n.m.r. ($CDCl_3$): δ 1.70 (m,4), 2.29 (s,3), 2.36 (t,2), 2.77 (s,1; D_2O exchange); 3.68 (t,2), 7.10 (d,2), 7.41 (d,2), 7.91 (s,1); i.r. (nujol) ν ; 3390 (sh,w), 3310 (w), 3200 (w), 3040 (w), 2930 (s), 2860 (s), 1656 (m), 1540 (m), 1590 (m), 1470 (m), 1460 (m), 1380 (m), 1060 (m), 905 (m), 820 (m), 875 (m) cm^{-1}.

N (m - Tolyl) 5 - Hydroxyvaleramide

m.pt. 69-70°C. (Found C, 69.44; H, 8.30; N, 6.53. $C_{12}H_{16}NO_2$ requires C, 69.54; H, 8.27; N, 6.76%); n.m.r. ($CDCl_3$); δ 1.66 (m,4), 2.29 (s,3), 2.36 (t,2), 2.91 (s,1; D_2O exchange); 3.65 (t,2), 7.20 (m,4), 8.08 (s,1); i.r. (nujol) ν : 3350 (m), 3250 (w), 3190 (w), 3050 (w), 2920 (s), 2860 (s), 1650 (m), 1555 (m), 1608 (m), 1490 (m), 1470 (m), 1380 (m), 1045 (m), 870 (m), 780 (m), 695 cm^{-1}.

N (m - Methoxyphenyl) 5 - Hydroxyvaleramide

m.pt. 65-66°C. (Found C, 64.56; H, 7.67; N, 6.27. $C_{12}H_{16}NO_3$ requires C, 64.27; H, 7.62; N, 6.56%); n.m.r. ($CDCl_3$); δ 1.71 (m,4), 2.40 (m,4; D_2O exchange gives m,3); 3.70 (t,2), 3.77 (s,3), 6.95 (m,4), 7.75 (s,1); i.r. (nujol) ν ; 3400 (m), 3295 (w), 3200 (w), 3020 (w), 2920 (s), 2855 (s), 1655 (m), 1535 (m), 1600 (m), 1485 (m), 1450 (m), 1370 (m), 1055 (m), 840 (m), 780 (m), 700 cm^{-1}.

Preparation of N - Nitrophenyl γ and δ Butyro - and Valero - Chloroamides

This series of nitroanilides were prepared by the standard method[103] from 4 - chlorobutyryl chloride and 5 - chlorovaleryl chloride.

The following were prepared by this method:-

N -(p - Nitrophenyl) 5 - Chlorovaleramide

m.pt. 109-110°C. (Found; C, 49.39; H, 4.65; N, 10.55. $C_{10}H_{11}N_2O_3Cl$ requires C, 49.28; H, 4.54; N, 11.54%); n.m.r. ($CDCl_3$) δ : 2.27 (q,2), 2.66 (t,2), 3.69 (t,2), 7.71 (d,2), 7.98 (s,1), 8.21 (d,2); i.r. (nujol) ν : 3480 (m), 3370 (w), 3050 (w), 2960 (s), 2880 (s), 1705 (m), 1565 (m), 1598 (m), 1505 (m), 1470 (m), 870 (m), 760 (m), 745 (m), 670 (m) cm^{-1}.

N - (p - Nitrophenyl) 5 - Chlorovaleramide

m.pt. 136°C. (Found C, 51.36; H, 5.06; N, 10.92. $C_{11}H_{13}N_2O_3Cl$ requires C, 51.46; H, 5.10; N, 10.91%); n.m.r. ($CDCl_3$) δ : 1.96 (m,4), 2.52 (t,2), 3.58 (t,2), 7.65 (d,2), 7.90 (s,1), 8.16 (d,2); i.r. (nujol) ν : 3300 (m), 3220 (w), 3040 (w), 2930 (s), 2870 (m), 1675 (m), 1553 (m), 1615 (m), 1595 (m), 1510 (m), 1460 (m), 1375 (m), 870 (m), 840 (m), 780 (m), 700 (m), 650 (m) cm^{-1}.

N - (m - Nitrophenyl) 4 - Chlorobutyramide

m.pt. 60°C. (Found: C, 48.98; H, 4.49; N, 11.10. $C_{10}H_{11}N_2O_3Cl$ requires C, 49.28; H, 4.54; N, 11.54%); n.m.r. ($CDCl_3$) δ : 2.25 (q,2), 2.62 (t,2), 3.70 (t,2), 7.56 (d,2), 7.85 (s,1), 8.00 (s,1), 8.35 (m,1); i.r. (nujol) ν : 3370 (m), 3300 (w), 2930 (s), 2860 (s), 1703 (m), 1575 (m), 1610 (m), 1595 (m), 1503 (m), 1475 (m), 1382 (m), 870 (m), 755 (m), 734 (m), 700 (m), 665 (m) cm^{-1}.

N - (m - Nitrophenyl) 5 - Chlorovaleramide

m.pt. 77-78°C. (Found: C, 52.01; H, 5.29; N, $C_{11}H_{13}N_2O_3Cl$ requires C, 51.46; H, 5.10; N, 10.91%); n.m.r. ($CDCl_3$) δ : 1.93 (m,4), 2.52 (t,2), 3.58 (t,2), 7.52 (d,2), 7.94 (m,2), 8.48 (m,2); i.r. (nujol) ν : 3280 (m), 3200 (w), 3040 (w), 2950 (s), 2880 (s), 1670 (m), 1550 (m), 1615 (m), 1535 (m), 1470 (m), 1380 (m), 835 (m), 815 (m), 745 (m) cm^{-1}.

Preparation of N - Nitrophenyl γ and δ Hydroxy Amides

N - nitrophenyl hydroxy amides were prepared, as described in the literature [99], from the corresponding N - nitrophenyl _ - chloroamide by alkaline hydrolysis of the alkyl halide residue in presence of the anilide.

The chloroanilide (1g) was taken up in a small amount of ethanol. This solution was then added to 150 mls of a refluxing mixture of 33% ethanol and sodium carbonate solution. After 2 hours, when analytical t.l.c. showed the desired product to be present (Rf 0.06, $CHCl_3$), the solution was cooled.

The ethanol was removed under reduced pressure and the aqueous solution was extracted with ether (3x150mls). The ethereal layer was dried with anhydrous $MgSO_4$ and the ether was evaporated under reduced pressure, leaving in all cases a yellowish crystalline solid. Preparative t.l.c. of this solid ($CHCl_3$) in which the lowest Rf band was removed gave in the order of 50mg, $2x10^{-4}$ mol, 5% of a yellowish solid in all cases. This solid was recrystallized from ethyl acetate and pet-ether (b.pt. 40-60°) to give off-white crystalline material.

This method was used in the synthesis of the following compounds:-

N - (m - Nitrophenyl) 4 - Hydroxybutyramide

m.pt. 125-126°C. (Found: C, 53.48; H, 5.27; N, 12.37. $C_{10}H_{12}N_2O_4$ requires C, 53.57; H, 5.39; N, 12.49%); n.m.r. (d^6DMSO) δ : 2.15 (q,2), 2.56 (t,2), 3.42 (t,2), 6.52 (s,1; D_2O exchange), 7.90 (m,4); i.r. (nujol) ν : 3450 (m), 3340 (w), 3290 (w), 3050 (w), 2920 (s), 2850 (s), 1675 (m), 1560 (m), 1605 (m), 1470 (m), 1460 (m), 1380 (m), 1060 (m), 900 (m), 810 (m), 750 (m) cm^{-1}.

N - (p - Nitrophenyl) 4 - Hydroxybutyramide.

m.pt. 112-114°C. (Found C, 53.35; H 5.33; N, 12.60. $C_{10}H_{12}N_2O_4$ requires C, 53.56; H, 5.39; N, 12.49%); n.m.r. (d^6DMSO) δ : 2.10 (q,2), 2.60 (t,2), 3.40 (t,2), 6.50 (s,1; D_2O exchange) i.r. (nujol) ν : 3360 (m), 3250 (w), 3195 (w), 3040 (w), 2920 (s), 2850 (s), 1680 (m), 1560 (m), 1590 (m), 1500 (m), 1460 (m), 1372 (m), 1050 (m), 900 (m), 850 (m), 750 cm^{-1}.

N - (p - Nitrophenyl) 5 - hydroxyvaleramide.

m.pt. 115-116°C. (Found: C, 55.28; H, 5.84; N, 11.97. $C_{11}H_{14}N_2O_4$ requires C, 55.46; H, 5.92; N, 11.76%); n.m.r. (d^6DMSO) δ : 1.62 (m,4), 2.46 (t,2), 3.47 (t,2), 6.48 (s,1; D_2O exchange) 7.91 (d,2), 8.27 (d,2); i.r. (nujol) ν : 3380 (m), 3260 (w), 3190 (w), 3040 (w), 2930 (s), 2850 (s), 1675 (m), 1555 (m), 1595 (m), 1460 (m), 1380 (m), 1040 (m), 900 (m), 840 (m), 770 (m) cm^{-1}.

N - (m - Nitrophenyl) 5 - Hydroxyvaleramide

m.pt. 87-88°C. (Found: C, 55.33; H, 5.95; N, 11.95. $C_{11}H_{14}N_2O_4$ requires C, 55.46; H, 5.92; N, 11.76%); n.m.r. (d^6DMSO) δ : 1.60 (m,4), 2.40 (t,2), 3.50 (t,2), 6.42 (t,1; D_2O exchange), 7.65(t,1), 7.98 (m,2), 8.75 (t,1); i.r. (nujol) ν : 3370 (m), 3300 (w), 3200 (w), 3040 (w), 2940 (s), 2870 (s), 1680 (m), 1535 (m), 1595 (m), 1490 (m), 1465 (m), 1380 (m), 1050 (m), 890 (m), 815 (m), 750 (m) cm^{-1}.

Preparation of N Aryl n - Butyramides

a) Preparation of n - Butyryl Chloride

Normal butyryl chloride was prepared by the standard method[103]. b.pt. 99-101°C. (lit b.pt. 100-101°C.).

b) Preparation of Some N Aryl n - Butyramides.

Some substituted n - butyranilides were prepared from n - butyryl chloride and the corresponding aniline by the standard method[103]. These compounds which were generally low melting solids were crystallized from ether/pet-ether (b.pt. 40-60°). In the case of meta methyl, meta bromo and meta nitro butyranilides no crystallization could be induced from solvents and hence these compounds were purified as oils by preparative t.l.c. (band at Rf. 0.31; $CHCl_3$). After this purification, the meta nitro isomer crystallized when left as an oil at -15°C.

Spectral data was in accord with expected values and was assigned as before.

The following compounds were prepared by this method:-

N - Phenyl - n - Butyramide.

m.pt. 94.5-95°C. (lit[103] m.pt. 95°C.) . (Found: C, 73.63; H, 8.09; N, 8.36. Calc. for $C_{10}H_{13}NO$ C, 73.59; H, 8.03; N, 8.58%); n.m.r. ($CDCl_3$) δ : 1.00 (t,3), 1.80 (m,2), 2.32 (t,2), 7.30 (m,5), 7.55 (s,1); i.r. (nujol) : 3280 (m), 3200 (m), 3030 (w), 2930 (s), 2860 (m), 1655 (m), 1545 (m), 1595 (m), 1500 (m), 1465 (m), 1380 (m), 905 (m), 865 (m), 855 (m), 700 (w) cm^{-1}.

N - (- m - Tolyl) - n - Butyramide.

An oil, Rf 0.31; $CHCl_3$. (Found: C, 74.22; H, 8.79; N, 7.26. Calc. for $C_{11}H_{14}NO$: C, 74.54; H, 8.53; N, 7.90%); n.m.r. ($CDCl_3$) δ : 0.96 (t,3), 1.72 (m,2), 2.30 (s,3), 2.33 (t,2), 7.11 (m,4), 7.45 (s,1); i.r. (nujol) ν : 3320 (m), 3270 (w), 3210 (w), 3060 (w), 2980 (s), 2870 (m), 1663 (m), 1558 (m), 1615 (m), 1598 (m), 1495 (m), 1460 (m), 1385 (m), 902 (m), 880 (m), 790 (m), 765 (m), 700 (m) cm^{-1}.

N - (m - Methoxyphenyl) n - Butyramide

m.pt. 33°C. (Found: C, 68.53; H, 7.97; N, 7.36. $C_{11}H_{14}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%); n.m.r. ($CDCl_3$) δ : 0.96 (t,3), 1.80 (m,2), 2.33 (t,2), 3.77 (s,3), 6.94 (m,4) 7.74 (s,1); i.r. (nujol) ν : 3320 (m), 3200 (m), 3160 (w), 3040 (w), 2960 (s), 2870 (m), 1660 (m), 1555 (m), 1620 (m), 1600 (m), 1485 (m), 1460 (m), 1380 (m), 970 (m), 905 (m), 880 (m), 780 (m), 735 (m), 700 (m) cm^{-1}.

N - (m - Bromophenyl) n - Butyramide.

An oil, Rf 0.31; $CHCl_3$. (Found: C,49.56; H, 5.20; N, 5.69. $C_{10}H_{12}NOBr$ requires C, 49.62; H, 5.00; N, 5.80%); n.m.r. ($CDCl_3$) δ : 0.96 (t,3), 1.75 (m,2), 2.33 (t,2), 7.40 (m,4), 7.92 (s,1); i.r. (nujol) ν : 3320 (m), 3200 (m), 3140 (w), 3090 (w), 2980 (s), 2890 (s), 1664 (m), 1545 (m), 1595 (m), 1480 (m), 1448 (m), 1385 (m), 915 (m), 880 (m), 785 (m), 760 (m), 690 (m) cm^{-1}.

N - (m - Nitrophenyl) n - Butyramide.

m.pt. 57-58°C. (lit m.pt. 59°C.). (Found: C, 58.11; H, 6.07; N, 13.44. Calc. for $C_{10}H_{12}N_2O_3$ C, 57.59; H, 5.81; N, 13.45%); n.m.r. ($CDCl_3$) δ : 1.00(t,3), 1.74 (m,2), 2.41 (t,2), 7.92 (m,4), 8.26 (s,1); i.r. (nujol) ν : 3320 (m), 3200 (w), 3150 (w), 3110 (w), 3050 (w), 2990 (s), 2890 (m), 1670 (m), 1540 (m), 1620 (m), 1600 (m), 1485 (m), 1355 (m), 900 (m), 830 (m), 745 (m), 685 (m) cm^{-1}.

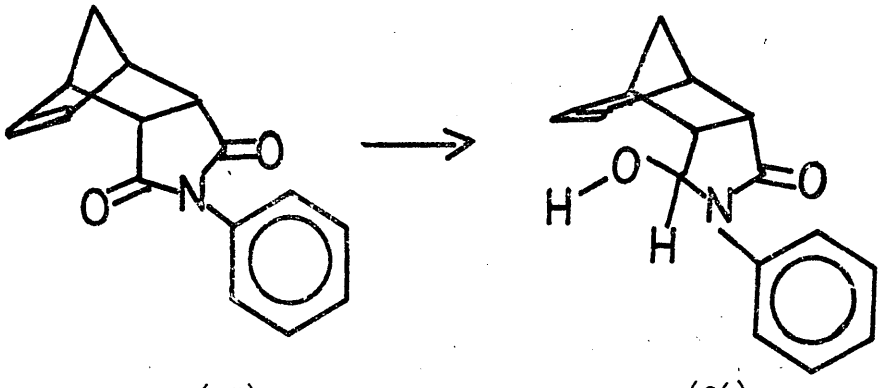
N - (p - Bromophenyl) n - Butyramide.

m.pt. 111-112°C. (lit m.pt. 114-115°C.[104]). (Found: C, 49.87; H, 5.05; N, 4.64. Calc. for $C_{10}H_{12}NOBr$. C, 49.62; H, 5.00; N, 5.80%); n.m.r. ($CDCl_3$) δ : 0.95 (t,3), 1.76 (m,2), 2.33 (t,2), 7.40 (s,4), 8.00 (s,1); i.r. (nujol) ν : 3300 (m), 3190 (w), 3125 (w), 3040 (w), 2950 (s), 2870 (m), 1657 (s), 1531 (m), 1494 (m), 1470 (m), 1380 (m), 935 (m), 925 (m), 835 (m), 825 (m), 750 (m) cm^{-1}.

Preparation of Bicyclic Hydroxy Anilides

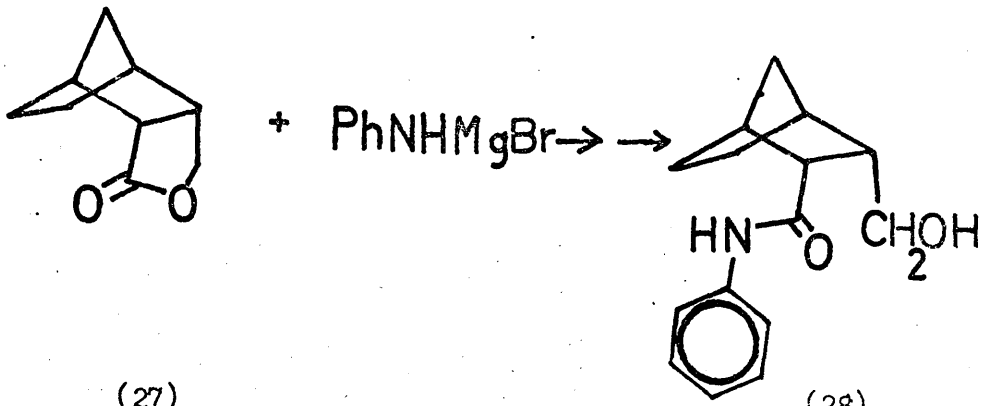
The preparation of this type of compound was attempted by several routes.

Reduction of the corresponding N - phenyl imide by sodium borohydride in methanol, by which method 4 - hydroxybutyranilide has been successfully produced from N - phenyl succinimide [101], led to the isolation of the imidine (26), with further reduction being unattainable under these conditions.



(25) (26)

A route involving a Diels - Alder reaction between cyclopentadiene and the dienophile, cis 4 - hydroxy crotonanilide was forestalled at the final stage by the successful preparation of the hydroxy anilide (28) from the corresponding lactone (27) by reaction with anilino magnesium bromide.



(27) (28)

I. Reduction of N - Phenyl, Endo, Cis, 2, 3, Imido, 5 - Norbornene

a) Preparation of the Imide

The imide (26) was produced by refluxing the corresponding endo norbornyl 2, 3 dicarboxylic acid anhydride (1.64g) with a slight molar excess of aniline (1.2 g.) overnight in glacial acetic acid (50ml).

This method was based upon that used by Horii et al[101] in the production of succinimide. The resultant oil was crystallized from ethyl acetate/pet-ether (b-pt. 60-80°) yielding the pure imide m.pt. 153°C. The i.r. and n.m.r. spectra were consistant with expected data.

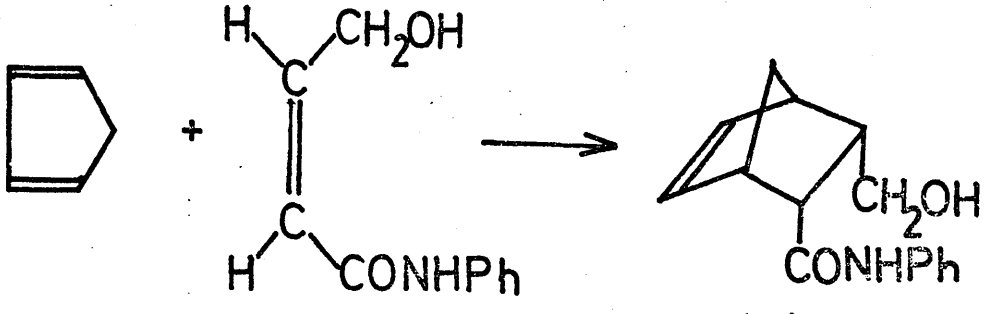
b) Reduction of the Imide.

This attempted reduction of the bicyclic imide to the corresponding bicyclic hydroxy anilide by the literature method produced a crystalline material which analytical t.l.c. showed to

consist of two compounds (Rfs 0.20 and 0.56 ; $CHCl_3$/ 20% ethyl acetate). The lower Rf compound was isolated by preperative t.l.c. . The resultant material was recrystallized from ether, m.pt. 144-145°C. . From i.r., n.m.r. and mass spectral evidence it was concluded that the compound isolated was the norbornyl endo, N - Phenyl 2,3 imidine. Parent ion : (m/e) 243 ; n.m.r. ($CDCl_3$) δ : 1.40 (m,6), 2.48 (m,3), 2.92 (m,1), 4.22 (d,1; D_2O exchange), 5.28 (d,1; goes to s,1 upon D_2O exchange), 7.40 (m,5), i.r. (nujol) ν : 3280 (m), 3050 (w), 2960 (s), 2875 (s), 1662 (m), 1612 (m), 1588 (m), 1502 (m), 1470 (m), 1385 (m), 1070 (m), 810 (m), 795 (m), 730 (m), 700 (m) cm^{-1}.

II. By a Diels - Alder Reaction

The proposed scheme involved finally a diene synthesis involving 1,2 cyclopentadiene and 4-hydroxy, cis crotonanilide as diene and dienophile respectively:



(29)

Preparation of the Dienophile.

4-hydroxy, but-2-ynoic acid was prepared from propargyl alcohol by the method of Jones[107].

Dry, redistilled ethyl bromide (100g, 0.92 mol) was added dropwise to a stirred mixture of oven-dried magnesium turnings (24g, 0.99 mol) and anhydrous ether (400 ml) in a 2 litre, 3-necked flask fitted with a reflux condenser, a dropping funnel and a mechanical stirrer.

When this addition was complete the reaction mixture was refluxed for 30 mins.

Propargyl alcohol (28g, 5×10^{-1} mol) in anhydrous ether (100 ml) was added dropwise, with vigorous stirring to this solution of ethyl magnesium bromide cooled to $0^{\circ}C$.

As this addition proceeds, the solid acetylenic Grignard reagent is precipitated and the reaction mixture becomes a thick slurry.

When the addition is complete the reaction mixture is allowed to come to room temperature. Carbon dioxide gas is then bubbled through the stirred slurry overnight.

The product salt is decomposed by acidification with ice-cold bench HCl. The resultant aqueous solution is saturated with NaCl and subjected to continuous ether extraction for 48 hours. The ether extracts are extracted with 5% $NaHCO_3$ solution. This solution is acidified with bench HCl and then extracted continuously with ether for 48 hours.

The ether extracts are dried over anhydrous $MgSO_4$ and the ether distilled off under reduced pressure to yield a tan cloured solid which was recrystallized from ethyl acetate to give 24.2g, 0.242mol, 48.5% of the fawn coloured acetylenic hydroxy acid m.pt. 120-121°C. n.m.r. (d^6DMSO) δ : 4.25 (s,2), 7.4 (b.s.,2; D_2O exchange); i.r. (nujol) : 3800-3100 (b,s)[H-bonded -O-H], 3400-2360 (b,s) [Intramolecular H-bonded -O-H], 2960 (m), 2890 (m), 2270 (m) and 2150 (m), [C≡Cstr.], 1710 (m) [C=O str.], 1035 (m)[C-O str.] cm^{-1}.

Preparation of the Anilide of 4 - Hydroxy 2 - Butynoic Acid

This acetylenic hydroxy anilide was prepared from 4 - hydroxy but-2-ynoic acid by the method of Belleau and Malek[98] using

EEDQ as condensing agent.

4 - hydroxy but-2-ynoic acid (2g, $2x10^{-2}$mol) is slurried in anhydrous ether (200ml). Aniline (1.90g, $2x10^{-2}$mol) and EEDQ (5g, $2x10^{-2}$mol) are added and the slurried solution of the reactants are stirred overnight. The hydroxy acid slowly dissolves in the solvent and the product is precipitated as a light coloured solid.

When the reaction is complete, ethyl acetate is added to dissolve the precipitated product and the mixed solvent organic layer is washed with bench HCl (2x100ml) to remove quinoline and excess aniline, with 10% $NaHCO_3$ solution (2x100ml) to remove unreacted acid, and finally with water (2x50ml).

The organic solvent layer is dried over anhydrous $MgSO_4$ and the solvents are distilled off under reduced pressure to yield (3.0g, $1.71x10^{-3}$mol, 87%) of the acetylenic hydroxy anilide.

This product is recrystallized from ethyl acetate to constant melting point.

m.pt. 143-144°C. (Found C,68.58; H,5.37; N,8.04. $C_{10}H_9NO_2$ requires C, 68.57; H,5.18; N,8.00%); n.m.r. (d^6DMSO) δ : 4.00 (d,2. D_2O exchange gives s,2), 5.51 (t,1; D_2O exchange), 7.33 (m,5), 10.70 (s,1; D_2O exchange); i.r. (nujol) ν : 3240 (w), 3180 (w), 3140 (w), 3050 (m), 2930 (s), 2860 (s), 2235 (w), 1635 (m), 1615 (m), 1605 (m), 1590 (m), 1562 (m), 1500 (m), 1435 (m), 1340 (m), 1070 (m), 902 (w), 890 (w), 802 (m), 755 (s), 735 (m), 690 (m) cm^{-1}.

4 - Hydroxy, Cis Crotonanilide.

This olefinic hydroxy anilide was produced by hydrogenation of the acetylenic hydroxy anilide over 5% Palladium on $BaSO_4$ catalyst poisoned with a measured amount of sulphur/quinoline poison.

The concentrated catalyst poison solution is produced by the standard method[108,113]. This concentrated solution is diluted 100 fold in ethyl acetate. The dilute solution of catalyst poison thus produced is added to the reaction mixture of substrate, catalyst and solvent immediately prior to exposure to the atmosphere of hydrogen (0.01ml of diluted poison solution per milligram of catalyst used). The ratio of catalyst to substrate used is approximately 1 : 3 (w/w).

The hydrogenation proceeds smoothly upon exposure of the stirred reaction mixture to the atmosphere of hydrogen. When the calculated amount of hydrogen has been absorbed the reaction is terminated, the catalyst filtered off and the solvent removed under reduced pressure leaving a fawn coloured solid which i.r. and n.m.r. spectra show to be the desired product. This solid is recrystallized from ethyl acetate. The yield of this reaction is quantitative.

m.pt. 150-151° C. (Found C, 67.69; H, 6.50; N, 7.84. $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 7.90%);

n.m.r.(d^6DMSO) δ : 4.58 (m,2; d,2 upon D_2O exchange), 4.93 (t,1; D_2O exchange), 6.16 (m,2), 7.36 (m,5), 10.04(s,1;

D_2O exchange); in a decoupling experiment, irradiation at 4.58ppm simplified the olefinic resonances to the following :- 6.01 (d,1; J = 12cps), 6.21 (d,1; J = 12cps);

i.r. (nujol) ν : 3400(m), 3300 (w), 3160 (w), 3040 (w), 2950 (s), 2880 (s), 1660 (m), 1555(m), 1638 (m), 1600 (m), 1497 (m), 1382 (m), 1040 (m), 812 (m), 788 (m), 765 (m), 704 (m) cm^{-1}.

III Preparation from the Corresponding Norbornyl Lactone

a) Endo Cis 2,3 Carbolactone Norbornane

This compound was prepared from norbornane 2,3 dicarboxylic acid anhydride by the method of Vaughn et al[109], as described in the following section.

b) Preparation of Endo, Cis 3 Hydroxymethyl, 2 - (N - Phenyl Carbonamide) Norbornane.

The hydroxy anilide (28) was prepared from the lactone (27) by reaction with anilino magnesium bromide based on the method described in the literature[114].

The anilino magnesium bromide was prepared by addition of aniline (0.65g, 1.79×10^{-2} mol) in anhydrous ether (10ml) to ethyl magnesium bromide (1.79×10^{-2} mol), prepared in the normal manner[103], in anhydrous ether (25mls). This milky suspension was refluxed for 15 minutes before dropwise addition to the lactone (1.36g, 8.84×10^{-3} mols) in anhydrous ether (15ml). The reaction was carried out under anhydrous conditions with stirring throughout. Stirring was continued for 60 minutes at ambient temperature and then at reflux temperature for 2 hours.

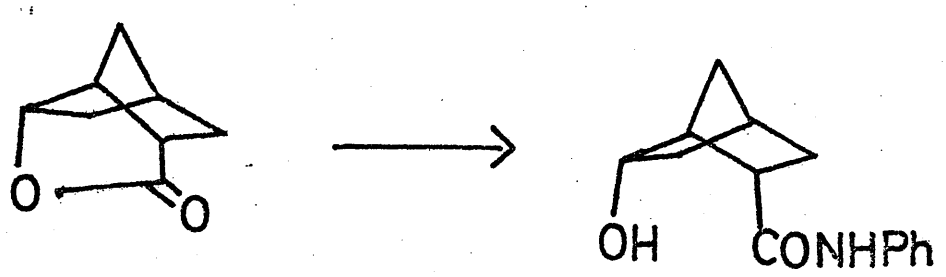
Water (20mls) was added and then sufficient normal HCl to decompose the salt formed (18mls). This mixture, in which the hydroxy anilide was precipitated, was filtered to give 75% of the theoretical yield of hydroxy anilide. The remainder was

obtained from the separated, dried (over anhydrous $MgSO_4$) ether layer. The product, a white crystalline solid was recrystallized from ethyl acetate to m.pt. 197-198°C. (Found: C,73.39; H,8.17; N,5.70. $C_{15}H_{19}NO_2$ requires C,73.44; H,7.81; N,5.71%); n.m.r. (d^6DMSO) δ : 1.51 (m,6), 1.66 (m,1), 2.33 (m,2), 2.90 (m,1), 3.61 (t,2), 4.21 (t,1; D_2O exchange), 7.32 (m,5),10.69 (s,1; D_2O exchange); i.r. (nujol) ν :3410 (m), 3260 (w), 3200 (w), 3150 (w), 3070 (w), 2960 (s), 2870 (s), 1667 (m), 1558 (m), 1600 (m), 1510 (m), 1470 (m), 1382 (m), 1024 (m), 800 (w), 766 (m), 752 (m), 700 (m) cm^{-1}.

In CCl_4 the amide I, amide II region had the following bands: 1686 (m), 1773(m), cm^{-1}. No band was observed between 1650 and 1450 cm^{-1}.

Preparation of Endo 2 - (N - Phenyl Carbonamide), Endo 6 - Hydroxy Norbornane

The hydroxy anilide (31) was prepared from the corresponding lactone (30) [115] by the method described above.



(30) (31)

Reaction of the lactone (30) (2.76g, $2x10^{-2}$mol) in anhydrous ether (15ml) with the anilino magnesium bromide ($4x10^{-2}$mol) in anhydrous ether (35ml) produced the hydroxy anilide (3.98g, 1.72 x 10^{-2}mol, 88 %), recrystallized from ethanol to m.pt. 151-152°C (Found C, 73.12; H, 7.55; N, 6.51 . $C_{15}H_{19}NO_2$ requires C, 72.70; H, 7.41; N, 6.06%); n.m.r. (d^6 DMSO) δ : 0.91 (m,1), 1.39(s,2), 1.80(m,3), 2.16(m,1), 2.74(m,2), 4.10(m,1), 4.42 (d,1; D_2O exchange) 7.30(m,5) 10.50(s,1; D_2O exchange). i.r.(nujol) ν : 3380(w) 3260 (m), 3100(m), 2940(s), 2875(s), 1660 (m), 1620(m), 1600(m), 1563(m), 1500(m), 1470(m), 1450(m), 1260(m), 1800(w), 770(m), 700(m).

In CCl_4 solution the following bands were observed in the amideI, amide II spectral region : 1728(w) 1680(m) cm^{-1}, no band was observed between 1650 and 1450 cm^{-1}.

Preparation of some Bicyclic γ - Lactones

A series of six bicyclic γ - lactones were prepared from the corresponding anhydride by reduction with sodium borohydride in isopropanol according to the method of Vaughn et al[109] .

Analar isopropanol (20mls) and powdered sodium borohydride (1.7×10^{-2}mol) were stirred at room temperature for 30 minutes. To this mixture a solution (or a stirred solution) of the bicyclic anhydride (1×10^{-2}mol) was added dropwise over 15 minutes with stirring. This mixture was stirred at room temperature for 36 hours whereupon the solvent was distilled off under reduced pressure yielding a white solid.

Concentrated hydrochloric acid (7.5ml) in crushed ice (25g) was added and the mixture was stirred for 60 minutes at room temperature over a steam bath for 30 minutes and again at room temperature for 3 hours. The mixture was extracted with ether (3x150ml). The ether extracts were washed with bicarbonate solution (5%, 2x50mls), with water (50mls) and were then dried over anhydrous magnesium sulphate. The ether was distilled off under reduced pressure generally yielding a clear oil which could be crystallized from ethyl acetate/pet-ether (b.p. 40-60°). In the case of the exo 2,3 γ - carbolactone $[2,2,1]$ heptane crystallization did not occur and preparative t.l.c. ($CHCl_3$) was used as the purification method. Preparative t.l.c. was used as

an additional purification method in the case of both the bicyclo-octane lactones since initial crystallization proved difficult. The infra red spectra of these compounds were simple with C=O stretch occurring in the 1750cm^{-1} region and C-O stretch in the 1380cm^{-1} region.

Endo 5 - norbornene 2,3 dicarboxylic acid anhydride and endo 2,3 dicarboxylic acid anhydride bicyclo 2,2,1 5 - octene were commercial samples. Exo 5 - norbornene 2,3 dicarboxylic acid anhydride was prepared from the endo anhydride by thermal isomerization by the literature method[116]. Selective crystallization from benzene and repeated recrystallizations from the same solvent produced the pure exo anhydride, m.pt. 142^{o}C (lit. m.pt. 142-144^{o}C [116]).

The saturated anhydrides were prepared by catalytic hydrogenation over supported Palladium catalysts[97] from the corresponding unsaturated compound.

The following compounds were prepared by this method:-

Endo 2,3 γ - Carbolactone Bicyclo [2,2,1] 5 - Heptene

m.pt. 130-131^{o}C (lit. m.pt. 130^{o}C).

(Found C,71.88; H,6.73. Calc. for $C_9H_{10}O_2$: C,71.98; H,6.71%).

n.m.r. ($CDCl_3$) δ : 1.56 (q,2), 3.23 (m,4), 3.81 (d,1), 4.30 (t,1), 6.32 (s,2); i.r. (nujol) ν : 3060 (w), 2940 (s), 2860 (s), 1750 (s), 1636 (w), 1465 (m), 1385 (m), 1050 (m) cm^{-1}.

Endo 2,3 γ - Carbolactone Bicyclo [2,2,1] Heptane

m.pt. 120-130°C. (sublimes)

(Found C,71.08; H,7.95. Calc. for $C_9H_{12}O_2$: C, 71.03; H, 7.95%); n.m.r. ($CDCl_3$) δ : 1.49 (s,6), 2.33 (m,1), 2.61 (m,1), 2.89 (m,2), 4.26 (d,2); i.r. (nujol) ν : 2930 (s), 2860 (m), 1755 (m), 1465 (m), 1383 (m), 1070 (m) cm^{-1}.

Exo 2,3 γ - Carbolactone Bicyclo [2,2,1] Hept - 5 - ene.

m.pt. 42°C. (Found C, 72.24; H, 7.00. $C_9H_{10}O_2$ requires C, 71.98; H, 6.71%); n.m.r. ($CDCl_3$) δ : 1.53 (s,2), 2.65 (s,2), 2.92 (m,1), 3.29 (m,1), 4.08 (d,2), 4.50 (t,1), 6.23 (m,2); i.r. (nujol) ν : 3060 (w), 2930 (m), 2860 (m), 1795 (m), 1630 (w), 1460 (m), 1387 (m), 1090 (m) cm^{-1}.

Exo 2,3 γ - Carbolactone Bicyclo [2,2,1] Heptane

An oil; purified by preparative t.l.c. (Rf 0.58; $CHCl_3$). (Found C, 71.11; H, 7.89. $C_9H_{12}O_2$ requires C, 71.03; H, 7.95%); n.m.r. ($CDCl_3$) δ : 1.45 (m,6), 2.18 (m,1), 2.49 (m,2), 2.66 (m,1); i.r. (nujol) ν : 2935 (m), 2860 (m), 1750 (m), 1465 (m), 1380 (m), 1060 (m) cm^{-1}.

Endo 2,3 γ - Carbolactone Bicyclo [2,2,2] Oct - 5 - ene

m.pt. 94-95°C. (Found C, 72.90; H, 7.11. $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37%); n.m.r. ($CDCl_3$) δ : 1.48 (q,4), 2.75 (m,3), 3.10 (m,1), 6.32 (m,2); i.r. (nujol) ν : 3050 (w), 2940 (s), 2870 (s), 1752 (m), 1670 (w), 1460 (m), 1378 (m), 1060 (m) cm^{-1}.

2,3 γ - Carbolactone Bicyclo [2,2,2] Octane

m.pt. 153-155°C. (sublimes 95°C.)

(Found C, 72.26; H, 8.77. Calc. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49%); n.m.r. ($CDCl_3$) δ : 1.62 (m,9), 2.06 (s,1), 2.67 (m,2), 4.36 (m,2); i.r. (nujol) ν : 2930 (s), 2865 (s), 1755 (m), 1465 (m), 1388 (m), 1065 (m) cm^{-1}.

Determination of the Hydrolysis Product(s) of Endo, Cis 3 Hydroxy-methyl, 2-(N-Phenyl Carbonamide) Norbornane in Aqueous Perchloric Acid (0.5M).

The bicyclic hydroxy anilide (20. mg) in absolute ethanol (5 ml) was added to aqueous perchloric acid solution (0.5 M, 500 ml) at 50°C and left for 20 hours (10 half-lives). This solution was cooled, extracted with 5x200 mls ether. The combined ether layers were washed with water (100 mls) dried over anhydrous $MgSO_4$ and evaporated off under reduced pressure. The ether was redistilled before use.

The product was further dried over P_2O_5 giving 11.25 mg of a dark brown oil (theoretical product of lactone : 12.72 mg). T.L.C. of this material showed that the main product was lactone (Rf 0.68). Other minor products at lower Rf values were observed. No carboxylic acid proton, olefinic or hydroxyl proton was observed in n.m.r. spectrum ($CDCl_3$). Infra-red spectrum of this material showed a carbonyl band typical of the expected lactone.

Determination of the Hydrolysis Product(s) of Endo 2-(N-Phenyl Carbonamide), Endo 6 Hydroxy Norbornane.

The bicyclic hydroxyanilide (20.0) mg in absolute ethanol (5 ml) was added to aqueous perchloric acid solution (0.5 M, 500 ml) at 50°C and left for 3 hours (>10 half lives). This solution was cooled extracted with 5x200 mls ether. The ether extracts were washed with water (100ml) dried over anhydrous $MgSO_4$ and the ether was removed under reduced pressure. The ether was redistilled before use.

The product, dried over P_2O_5 under oil pump vacuum was a dark oil and weighed 11.05 mg. (theoretical weight of a lactone product: 12.30 mg). TLC of this material showed that the major product was lactone (Rf o.64). TLC showed that other minor products of lower Rf had been formed.

No carboxylic olefinic or hydroxyl proton was observed in n.m.r. spectrum of this material in $CDCl_3$. Infra-red spectrum showed carbonyl band typical of the expected lactone.

Kinetic Experimental

Solutions

Perchloric acid solutions were prepared by dilution of Analar 72% $HClO_4$. This dilution was carried out approximately in the first instance. Upon temperature equilibration, the diluted solution was titrated against standard sodium hydroxide. The volume of water required to bring the molarity of the approximately diluted acid to the required level was then added. Distilled water was used in the preparation of all acid solutions.

Stock solutions of substrates were made up in Analar 'Absolute' ethanol and was either used freshly prepared or stored at deep freeze temperatures which greatly extended the useful life of the solution.

Spectrophotometric Rate Determinations.

The reported rate constants were determined on a Cary Model 14 spectrophotometer. This spectrophotometer was fitted with a five-cell holder and thermostatting arrangements. Constant temperature was achieved by using a Lauda electronically thermostatted water bath. Circulation of the water from this bath through the central spindle of the cell holder, through channels in the cell compartment and finally around the reference cell holder enabled temperatures constant to $\pm 0.03^{\circ}C$ to be achieved. The temperature drop between the water bath and the cell holder was $1\text{-}2^{\circ}$ over the range $45\text{-}65^{\circ}C$.

The temperature was measured in the cell by a thermometer calibrated by a N.P.L. calibrated thermometer, the cell compartment being temporarily sealed by a close fitting 'perspex' lid.

Stoppered, 10 mm., Spectrosil, quartz u.v. cells were used. Generally 3 mls of acid was added and approximately 30 minutes allowed for temperature equilibrium. 10, 15 or 20 microlitres of the stock 1.5×10^{-2} molar solution of the substrate in ethanol was injected into the acid solution depending upon the molar extinction coefficient of the substrate. All reported rate constants for aqueous acid solutions therefore refer to solutions approximately 0.5% in ethanol.

After addition of the substrate stock solution to the u.v.

cell, the contents of the cell were stirred with a 'polythene' stirring rod. Absorbance changes were then monitored. The pen recorder slide wire on the spectrophotometer drove a highly accurate linear potentiometer across the ends of which was applied a constant voltage from a Mallory 1.35 volt battery, type RM-42 R. The output from this potential divider was fed to a Solartron Compact Data Logger which digitized the absorbance reading. The digitized reading was then transferred onto 5-channel paper tape, via a Creed punch, at convenient time intervals. Usually 100-700 values were taken.

The first order rate constants were determined using a generalized least-squares program, written by Dr. B. Capon, based on the procedure of Wentworth[117] and Deming[118]. Evaluation was performed on an English Electron KDF9 computer. The slopes and intercepts of all linear activation parameter, rate-acidity correlation plots and amide pK_{AH^+} determinations were also determined by a generalized least-squares procedure on the above device and on a Digico Micro 16P computer.

Statistical errors arising from the computations of rate constants, slopes of lines and other parameters where recorded refer to standard deviations unless otherwise stated.

Determination of Dissociation Constants

To determine the dissociation constants of the conjugate acids of the series of anilides under study, their u.v. spectra in 1M and 9M perchloric acid were first recorded on a Unicam SP800 spectrophotometer. In general the spectra of these anilides exhibited a band in the range 240-250 nm.

It was noted that in the large majority of cases the only change which took place on going from lower to higher acid concentration was a decrease in the absorbance of the maximum.

Only in the cases of p-Methyl, p-Methoxy and p-Nitrosubstituted anilides were shifts of the maxima observed. The p-Methyl anilides exhibited a slight blue shift (approximately 2 nm), the p-Methoxy anilide a red shift (approximately 10 nm). The p-Nitroanilides exhibited two maxima in 1.0m perchloric acid at 315 nm and 222.0 nm The most intense of these maxima at higher wavelengh exhibited a very large blue shift over this concentration range with a corresponding decrease in molar extinction coefficient, whilst the band at lower wavelength exhibited a small blue shift (2.0nm), the molar extinction coefficient decreasing greatly.

Thus, in general, the molar extinction coefficient at the single wavelength of the maximum was observed for each anilide for a series of acid concentrations. From the plot of ϵ_{max} against H_o[119] and H_A[120] for this single wavelength the extinction coefficient of the non-protonated and fully protonated amides

were estimated according to the criteria of Yates et al[55]. From the values of the molar extinction coefficient ϵ_B, for the non-protonated species, ϵ_{BH^+} for the fully protonated species and ϵ for the amide/protonated amide mixture at intermediate acid concentrations, the ionization ratio I ($[BH^+] / [B]$) was determined by the equation

$$I = \frac{\epsilon_B - \epsilon}{\epsilon - \epsilon_{BH^+}} \qquad (43)$$

The operation to determine the individual absorbance values for each anilide at different acid concentrations involved a rapid injection - stirring - absorbance reading sequence which was complete within a range of 5 to 10 seconds. These operations were carried out at 50.0° using the same equipment described in the previous section. Generally, each absorbance value used was the mean of two or three readings. From these readings ϵ values were derived . However, for some more reactive compounds a graphical method of correction was required. The wavelengths at which this data was observed are listed as λ_{max} in tables 3 to 24 for each anilide; derived values of ϵ , ϵ_{BH^+}, ϵ_B, I and log I are also listed in these tables.

The logarithms of the ionization ratios thus determined were plotted against H_o and H_A values for perchloric acid solutions according to equations (44) and (45).

$$\log I = M\,(pK - H_o) \qquad (44)$$

$$\log I = d + cH_A \qquad (45)$$

Results from equation (44) are listed in table(25). M is a measure of the protonation behaviour of the amide relative to primary aromatic amines used in the determination of H_o and is listed as the slope of the plot. The value pK is the H_o value at 50% protonation of the amide substrate.

Results from equation (45) are listed in table (26). The slopes of the plot log I against H_A in general lie fairly close to unity. The value -d/c is the H_A value at 50% protonation and is taken to represent the thermodynamic pK_{SH}^+ values of the amides. The derived values of log I were also used in equation (46) in order to estimate pK_{SH}^+ values according to the method of Bunnett and Olsen[56].

$$\log I + H_o = \phi_e\,(H_o + \log [H^+]) + pK_{SH}^+ \qquad (46)$$

Results of these plots are listed in table (26A).

TABLES OF RESULTS

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TABLE 1 : Classification of the Function of Water in the Rate Determining Step of Reactions in Moderately Concentrated Solutions of Mineral Acid According to Bunnett's Hydration Parameter and L.F.E.R. Treatments.

Function of Water	ω	ω^*	ϕ
Is not involved	-2.5 to 0.0		0.0
Acts as nucleophile	1.2 to 3.3	-2	0.22 to 0.56
Acts as proton transfer agent	3.3	-2	0.58

Some typical values [57] of these parameters for amides are listed below:

	ω	ϕ
Propionamide ($HCl, 40^o$)	2.69	0.57
Benzamide ($HCl, 25^o$)	3.19	0.60
($HClO_4 95^o$)	1.97	0.59
pNO_2Benzamide ($H_2CO_4, 25^o$)	1.79	0.44

TABLE 2 : Concentration, Acidity Function, Water Activity and Related Parameters for Aqueous Perchloric Acid Solutions

Acid Molarity	$-H_o$ [119]	$-(H_o+\log H^+)$	$-H_A$ [120]	$-\log a_w$ [121]
0.01	-0.18		-0.43	
0.10	-0.13		-0.37	
0.5	0.06		-0.18	0.008
1.0	0.32	0.32	0.03	0.018
2.0	0.82	0.519	0.45	0.043
3.0	1.32	0.843	0.76	0.081
4.0	1.80	1.198	1.08	0.135
5.0	2.33	1.531	1.42	0.215
6.0	2.89	2.112	1.75	0.330
7.5	3.75	2.875	2.30	0.602
9.0	5.14	4.186	3.00	0.983
10.5	6.65	5.629	3.71	

TABLE 3 : The Degree of Protonation of Butyranilide in Perchloric Acid Solutions

Acid molarity	$10^{-1}\epsilon$	I	logI
0.001	1020		
0.01	982	0.0227	-1.644
0.1	1030		
1.0	976	0.0465	-1.3325
2.0	970	0.0764	-1.1175
3.0	906	0.427	-0.3696
4.0	882	0.636	-0.2965
5.0	835	1.278	0.1096
6.0	778	3.425	0.5346
7.5	752	6.04	0.7810
9.0	723	44.00	1.6435
10.5	712		

λ_{max} 240.5nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of 9900 and 7150 respectively.

Linear least squares treatments yield :-

1) Slope -0.612 ± 0.032, intercept -1.412 ± 0.098 and

2) Slope -0.9998 ± 0.027, intercept -1.358 ± 0.064

for plots of log I versus H_o and H_A respectively. Derived values of H_o values at 50% protonation and of pK_{AH^+} are -2.31 ± 0.12 and 1.359 ± 0.081

TABLE 4 : The Degree of Protonation of N - Phenyl 4-Hydroxy-butyramide in Perchloric Acid Solutions.

Acid molarity	$10^{-1} \times \epsilon$	I	logI
0.01	1064		
0.1			
0.5	1027	0.074	-1.1308
1.0	1012	0.1417	-0.8488
2.0	964	0.408	-0.3898
3.0	945	0.551	-0.2590
4.0	878	1.417	0.1512
5.0	842	2.452	0.3892
6.0	810	4.590	0.6670
7.5	778	13.50	1.130
9.0	768	28.00	1.4473
10.5	755		

λ_{max} 240.5 nm.

Plots of ϵ against H_o and H_A yielded common values of ϵ_B and ϵ_{BH^+} of 10,500 and 7,600 respectively.

Linear least squares treatments yielded :-

1) Slope -0.512 $\pm$0.037, intercept -0.953 $\pm$0.095

2) Slope -0.822 $\pm$0.037, intercept -0.841 $\pm$0.058

for plots of log I versus H_o and H_A respectively. Derived H_o and H_A values at 50% protonation are displayed in tables 25 and 26.

TABLE 5 : The Degree of Protonation of N - (p-Tolyl) 4-Hydroxy-butyramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	logI
0.01	1185		
0.1			
0.5	1146	0.0574	-1.2413
1.0	1119	0.1546	-0.8110
2.0	1088	0.282	-0.5500
3.0	1049	0.498	-0.3030
4.0	989	1.012	0.0053
5.0	935	1.917	0.2822
6.0	897	3.228	0.5090
7.5	860	6.776	0.8310
9.0	830	33.5	1.5248
10.5	790		

λ_{max} 243.0 nm

Plots of ϵ against H_0 and H_A yields common values of ϵ_B and ϵ_{BH^+} of 11,650 and 8150 respectively.

Linear least squares treatments yield

1) Slope -0.512 $\pm$0.026, intercept -1.020 $\pm$0.068

2) Slope -0.816 $\pm$0.030, intercept -0.934 $\pm$0.046

for plots of log I versus H_0 and H_A respectively. Derived H_0 and H_A values at 50% protonation are listed in tables 25 and 26.

TABLE 6 : The Degree of Protonation of N - (m-Tolyl) 4-Hydroxy-butyramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	logI
1.0	1102	0.0514	-1.2890
2.0	1036	0.269	-0.5702
3.0	999	0.428	-0.3686
4.0	936	0.830	-0.0809
5.0	874	1.53	0.1847
6.0	816	2.96	0.4713
7.5	746	11.05	1.0435
9.0	719	57.57	1.7602
10.5	697		

λ_{max} 242.0 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of of 1120x10 and 710 x10 respectively.

Linear least squares treatments yield

1) Slope -0.594 ± 0.032 , intercept -1.220 ± 0.088

2) Slope -0.974 ± 0.037 , intercept -1.177 ± 0.060

for plots of log I versus H_o and H_A respectively. Derived H_o and H_A values at 50% protonation are listed in tables 25 and 26.

TABLE 7 : The Degree of Protonation of N - (p-Methoxyphenyl) 4-Hydroxyvaleramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	1276	0.0328	-1.4841
0.10	1310		
0.5	1283	0.0162	-1.7905
1.0	1260	0.0732	-1.1355
2.0	1234	0.146	-0.8356
3.0	1165	0.397	-0.4012
4.0	1063	1.065	0.0274
5.0	1030	1.445	0.1599
6.0	937	4.055	0.608
7.5	875	16.6	1.2201
9.0	855	87.0	1.9395
10.5	811		

λ_{max} 246.0 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of 12,900 and 850 respectively.

Linear least squares treatments yield :-

1) Slope -0.694 ± 0.041, intercept -1.444 ± 0.108

2) Slope -1.112 ± 0.045, intercept -1.340 ± 0.047

for plots of log I versus H_o and H_A respectively. Derived H_o and H_A values at 50% protonation are listed in tables 25 and 26.

TABLE 8 : The Degree of Protonation of N - (m-Methoxyphenyl) 4-Hydroxybutyramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	986	0.0265	-1.5768
0.1	976	0.114	-1.9431
0.5	981	0.109	-0.9626
1.0	950	0.293	-0.5331
2.0	906	0.342	-0.4660
3.0	896	0.758	-0.1203
4.0	832	2.02	0.3054
5.0	754	3.80	0.5798
6.0	704	9.76	0.9894
7.5	663	87.75	1.9432
9.0	634	87.75	1.9432
10.5	634		

λ_{max} 244.0 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of 9850 and 6300 respectively.

Linear least squares treatments yield

1) Slope -0.570 ± 0.052 , intercept -1.278 ± 0.0

2) Slope -0.982 ± 0.041 , intercept -1.122 ± 0.0

for plots of log I versus H_o and H_A respectively. Derived H_o and H_A values for 50% protonation are displayed in tables 25 and 26.

TABLE 9 : The Degree of Protonation of N - (p-Chlorophenyl) 4-Hydroxybutyramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	1440		
0.5	1419	0.02757	-1.5600
1.0	1425	0.01235	-1.9080
2.0	1408	0.05665	-1.2468
3.0	1340	0.281	-0.5515
4.0	1262	0.695	-0.1580
5.0	1217	1.081	0.0340
6.0	1153	2.085	0.3192
7.5	1078	6.065	0.7830
9.0	1030	40.00	1.6010
10.5	1000		

λ_{max} 247.0 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of 14.300 and 10,200 respectively.

Linear least squares treatments yield:-

1) Slope -0.670 $\pm$0.053, intercept -1.671 $\pm$0.135

2) Slope -1.069 $\pm$0.073, intercept -1.559 $\pm$0.112

for plots of log I versus H_o and H_A respectively. Derived values of H_o and H_A at 50% protonation are displayed in tables 25 and 26.

TABLE 10 : The Degree of Protonation of N-(m-Chlorophenyl) 4-Hydroxybutyramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	1143	0.021	-1.678
0.5	1141		
1.0	1138	0.0272	-1.5655
2.0	1103	0.0366	-1.4367
3.0	1090	0.1605	-0.7945
4.0	1061	0.2141	-0.6690
5.0	976	0.354	-0.4510
6.0	942	1.049	0.0208
7.5	845	1.576	0.1972
9.0	822	8.72	0.9402
10.5	807	27.32	1.4361

λ_{max} 242.5 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of 11,500 and 8100 respectively.

Linear least squares treatments yield :-

1) Slope -0.607 ± 0.027, intercept -1.507 ± 0.066

2) Slope -0.942 ± 0.030, intercept -1.359 ± 0.044

for plots of log I versus H_o and H_A respectively. Derived values of H_o and H_A at 50% protonation are displayed in tables 25 and 26.

TABLE 11 : The Degree of Protonation of N - (p - Bromophenyl) 4-Hydroxybutyramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	1657	0.0068	-2.1675
0.5	1656	0.0091	-2.0200
1.0	1680		
2.0	1615	0.1125	-0.9515
3.0	1553	0.317	-0.5015
4.0	1485	0.648	-0.1888
5.0	1405	1.340	0.1270
6.0	1368	1.910	0.2810
7.5	1296	4.495	0.6522
9.0	1236	20.160	1.3200
10.5	1209		

λ_{max} 250.0 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of 16,600 and 12,150 respectively.

Linear least squares treatments yield :-

1) Slope -1.025 $\pm$0.075, intercept -1.541 $\pm$0.116

2) Slope -0.650 $\pm$0.067, intercept, -1.679 $\pm$0.173

for plots of log I versus H_o and H_A respectively. Derived values of H_o and H_A at 50% protonation are displayed in tables 25 and 26.

TABLE 12 : The Degree of Protonation of N-(m-Bromophenyl) 4-Hydroxybutyramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	1384		
0.5	1356	0.0354	-1.452
1.0	1356	0.0354	-1.452
2.0	1300	0.2060	-0.686
3.0	1274	0.3057	-0.5149
4.0	1226	0.5410	-0.2665
5.0	1148	1.181	0.0722
6.0	1098	1.971	0.2948
7.5	1015	6.460	0.8102
9.0	974	28.29	1.4520
10.5	953		

λ_{max} 245.0nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of 13700 and 9600 respectively.

Linear least squares treatments yield :-

1) Slope -0.575 ± 0.033, intercept -1.371 ± 0.085

2) Slope -0.919 ± 0.036, intercept -1.277 ± 0.056

for plots of log I versus H_o and H_A respectively. Derived values of H_o and H_A at 50% protonation are displayed in tables 25 and 26.

TABLE 13 : The Degree of Protonation of N - (p-Nitrophenyl) 4-Hydroxybutyramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	990	0.0211	-1.6755
0.5	1011		
1.0	998	0.007	-2.158
2.0	986	0.051	-1.2945
3.0	980	0.074	-1.1307
4.0	955	0.184	-0.7352
5.0	945	0.234	-0.6310
6.0	909	0.457	-0.3400
7.5	837	1.284	0.1085
9.0	786	2.815	0.4490
10.5	729	14.26	1.1540

λ_{max} 222.0

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of 10000 and 7100 respectively.

Linear least squares treatments yield:-

1) Slope -0.451 $\pm$0.036, intercept -1.746 $\pm$0.117

2) Slope -0.750 $\pm$0.056, intercept -1.681 $\pm$0.107

for plots of log I versus H_o and H_A respectively. Derived H_o and H_A values at 50% protonation are listed in tables 25 and 26.

TABLE 14 : The Degree of Protonation of N - (m-Nitrophenyl) 4-Hydroxybutyramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	2095	0.008	- 2.101
0.5	2091	0.0155	-1.810
1.0	2081	0.0245	-1.611
2.0	2008	0.0603	-1.220
3.0	1995	0.2181	-0.661
4.0	2011	0.1741	-0.759
5.0	1874	0.600	-0.222
6.0	1723	1.663	0.221
7.5	1604	4.846	0.685
9.0	1522	26.390	1.421
10.5	1494		

λ_{max} 242.0 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of 2100 and 1500 respectively.

Linear least squares treatments yield:-

1) Slope 0.656 ± 0.029, intercept -1.803 ± 0.070

2) Slope 1.019 ± 0.033, intercept 1.640 ± 0.049

for plots of log I versus H_o and H_A respectively. Derived H_o and H_A values for 50% protonation are displayed in tables 25 and 26.

TABLE 15 : The Degree of Protonation of 5-Hydroxyvaleranilide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.001	1124	0.048	1.3188
0.01	1130	0.0296	1.5287
0.5	1138	0.0058	2.2403
1.0	1135	0.145	1.8386
2.0	1063	0.282	0.5498
3.0	1015	0.533	0.2733
4.0	972	0.924	0.0343
5.0	927	1.554	0.1914
6.0	886	2.67	0.4265
7.5	830	7.74	0.8887
9.0	795	69.0	1.8388
10.5	787		

λ_{max} 224.0 nm.

Estimated values for ϵ_B and ϵ_{BH^+} are 11,400 and 7900 respectively.

Linear least squares treatments yield :-

1) Slope -0.634 ± 0.056, intercept -1.365 ± 0.138

2) Slope -0.976 ± 0.084, intercept 1.201 ± 0.135 for

plots of log I versus H_o and H_A respectively. Derived pK_{AH^+} values are displayed in tables 25 and 26.

TABLE 16 : The Degree of Protonation of N-(p-Tolyl) 5-Hydroxyvaleranilide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.001	1276	0.0098	-2.007
0.01	1281		
0.5	1265	0.038	-1.4202
1.0	1264	0.041	-1.3915
2.0	1261	0.048	-1.3114
3.0	1178	0.332	-0.4789
4.0	1121	0.634	-0.1979
5.0	1050	1.280	0.1072
6.0	998	2.20	0.3424
7.5	930	5.84	0.7664
9.0	884	28.30	1.4518
10.5	866		

λ_{max} 244.0 nm

Estimated values of ϵ_B and ϵ_{BH^+} are 12,800 and 8,700 respectively.

Linear least squares treatments yield:-

1) Slope -0.603 $\pm$0.054, intercept -1.481 $\pm$0.117

2) Slope -0.964 $\pm$0.066, intercept -1.388 $\pm$0.103

for plots of log I versus H_o and H_A respectively. Derived values of pK_{AH^+} are displayed in tables 25 and 26.

TABLE 17 : The Degree of Protonation of N - (m-Tolyl) 5-Hydroxy-valeramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
1.0	1092	0.023	-1.4383
2.0	1022	0.195	-0.7100
3.0	977	0.343	-0.4647
4.0	912	0.634	-0.1979
5.0	824	1.060	0.0253
6.0	749	2.58	0.4116
7.5	672	7.16	0.8549
9.0	621	48.0	1.6812
10.5			

λ_{max} 242.0 nm

Estimated values of ϵ_B and ϵ_{BH^+} are 11,000 and 6,100 respectively.

Linear least squares treatments yield:-

1) Slope -0.601 $\pm$0.033, intercept 1.359 $\pm$0.091

2) Slope -0.984 $\pm$0.041, intercept 1.314 $\pm$0.067 for plots of log I versus H_o and H_A respectively. Derived H_o and H_A values at 50% ionization are displayed in tables 25 and 26.

TABLE 18 : The Degree of Protonation of N-(p-Methoxyphenyl) 5-Hydroxyvaleramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	1165	0.0345	-1.4622
0.1	1185		
0.5	1161	0.0396	-1.4023
1.0	1154	0.0613	-1.2125
2.0	1112	0.178	-0.7496
3.0	1068	0.332	-0.4789
4.0	994	0.705	-0.1518
5.0	908	1.530	0.1847
6.0	831	3.450	0.5378
7.5	755	17.00	1.2304
9.0	733	149.0	2.1732
10.5	682		

λ_{max} 246.0 nm

Plots of ϵ against H_o and H_A yield common estimates of ϵ_B and ϵ_{BH^+} of 1180 and 7300 respectively.

Linear least squares treatments yield :-

1) Slope -0.690 ± 0.009, intercept -1.395 ± 0.024

2) Slope -1.065 ± 0.038, intercept 1.224 ± 0.056

for plots of log I against H_o and H_A respectively. Derived values of H_o and H_A at 50% protonation are listed in tables 25 and26.

TABLE 19 : The Degree of Protonation of N-(m-Methoxyphenyl) 5-Hydroxyvaleramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	933		
0.1	926	0.012	-1.9245
0.5	918	0.037	-1.4365
1.0	909	0.072	-1.1421
2.0	861	0.255	-0.5935
3.0	831	0.410	-0.3872
4.0	776	0.840	-0.0757
5.0	715	1.720	0.2355
6.0	645	5.180	0.7143
7.5	601	29.90	1.4757
9.0	574		
10.5	574		

λ_{max} 244.0 nm

Plots of ϵ against H_o and H_A yielded common values of ϵ_B and ϵ_{BH^+} of 9300 and 5900 respectively.

Linear least squares treatments yielded :-

1) Slope -0.743 $\pm$0.030, intercept -1.388 $\pm$0.062

2) Slope -1.119 $\pm$0.045, intercept $\pm$1.224 -0.056 for plots of log I versus H_o and H_A respectively. Derived H_o and H_A values at 50% protonation are displayed in tables 25 and 26.

Table 20 : The Degree of Protonation of N-(p-Chlorophenyl) 5-Hydroxyvaleramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	1464		
0.1	1440	0.023	-1.6440
0.5	1398	0.131	-0.8827
1.0	1417	0.079	-1.1018
2.0	1334	0.348	-0.4584
3.0	1288	0.563	-0.2495
4.0	1215	1.091	0.0378
5.0	1130	2.460	0.3909
6.0	1055	7.190	0.8567
7.5	1020	21.50	1.3324
9.0	996		
10.5	976		

λ_{max} 246.0 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} for aqueous Perchloric Acid of 145.00 and 10000.

Linear least squares treatments yield :-

1) Slope -0.648 $\pm$0.037, intercept -1.085 $\pm$0.075

2) Slope -0.972 $\pm$0.062, intercept 0.941 $\pm$0.078

for plots of log I versus H_o and H_A respectively. Derived H_o and H_A values for 50% protonation are listed in tables 25 and 26.

TABLE 24 : The Degree of Protonation of N-(m-Chlorophenyl) 5-Hydroxyvaleramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	1170		
0.1	1141	0.048	-1.3188
0.5	1128	0.084	-1.0780
1.0	1111	0.1334	-0.8730
2.0	1062	0.3091	-0.5102
3.0	985	0.729	-0.1375
4.0	948	1.045	0.019
5.0	903	1.626	0.211
6.0	893	1.985	0.298
7.5	803	5.95	0.774
9.0	750	82.00	1.914
10.5	745		

λ_{max} 245.0 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} for aqueous Perchloric Acid solutions of 11600 and 745 respectively.

Linear least squares treatments yield :-

1) Slope 0.551 $\pm$0.032, intercept 1.079 $\pm$0.078

2) Slope 0.860 $\pm$0.052, intercept 0.953 $\pm$0.076

for plots of log I against H_o and H_A respectively. Derived H_o and H_A values for 50% protonation are listed in tables 25 and 26.

TABLE 22 : The Degree of Protonation of N-(p-Bromophenyl) 5-Hydroxyvaleramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1}\epsilon$	I	log I
0.1	1255		
1.0	1225	0.0101	-1.996
2.0	1224	0.0142	-1.8476
3.0	1175	0.1209	-0.9175
4.0	1135	0.2348	-0.629
5.0	1050	0.5635	-0.250
6.0	990	0.925	-0.035
7.5	790	7.33	0.865
9.0	737	70.45	1.8475
10.5	705		

λ_{max} 250.0 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of 12300 and 7300.

Linear least squares treatments yield:-

1) Slope -0.805 $\pm$0.043, intercept 2.220 $\pm$0.117

2) Slope -1.316 $\pm$0.066, intercept 2.155 $\pm$0.106

for plots og log I against H_o and H_A respectively. Derived H_o and H_A values for 50% protonation are listed in tables 25 and 26.

TABLE 23 : The Degree of Protonation of N-(p-Nitrophenyl) 5-Hydroxyvaleramide in Perchloric Acid Solutions.

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	987	0.01046	-1.9810
0.5	984	0.02113	-1.6755
1.0	987	0.01046	-1.9810
2.0	940	0.2084	-0.6810
3.0	952	0.1510	-0.8210
4.0	934	0.2392	-0.6213
5.0	902	0.4360	-0.3600
6.0	888	0.543	-0.2652
7.5	834	1.165	0.0660
9.0	734	7.54	0.8770
10.5	720	13.50	1.1304

λ_{max} 222.0 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of of 9900 and 700 respectively.

Linear least squares treatments yield :-

1) Slope -0.455 $\pm$0.045, intercept -1.605 $\pm$0.138 and

2) Slope -0.758 $\pm$0.061, intercept -1.531 $\pm$0.109

for plots of log I versus H_o and H_A respectively. Derived values of H_o and H_A for 50% protonation are displayed in tables 25 and 26.

TABLE 24 : The Degree of Protonation of N-(m-Nitrophenyl) 5-Hydroxyvaleramide in Perchloric Acid Solutions

Acid Molarity	$10^{-1} \times \epsilon$	I	log I
0.01	2140		
0.5	2070	0.0176	-1.7555
1.0	2136		
2.0	2029	0.0964	-1.0160
3.0	1994	0.1741	-0.7590
4.0	1898	0.4570	-0.3396
5.0	1857	0.634	-0.1980
6.0	1740	1.417	0.1512
7.5	1664	2.538	0.4044
9.0	1545	11.90	1.0758
10.5	1506	97.80	1.9900

λ_{max} 242.5 nm

Plots of ϵ against H_o and H_A yield common values of ϵ_B and ϵ_{BH^+} of 20,800 and 15,000 respectively.

Linear least squares treatments yield:-

1) Slope -0.526 $\pm$0.026, intercept -1.495 $\pm$0.090

2) Slope -0.897 $\pm$0.037, intercept -1.475 $\pm$0.074

for plots of log I versus H_o and H_A respectively. Derived values of H_o and H_A for 50% protonation are displayed in tables 25 and 26.

TABLE 25 : H_o Values for Aryl Substituted, 4-Hydroxybutyranilides at 50% Protonation derived from log I versus H_o plots.

Substituent	-Slope	-Intercept	$-H_o(50\%)$
H	0.512 $\pm$0.037	0.921 $\pm$0.095	1.800
p-CH_3	0.511 $\pm$0.026	1.020 $\pm$0.068	1.997
m-CH_3	0.594 $\pm$0.032	1.220 $\pm$0.088	2.055
p-OCH_3	0.694 $\pm$0.041	1.440 $\pm$0.108	2.080
m-OCH_3	0.570 $\pm$0.052	1.278 $\pm$0.162	2.240
p-Cl	0.670 $\pm$0.052	1.671 $\pm$0.136	2.495
m-Cl	0.740 $\pm$0.058	1.611 $\pm$0.143	2.180
p-Br	0.650 $\pm$0.067	1.679 $\pm$0.173	2.683
m-Br	0.575 $\pm$0.033	1.371 $\pm$0.085	2.386
p-NO_2	0.451 $\pm$0.036	1.746 $\pm$0.117	3.868
m-NO_2	0.656 $\pm$0.028	1.803 $\pm$0.070	2.748

TABLE 25 (continued) : H_o Values for Aryl Substituted 5-Hydroxy-valeranilides at 50% Protonation

Substituent	-Slope	-Intercept	$-H_o$(50%)
H	0.634 ±0.056	1.365 ±0.138	2.150
p-CH_3	0.603 ±0.054	1.481 ±0.117	2.455
m-CH_3	0.601 ±0.033	1.359 ±0.091	2.260
p-OCH_3	0.690 ±0.009	1.395 ±0.024	2.020
m-OCH_3	0.743 ±0.030	1.388 ±0.062	1.870
p-Cl	0.590 ±0.018	1.449 ±0.043	1.675
m-Cl	0.551 ±0.032	1.079 ±0.078	1.957
p-Br	0.804 ±0.043	2.220 ±0.118	2.758
p-NO_2	0.455 ±0.045	1.604 ±0.138	3.528
m-NO_2	0.526 ±0.026	1.495 ±0.090	2.840

TABLE 26 : H_A Values for Aryl Substituted, 4-Hydroxybutyranilides at 50% Protonation derived from log I versus H_A plots

Substituent	-Slope	-Intercept	$-H_A(50\%)$
H	0.821 $\pm$0.037	0.840 $\pm$0.037	1.022
p-CH_3	0.816 $\pm$0.030	0.934 $\pm$0.046	1.145
m-CH_3	0.974 $\pm$0.037	1.177 $\pm$0.060	1.208
p-OCH_3	1.112 $\pm$0.045	1.340 $\pm$0.047	1.204
m-OCH_3	0.982 $\pm$0.041	1.122 $\pm$0.064	1.144
p-Cl	1.069 $\pm$0.073	1.559 $\pm$0.112	1.458
m-Cl	0.942 $\pm$0.030	1.359 $\pm$0.044	1.441
p-Br	1.025 $\pm$0.075	1.541 $\pm$0.116	1.502
m-Br	0.919 $\pm$0.036	1.277 $\pm$0.056	1.390
p-NO_2	0.750 $\pm$0.056	1.681 $\pm$0.107	2.240
m-NO_2	0.924 $\pm$0.044	1.607 $\pm$0.110	1.740

TABLE 26 (continued): H_A Values for Aryl Substituted 5-Hydroxy-valeranilides at 50% Protonation.

Substituent	-Slope	-Intercept	$-H_A(50\%)$
H	0.976 ±0.084	1.201 ±0.135	1.230
p-CH_3	0.964 ±0.066	1.388 ±0.103	1.440
m-OH_3	0.984 ±0.041	1.314 ±0.067	1.338
p-OCH_3	1.065 ±0.038	1.224 ±0.056	1.150
m-OCH_3	1.119 ±0.045	1.224 ±0.056	1.095
p-Cl	0.910 ±0.038	1.298 ±0.056	1.426
m-Cl	0.857 ±0.051	0.953 ±0.076	1.113
p-Br	1.316 ±0.065	2.155 ±0.106	1.572
p-NO_2	0.758 ±0.061	1.531 ±0.110	2.020
m-NO_2	0.900 ±0.037	1.475 ±0.073	1.638

TABLE 26A : pK_{SH+} values from LFER plots for 4-Hydroxy-butyranlides and 5-Hydroxyvaleranilides at 50°.

Substituent	pK_{SH+} (4-OH)	pK_{SH+} (5-OH)
H	0.943 ±0.048	1.209 ±0.089
p-Me	1.054 ±0.034	1.509 ±0.104
m-Me	1.307 ±0.061	1.444 ±0.066
p-Meo	1.435 ±0.075	1.441 ±0.045
m-Meo	0.937 ±0.227	1.379 ±0.073
p-Cl	1.684 ±0.149	1.114 ±0.098
m-Cl	1.517 ±0.063	1.074 ±0.10
p-Br	1.536 ±0.114	2.257 -0.103
m-Br	1.396 ±0.056	
p-NO_2	1.767 ±0.160	1.590 ±0.133
m-NO_2	1.773 ±0.067	1.549 ±0.049

The value of the ϕ_e parameters derived from the plots of log I + H_o which produce the above pK_{SH+} values are listed in tables 49 and 50 respectively.

TABLE 27 : Data for the Hydrolysis of Butyranilide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^5 k_{obs}$	$-\log k_{obs}$	$-\log k_p^{\dagger}$	$-(H_o + \log I)$
1.0	1.887	4.7264	3.3744	1.625
	1.868			
2.0	3.059	4.5150	3.3665	1.937
	3.052			
3.0	3.418	4.4648	3.9414	1.690
	3.440			
4.0	2.971	4.5313	4.1213	2.097
	2.915			
5.0	2.458	4.6094	4.3594	2.220
6.0	1.326	4.8952	4.7837	2.355
	1.219			
7.5	0.356	5.449	5.3825	2.969
9.0	0.0037	6.440	6.430	3.496

TABLE 27(continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$	$-\log k_p^4$	$\frac{k_{obs}}{a_{Br^-}.\alpha}$	$\frac{H^+(1-\alpha)}{\alpha}$
1.0	3.6490	3.4054	3.3284	43.30	21.10
2.0	3.9092	3.5547	3.3460	30.70	16.26
3.0	4.1878	3.8148	3.3006	18.45	10.40
4.0	4.3968	4.0198	3.1985	13.05	8.99
5.0	4.5650	4.3370	2.9342	7.54	4.36
6.0	4.8822	4.7467	2.7712	3.83	2.45
7.5	5.438	5.402	2.8160	0.905	0.85
9.0	6.440	6.430	2.202	0.370	0.203

The data listed in this table are plotted in graphs 1,3,6,7.

TABLE 28 : Data for the Hydrolysis of N-Phenyl 4-Hydroxy-butyramide in Perchloric Acid Solutions at 50°C.

Acid Molarity	$10^3 k_{obs}$ (S^{-1})	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o + \log I)$
0.5				1.1903
1.0	0.437	3.3591	2.4521	1.1688
	0.437			
2.0	0.931	3.0338	2.4963	1.1898
	0.911			
	0.928			
3.0	1.188	2.9165	2.4665	1.5790
	1.194			
4.0	1.958	2.7201	2.4881	1.6988
	1.848			
	1.908			
5.0	1.992	2.7042	2.5555	1.9408
	1.959			
	1.948			
6.0	1.432	2.8404	2.7554	2.2280
	1.457			
7.5	0.583	3.2344	3.2055	2.6200
	0.581			
	0.580			
9.0	0.120	3.9191	3.9043	3.6927

TABLE 28 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$	$-\log k_p^4$	$\frac{10^3 k_{obs}}{a_w \cdot \alpha}$	$\frac{H^+ (1-\alpha)}{\alpha}$
1.0	2.5781	2.3251	2.2391	4.93	9.81
2.0	2.6226	2.3581	2.0997	4.84	7.47
3.0	2.7395	2.4124	1.8965	4.78	4.77
4.0	2.6533	2.5027	1.4545	5.27	4.11
5.0	2.6824	2.5575	1.0521	4.54	2.00
6.0	2.8343	2.7656	0.7224	3.66	1.13
7.5	3.2315	3.2133	0.3593	2.45	0.395
9.0	3.9191	3.9150	-0.2667	1.17	0.091

Parameters derived by linear least - squares (LLSQ) treatments of these data are listed in table (49).

TABLE 29 : Data for the Hydrolysis of N-(p-Tolyl) 4-Hydroxy-butyramide in Perchloric Acid Solutions at 50°.

Acid	$10^3 k_{obs}$	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o+\log I)$
1.0	0.339	3.4710	2.2055	1.1310
	0.338			
2.0	0.681	3.1688	2.5103	1.3700
	0.678			
	0.675			
3.0	1.080	2.9669	2.4887	1.6230
	1.088			
	1.068			
4.0	1.344	2.8845	2.5665	1.7947
	1.288			
	1.302			
5.0	1.221	2.9162	2.7337	2.0478
	1.205			
6.0	0.859	3.0685	2.9514	2.3810
	0.848			
7.5	0.296	3.5186	3.4586	2.9190
	0.313			
	0.300			
9.0	0.0747	4.1221	4.1096	3.6152
	0.0763			

TABLE 29(continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$	$-\log k_p^4$	$\frac{10^3 k_{obs}}{a_w \cdot \alpha}$	$\frac{H^+ (1-\alpha)}{\alpha}$
1.0	2.5882	2.3242	2.266	4.96	13.05
2.0	2.6778	2.3920	2.156	4.47	9.96
3.0	2.7448	2.4548	1.905	4.03	6.31
4.0	2.8356	2.5113	1.600	4.21	5.45
5.0	2.8893	2.7191	1.259	3.15	2.91
6.0	3.0604	2.9725	0.950	2.28	1.49
7.5	3.5180	3.4896	0.643	1.29	0.52
9.0	4.1220	4.1161	-0.064	0.77	0.13

Parameters derived by LLSQ treatments of these data are listed in table (49).

TABLE 30 : Data for the Hydrolysis of N-(m-Tolyl) 4-Hydroxy-butyramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (S^{-1})	-log k_{obs}	-log k_p^1	-(H_o+logI)
1.0	0.4323	3.3619	2.0501	1.6090
	0.437			
2.0	0.916	3.0389	2.3654	1.3902
	0.894			
	0.934			
3.0	1.610	2.7988	2.2758	1.6886
	1.570			
4.0	2.031	2.6906	2.3476	1.8809
	2.047			
5.0	1.796	2.7638	2.5448	2.1453
	1.651			
6.0	1.282	2.8921	2.7656	2.4187
	1.141			
7.5	0.473	3.3251	3.2871	2.7065
	0.472			
9.0	0.0947	4.0238	4.0163	3.3800

TABLE 30 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$	$-\log k_p^4$
1.0	2.4206	2.1564	2.1004
2.0	2.5021	2.2109	1.9823
3.0	2.5498	2.2628	1.7073
4.0	2.5921	2.2786	1.3930
5.0	2.7370	2.5566	1.1018
6.0	2.8830	2.7831	0.7721
7.5	3.3241	2.2911	0.4490
9.0	4.0238	4.0170	-0.1620

Parameters derived by LLSQ treatments of these data are listed in table (49).

TABLE 31 : Data for the Hydrolysis of N-(p-Methoxyphenyl) 4-Hydroxybutyramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (S^{-1})	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o+\log I)$
1.0	0.254	3.0513	2.4853	1.456
	0.253			
	0.252			
2.0	0.525	3.2827	2.3877	1.656
	0.520			
	0.520			
3.0	0.822	3.0894	2.5849	1.721
	0.806			
4.0	0.993	2.9881	2.7001	1.773
	1.064			
5.0	0.826	3.0718	2.8428	2.170
	0.869			
6.0	0.584	3.2332	3.1372	2.280
	0.585			
7.5	0.228	3.6415	3.6360	2.530
	0.229			
	0.220			
9.0	0.055	4.258	4.252	3.200

TABLE 31 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	2.7140	2.4488
2.0	2.7470	2.4577
3.0	2.8424	2.5550
4.0	2.8901	2.5781
5.0	3.0403	2.8658
6.0	3.2244	3.1242
7.5	3.6406	3.6075
9.0	4.258	4.258

Parameters derived by LLSQ treatments of these data are listed in table (49).

TABLE 32 : Data for the Hydrolysis of N-(m-Methoxyphenyl) 4-Hydroxybutyramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (S^{-1})	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o + \log I)$
1.0	0.5173	3.2866	2.2793	1.2826
	0.5154			
2.0	1.151	2.9366	2.4916	1.3531
	1.162			
3.0	2.380	2.6119	2.0179	1.7860
	2.507			
4.0	2.538	2.5874	2.2219	1.920
	2.634			
5.0	2.695	2.5528	2.3788	2.025
	2.911			
6.0	2.422	2.6330	2.5180	2.310
	2.234			
7.5	0.917	3.0301	2.9881	2.761
	0.949			
9.0	0.211	3.6970	3.6920	3.20
	0.191			
10.5				5.710

TABLE 32 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	2.4981	2.1401
2.0	2.4429	2.1621
3.0	2.3899	2.1329
4.0	2.5002	2.2134
5.0	2.5250	2.3468
6.0	2.6250	2.5370
7.5	3.0292	3.0011
9.0	3.6970	3.6910

Parameters derived by LLSQ treatments of these data are listed in table (49).

TABLE 33 : Data for the Hydrolysis of N-(p-Chlorophenyl) 4-Hydroxybutyramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (S^{-1})	-log k_{obs}	-log k_p^1	-(H_o+log I)
0.5				1.6200
1.0	0.533	3.2866	1.3748	2.2280
	0.508			
2.0	1.088	2.9645	1.6945	2.0668
	1.083			
3.0	1.647	2.7760	2.1168	1.8715
	1.703			
4.0	2.360	2.6283	2.2411	1.9580
	2.345			
5.0	2.551	2.5933	2.3083	2.2960
	2.543			
6.0	2.218	2.6524	2.4824	2.5708
	2.234			
7.5	0.954	3.0255	2.9600	2.9670
	0.932			
9.0	0.1678	3.7305	3.7205	3.5390
	0.1800			

TABLE 33(continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	2.1166	1.8428
2.0	2.2400	1.9165
3.0	2.4000	2.0485
4.0	2.4660	2.0473
5.0	2.5390	2.2723
6.0	2.6365	2.4732
7.5	3.0244	2.9675
9.0	3.7305	3.7184

Parameters derived by LLSQ treatments of these data are listed in tables (49).

TABLE 34 : Data for the Hydrolysis of N-(m-Chlorophenyl) 4-Hydroxybutyramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o+\log I)$
0.5				1.6255
1.0	0.605	3.2154	1.7634	1.7567
	0.612			
	0.609			
2.0	1.365	2.8665	2.0065	1.6145
	1.307			
3.0	2.135	2.6721	1.9187	1.9990
	2.121			
4.0	2.360	2.5318	1.9318	2.2510
	2.345			
5.0	3.462	2.4672	2.1762	2.3092
	3.484			
	3.543			
6.0	3.351	2.4718	2.2586	2.6928
	3.399			
7.5	1.507	2.8254	2.7786	2.8098
	1.483			
9.0	0.348	3.4291	3.4131	3.7039
	0.396			

TABLE 34 (continued)

Acid	$-\log k_p^2$	$-\log k_p^3$	$-\log k_p^4$	$\frac{10^3 k_{obs}}{a_w \cdot \alpha}$	$\frac{H^+ (1-\alpha)}{\alpha}$
1.0	2.0638	1.7880	1.8695	16.96	25.74
2.0	2.1525	1.8334	1.6330	16.20	19.56
3.0	2.3066	1.9580	1.4632	13.27	12.51
4.0	2.3748	1.9630	1.1760	14.84	10.81
5.0	2.4141	2.1552	0.7832	11.45	5.24
6.0	2.4567	2.2498	0.3456	12.01	4.00
7.5	2.8232	2.7691	-0.0518	6.80	1.04
9.0	3.4290	3.4170	-0.7567	3.68	0.25

Parameters derived by LLSQ treatments of the data are listed in table (49).

TABLE 35 : Data for the Hydrolysis of N-(p-Bromophenyl) 4-Hydroxy-butyramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	-log k_{obs}	-log k_p^1	-(H_o+log I)
1.0	0.545	3.2733		
	0.521			
2.0	1.161	2.9290	1.9340	1.7715
	1.194			
3.0	1.841	2.7383	2.1203	1.8215
	1.775			
	1.813			
4.0	2.591	2.5994	2.1934	1.9888
	2.452			
	2.497			
5.0	2.816	2.5514	2.3088	2.2030
	2.813			
6.0	2.459	2.6050	2.422	2.609
	2.508			
7.5	1.079	2.9714	2.8838	3.0978
	1.068			
	1.059			
9.0	0.230	3.6403	3.6188	3.820
	0.227			

TABLE 35 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	2.0633	1.7873
2.0	2.1650	1.8400
3.0	2.3283	1.9747
4.0	2.4190	1.9854
5.0	2.4914	2.2070
6.0	2.5877	2.4102
7.5	2.9684	2.9073
9.0	3.6400	3.6262

Parameters derived by LLSQ treatments of these data are listed in table (49).

TABLE 36 : Data for the Hydrolysis of N-(m-Bromophenyl) 4-Hydroxybutyramide in Perchloric Acid at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	-log k_{obs}	-log k_p^1	-(H_o+logI)
0.5				1.5120
1.0	0.5968	3.2248	1.7578	1.7720
	0.5952			
2.0	1.379	2.8630	2.0952	1.5060
	1.364			
3.0	2.080	2.6586	2.0276	1.8350
	2.309			
4.0	2.665	2.5583	2.1038	2.0665
	2.864			
5.0	3.608	2.4324	2.1662	2.2528
	3.781			
6.0	3.500	2.4688	2.2908	2.5952
	3.300			
7.5	1.643	2.7892	2.7269	2.9498
	1.608			
9.0	0.315	3.5045	3.4897	3.6880
	0.311			

TABLE 36 (continued)

Acid	$-\log k_p^2$	$-\log k_p^3$	$-\log k_p^4$
1.0	2.1190	1.8460	1.7990
2.0	2.1890	1.8800	1.6700
3.0	2.3212	1.9850	1.4846
4.0	2.4158	2.0260	1.2173
5.0	2.3840	2.1460	0.7548
6.0	2.4558	2.3113	0.3394
7.5	2.7876	2.738	-0.0868
9.0	3.5045	3.4945	-0.6815

Parameters derived by LLSQ treatments of these data are listed in table (49).

TABLE 37 : Data for the Hydrolysis of N-(m-Nitrophenyl)4-Hydroxy-butyramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o + \log I)$
1.0	0.7516	3.1244	1.5024	1.931
	0.7505			
2.0	1.731	2.7686	1.5230	2.011
	1.683			
	1.697			
3.0				1.981
4.0	4.097	2.3942	1.5660	2.559
	3.972			
5.0	5.516	2.2585	1.8325	2.552
	5.511			
6.0	6.108	2.2116	1.9716	2.669
	6.178			
7.5	3.816	2.4816	2.4097	3.065
	3.812			
9.0	1.007	3.0031	2.9871	3.7199
	0.979			

TABLE 37 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	1.7824	1.5044
2.0	1.8886	1.5536
3.0		
4.0	2.1662	1.6732
5.0	2.1875	1.8465
6.0	2.1876	1.9626
7.5	2.4771	2.3956
9.0	3.003	2.9841

Parameters derived by LLSQ treatments of these data are listed in table (49).

TABLE 38 : Data for the Hydrolysis of N-(p-Nitrophenyl)4-Hydroxy-butyramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o+\log I)$
1.0	1.630	2.7872	0.6260	2.478
	1.632			
2.0	3.669	2.4347	1.1187	2.1143
	3.799			
	3.555			
3.0	6.480	2.1892	1.0272	2.4507
	6.458			
4.0	10.685	1.9689	1.1608	2.5307
	10.796			
5.0	13.843	1.8587	1.1370	2.9610
6.0	18.245	1.7314	1.2240	3.2300
	18.892			
7.5	14.579	1.8423	1.5923	3.6415
	14.183			
9.0	5.039	2.3089	2.1768	4.6910
	4.781			
10.5	1.1136	2.9710	2.9418	6.4960
	1.025			

TABLE 38 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$	$-\log k_p^4$
1.0	0.8627	0.575	0.541
2.0	1.0127	0.639	0.4793
3.0	1.539	0.7532	0.3768
4.0	1.3947	0.7123	0.1967
5.0	1.600	0.9777	-0.031
6.0	1.6424	1.3204	-0.4676
7.5	1.8295	1.5693	-1.048
9.0	2.3079	2.2389	-1.8773

Parameters derived by LLSQ treatments of these data are listed in table (49).

TABLE 39 : Data for the Hydrolysis of N-Phenyl 5-Hydroxy-valeramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o + \log I)$
1.0	0.434	3.3622	1.5175	2.1586
	0.436			
	0.428			
2.0	0.949	3.0131	2.3551	1.370
	0.981			
3.0	1.592	2.7890	2.3395	1.5933
	1.591			
4.0	2.188	2.6593	2.3403	1.8343
	2.193			
5.0	2.287	2.6502	2.4352	2.1386
	2.193			
6.0	1.657	2.7649	2.6264	2.4635
	1.738			
	1.760			
7.5	0.636	3.1958	3.1428	2.8613
	0.643			
	0.633			
9.0	0.441	3.5410	3.5280	3.3012
	0.439			

TABLE 39 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$	$-\log k_p^4$	$\frac{k_{obs}}{a_w \cdot \alpha}$	$\frac{H_A (1-\alpha)}{\alpha}$
1.0	2.4012	2.1360	2.0812	7.63	15.84
2.0	2.460	2.1669	1.9411	7.52	12.04
3.0	2.5395	2.245	1.6962	6.85	7.72
4.0	2.613	2.233	1.3573	7.97	6.67
5.0	2.616	2.434	0.9866	6.02	3.22
6.0	2.7554	2.650	0.6440	4.78	1.82
7.5	3.1948	3.1608	0.3196	2.765	0.634
9.0	3.5410	3.5337	0.3440	0.143	0.147

Parameters derived by LLSQ treatments of these data are listed in table (50).

TABLE 40 : Data for the Hydrolysis of N-(p-Tolyl) 5-Hydroxy-valeramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o + \log I)$
0.5				1.4802
1.0	0.346	3.3555	1.9475	1.7115
	0.336			
	0.330			
2.0	0.774	3.1067	1.7767	2.2115
	0.776			
	0.796			
3.0	1.141	2.9374	2.3334	1.7989
	1.155			
	1.169			
4.0	1.453	2.8294	2.4184	1.9979
	1.509			
5.0	1.6172	2.8224	2.5714	2.2228
	1.3934			
6.0	0.997	2.9971	2.8336	2.5476
	1.018			
7.5	0.329	3.4993	3.4313	2.9836
	0.304			
9.0	0.050	4.3512	4.3362	3.6882
	0.049			

TABLE 40 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	2.2055	1.9283
2.0	2.294	2.075
3.0	2.5732	2.2254
4.0	2.671	2.261
5.0	2.7694	2.5114
6.0	2.982	2.775
7.5	3.476	3.442
9.0	4.3512	4.3492

Parameters derived by LLSQ treatments of these data are listed in table (50).

TABLE 41 : Data for the Hydrolysis of N-(m-Tolyl) 5-Hydroxy-valeramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o+\log I)$
1.0	0.446	3.3507	1.6977	1.758
	0.441			
	0.448			
2.0	1.018	2.9953	2.2073	1.530
	0.997			
3.0	1.868	2.8171	2.2236	1.785
	1.933			
4.0	1.868	2.7210	2.310	1.998
	1.933			
5.0	1.893	2.7104	2.4224	2.305
	2.003			
6.0	1.589	2.8400	2.6970	2.478
	1.300			
7.5	0.511	3.2867	3.2297	2.895
	0.523			
9.0	0.111	3.9621	3.9531	3.459
	0.106			

TABLE 41 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	2.293	2.022
2.0	2.362	2.054
3.0	2.507	2.184
4.0	2.593	2.225
5.0	2.668	2.449
6.0	2.828	2.6985
7.5	3.286	3.242
9.0	3.962	3.952

Parameters derived by LLSQ treatments of these data are listed in table (50).

TABLE 42 : Data for the Hydrolysis of N-(p-Methoxyphenyl)5-Hydroxy-valeramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o + \log I)$
0.5				1.4623
1.0	0.280	3.5508	2.312	1.5325
	0.283			
2.0	0.603	3.2202	2.399	1.5700
	0.599			
	0.605			
3.0	0.882	3.0492	2.445	1.799
	0.903			
4.0	1.116	2.9417	2.558	1.952
	1.172			
5.0	1.036	2.9666	2.749	2.145
	1.125			
6.0	0.691	3.1513	3.041	2.352
	0.720			
7.5	0.208	3.6551	3.630	2.520
	0.236			
9.0	0.036	4.452	4.449	2.967
	0.037			
	0.033			

TABLE 42 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	2.6608	2.3990
2.0	2.7240	2.4412
3.0	2.8247	2.5520
4.0	2.8550	2.5650
5.0	2.9386	2.7806
6.0	3.1433	3.0543
7.5	3.6542	3.6251
9.0	4.452	4.4455

Parameters derived by LLSQ treatments of these data are listed in table (50).

TABLE 43 : Data for the Hydrolysis of N-(m-Methoxyphenyl) 5-Hydroxyvaleramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o + \log I)$
0.5				1.4970
1.0	0.549	3.2690	2.097	1.4621
	0.514			
	0.552			
2.0	1.201	2.9180	2.2255	1.3935
	1.215			
3.0	1.914	2.7147	2.1787	1.7070
	1.944			
4.0	2.760	2.5486	2.2076	1.8960
	2.896			
5.0	2.936	2.4846	2.2856	2.0950
	3.168			
6.0	2.572	2.5994	2.5224	2.1760
	2.457			
7.0	1.107	2.9622	2.9477	2.2740
	1.075			
9.0	0.166	3.3484	3.348	
	0.193			
	0.176			

TABLE 43 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	2.4265	2.169
2.0	2.3457	2.1845
3.0	2.5127	2.2547
4.0	2.4706	2.202
5.0	2.4591	2.317
6.0	2.5926	2.5124
7.5	2.9618	2.9362
9.0	3.3480	3.3432

Parameters derived by LLSQ treatments of these data are listed in table (50).

TABLE 44 : Data for the Hydrolysis of N-(p-Chlorophenyl) 5-Hydroxyvaleramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o + \log I)$
0.01				1.2800
0.5				1.4600
1.0	0.519	3.2870	1.827	1.7800
	0.514			
2.0	1.182	2.9268	1.9558	1.740
	1.184			
3.0	1.868	2.7225	1.9925	1.960
	1.924			
4.0	2.852	2.564	2.008	2.215
	2.606			
5.0	3.058	2.510	2.148	2.429
	3.120			
6.0	2.737	2.563	2.405	2.532
	2.613			
7.5	1.130	2.948	2.884	2.981
	1.124			
9.0	0.185	3.730	3.777	3.600
	0.186			
	0.188			

TABLE 44 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	2.1940	1.8750
2.0	2.2248	1.9073
3.0	2.3645	2.0025
4.0	2.4110	2.0060
5.0	2.4504	2.2060
6.0	2.5486	2.3961
7.5	2.9480	2.8942
9.0	3.7297	3.7184

Parameters derived by LLSQ treatments of these data are listed in table (50).

TABLE 45 : Data for the Hydrolysis of N-(m-Chlorophenyl) 5-Hydroxyvaleramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o+\log I)$
0.1				1.1788
0.5				1.1280
1.0	0.616	3.216	2.297	1.183
	0.604			
2.0	1.387	2.859	2.283	1.320
	1.383			
3.0	2.256	2.445	2.077	1.4475
	2.267			
4.0	3.269	2.485	2.198	1.771
	3.283			
5.0	3.925	2.401	2.197	2.109
	4.023			
6.0	3.832	2.415	2.242	2.5820
	3.851			
7.5	1.769	2.750	2.684	2.9658
	1.789			
9.0	0.336	3.474	3.468	3.2162
	0.336			

TABLE 45 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	2.360	2.100
2.0	2.387	2.107
3.0	2.230	1.973
4.0	2.404	2.130
5.0	2.376	2.226
6.0	2.408	2.325
7.5	2.749	2.732
9.0	3.474	3.468

Parameters derived by LLSQ treatments of these data are listed in table (50).

TABLE 46 : Data for the Hydrolysis of N-(p-Bromophenyl) 5-Hydroxyvaleramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$-\log k_p^1$	$-(H_o + \log I)$
1.0				2.316
2.0	1.171	2.934	1.082	2.668
	1.178			
	1.118			
3.0	1.997	2.301	1.334	2.238
	1.985			
	1.994			
4.0	2.573	2.591	1.871	2.429
	2.557			
5.0	3.159	2.490	2.045	2.580
	3.176			
	3.382			
6.0	2.921	2.531	2.212	2.925
	2.971			
7.5	1.277	2.894	2.838	2.885
	1.280			
9.0				3.293

TABLE 46 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^1$
2.0	2.113	1.781
3.0	1.856	1.480
4.0	2.380	1.923
5.0	2.420	2.107
6.0	2.511	2.311
7.5	2.891	2.820

Parameters derived by LLSQ treatments of these data are listed in table (50).

TABLE 47 : Data for the Hydrolysis of N-(p-Nitrophenyl) 5-Hydroxy-valeramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$-\log k'_p$	$-(H_0+\log I)$
0.5				1.7355
1.0	1.382	2.8645	0.8792	2.3010
	1.353			
2.0	3.281	2.480	1.7170	1.4010
	3.342			
3.0	6.250	2.212	1.3297	2.1410
	6.030			
4.0	10.242	1.997	1.2827	2.4213
	9.920			
5.0	14.788	1.828	1.3104	2.6900
	14.966			
6.0	20.860	1.691	1.2173	3.1552
	19.900			
7.5	16.110	1.797	1.5276	3.6840
	15.794			
9.0	4.899	2.296	2.2418	4.2623
	5.215			
10.5	0.826	3.072	3.0417	5.5196
	0.867			

TABLE 47 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0	1.1457	0.8705
2.0	1.2538	0.8985
3.0	1.3338	0.9856
4.0	1.5726	0.9450
5.0	1.6536	1.1291
6.0	1.6356	1.2318
7.5	1.7892	1.6144
9.0	2.2950	2.2530
10.5	3.0720	3.0632

Parameters derived by LLSQ treatments of these data are listed in table (50).

TABLE 48 : Data for the Hydrolysis of N-(m-Nitrophenyl) 5-Hydroxy-valeramide in Perchloric Acid Solutions at 50°.

Acid Molarity	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$-\log k_p'$	$-(H_o+\log I)$
0.5				1.816
1.0				
2.0	1.735	2.773	1.7174	1.836
	1.623			
	1.707			
3.0	3.144	2.526	1.6970	2.079
	2.950			
	2.680			
4.0	4.938	2.304	1.8010	2.139
	4.994			
5.0	5.886	2.216	1.805	2.528
	6.278			
6.0	7.165	2.150	1.9123	2.739
	7.022			
7.5	4.810	2.331	2.187	3.346
	4.527			
9.0	1.057	2.976	2.941	4.064
	1.065			

TABLE 48 (continued)

Acid Molarity	$-\log k_p^2$	$-\log k_p^3$
1.0		
2.0	1.8928	1.5568
3.0	2.0371	1.6455
4.0	2.0770	1.5823
5.0	2.1350	1.7920
6.0	2.1255	1.9005
7.5	2.3275	2.2448
9.0	2.9758	2.9573

Parameters derived by LLSQ treatments of these data are listed in table (50).

TABLE 49 : Correlation Parameters for Aryl-Substituted N-Aryl 4-Hydroxybutyramides in Perchloric Acid at 50°

Substituent	ω	r	b
H	1.336±0.116	1.637±0.046	1.52±0.10
p-Me	1.463±0.084	1.801±0.094	1.85±0.09
m-Me	1.620±0.041	1.954±0.048	1.92±0.09
p-MeO	1.593±0.015	1.932±0.066	1.92±0.08
m-MeO	1.293±0.116	1.646±0.061	1.51±0.20
p-Cl	1.527±0.086	1.909±0.039	2.08±0.25
m-Cl	1.288±0.086	1.666±0.045	1.63±0.09
p-Br	1.504±0.081	1.889±0.035	1.69±0.07
m-Br	1.299±0.110	1.668±0.050	1.59±0.12
p-NO_2	1.221±0.239	1.707±0.099	1.27±0.16
m-NO_2	1.131±0.114	1.524±0.024	1.58±0.06

The corresponding values of these parameters for n-Butyranilide are as follows:

ω : 2.66±0.18

r : 3.04±0.16

ω_r^1 : 3.55

ϕ_r : 0.79±0.03

ϕ_e : 0.48±0.06

$\phi_{overall}$: 1.27

b : 3.05±0.025

TABLE 49 (continued)

Substituent	$\phi_{overall}$	ϕ_e	ϕ_r	ω'_r
H	1.108	0.631±0.046	0.376±0.048	1.69
p-Me	1.063	0.626±0.017	0.437±0.022	1.97
m-Me	0.989	0.498±0.029	0.486±0.038	2.19
p-MeO	0.888	0.400±0.038	0.488±0.024	2.19
m-MeO	1.092	0.724±0.083	0.368±0.070	1.66
p-Cl	0.974	0.429±0.052	0.545±0.044	1.58
m-Cl	0.921	0.512±0.032	0.409±0.041	1.84
p-Br	0.967	0.523±0.054	0.444±0.033	2.00
m-Br	0.947	0.548±0.028	0.399±0.044	1.80
p-NO_2	1.146	0.764±0.059	0-382±0.034	1.72
m-No_2	0.856	0.460±0.039	0.396±0.034	1.80

TABLE 50 : Correlation Parameters for Aryl-Substituted N-Aryl 5-Hydroxyvaleramides in Perchloric Acid at 50°.

Substituent	ω	r	b
H	1.179±0.056	1.529±0.046	1.62±0.30
p-Me	2.084±0.102	2.445±0.049	2.23±0.04
m-Me	1.661±0.049	2.024±0.038	2.06±0.17
p-MeO	1.814±0.064	2.157±0.037	2.22±0.23
m-MeO	1.000±0.080	1.273±0.062	1.82±0.07
p-Cl	1.518±0.097	1.900±0.053	1.52±0.12
m-Cl	1.133±0.160	1.449±0.115	1.26±0.21
p-Br	1.542±0.360	2.135±0.101	0.71±0.08
p-NO_2	1.028±0.137	1.412±0.058	0.91±0.30
m-NO_2	1.006±0.126	1.462±0.086	1.27±0.13

TABLE 50 (continued)

Substituent	ϕ_e	ϕ_r	ω_r^1
H	0.535±0.040	0.425±0.069	1.91
p-Me	0.508±0.053	0.630±0.036	2.84
m-Me	0.490±0.032	0.527±0.039	2.37
p-MeO	0.384±0.022	0.561 ±0.034	2.53
m-MeO	0.357±0.049	0.331 ±0.031	1.49
p-Cl	0.469±0.065	0.377±0.051	1.70
m-Cl	0.586±0.053	0.312±0.066	1.41
p-Br	0.241±0.050	0.711±0.077	3.20
p-NO_2	0.687±0.051	0.320±0.066	1.44
m-NO_2	0.600±0.023	0.328±0.048	1.48

TABLE 51 : Rates of Hydrolysis of 4-Hydroxybutyranilide and 5-Hydroxyvaleranilide in Aqueous Perchloric Acid (1.00M).

Temperature	5-Hydroxyvaleranilide		4-Hydroxybutyranilide.	
	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$10^3 k_{obs}$ (s^{-1})	$-\log k_{obs}$
45.00°	0.298	3.5307	0.299	3.5432
	0.288		0.274	
50.00°	0.428	3.3622	0.454	3.3591
	0.434		0.437	
	0.436		0.437	
54.90°	0.674	3.1690	0.726	3.1424
	0.682		0.713	
60.00°	1.004	2.9893	1.039	2.9821
	1.046		1.045	
64.70°	1.565	2.8128	1.739	2.7770
	1.514		1.603	

LLSQ treatment of data yields

5-Hydroxyvaleranilide

ΔH^* = 17.08 $\pm$0.08 K cal. mol^{-1}

ΔS^* =-21.19 $\pm$0.07 e.u.at 50°

4-Hydroxybutyranlide

ΔH^* = 18.07 $\pm$0.04 K cal mol^{-1}

ΔS^* =-18.11 $\pm$0.05 e.u. at 50°

TABLE 52 : The Rates of Hydrolysis of N-(p-Tolyl and m-Tolyl) 4-Hydroxybutyramides in Aqueous Perchloric Acid (1.00M).

Temperature	p-CH_3 $10^3 k_{obs}$ (s^{-1})	-log k_{obs}	m-CH_3 $10^3 k_{obs}$ (s^{-1})	-log k_{obs}
45.00°	0.200	3.6988	0.267	3.5781
	0.200		0.262	
50.00°	0.338	3.4710	0.432	3.3619
	0.339		0.437	
54.90°	0.550	3.2446	0.692	3.1673
	0.589		0.669	
60.00°	0.793	3.1071	0.975	3.0102
	0.770		0.978	
64.70°	1.345	2.8880	1.567	2.8034
	1.243		1.578	

LLSQ treatment of data yields

p-Tolyl

$\Delta H^* = 18.96 \pm 0.029$ K cal.mol.$^{-1}$

$\Delta S^* = -15.93 \pm 0.028$ e.u. at 50°

m-Tolyl

$\Delta H^* = 18.15 \pm 0.034$ K cal.mol.$^{-1}$

$\Delta S^* = -17.95 \pm 0.042$ e.u.at 50°

TABLE 53 : Rates of Hydrolysis of N-(H-Methoxyphenyl and m-Methoxy phenyl) 4-Hydroxybutyramides in Aqueous Perchloric Acid(1.00M)

Temperature	p-OCH_3 $10^3 k_{obs}$ (s^{-1})	p-OCH_3 -log k_{obs}	m-OCH_3 $10^3 k_{obs}$ (s^{-1})	m-OCH_3 -log k_{obs}
45.00°	0.157	3.7872	0.382	3.4300
	0.169		0.362	
50.00°	0.254	3.6513	0.517	3.2866
	0.252		0.515	
	0.253			
54.90°	0.392	3.3973	0.821	3.0916
	0.409		0.810	
	0.419			
60.00°	0.591	3.2129	1.266	2.2876
	0.634		1.325	
64.70°	0.960	3.0142	1.890	2.711
	0.976		2.000	

LLSQ treatment yields

p-Methoxy

$\Delta H^* = 18.78 \pm 0.037$ K cal.mol.$^{-1}$

$\Delta S^* = -17.27 \pm 0.071$ e.u. at 50°

m-Methoxy

$\Delta H^* = 17.33 \pm 0.06$ K cal.mol.$^{-1}$

$\Delta S^* = -20.07 \pm 0.03$ e.u. at 50°

TABLE 54 : Rates of Hydrolysis of N-(p-Bromophenyl and m-Bromophenyl) 4-Hydroxybutyramides in Aqueous Perchloric Acid (1.00M).

Temperature	p-Br $10^3 k_{obs}$ (s^{-1})	p-Br $-\log k_{obs}$	m-Br $10^3 k_{obs}$ (s^{-1})	m-Br $-\log k_{obs}$
45.00°	0.305	3.5271		
	0.289			
50.00°	0.532	3.2773	0.597	3.2247
	0.534		0.595	
54.90°	0.807	3.0922	0.950	3.0162
	0.811		0.976	
60.00°	1.201	2.9198	1.455	2.8375
	1.208		1.452	
64.70°	1.908	2.7178	2.164	2.6642
	1.923		2.169	

LLSQ treatments yields

p-Bromo

$\Delta H^* = 18.73 \pm 0.03$ K cal mol^{-1}

$\Delta S^* = -15.68 \pm 0.05$ e.u. at 50°

m-Bromo

$\Delta H^* = 18.36 \pm 0.05$ K cal mol^{-1}

$\Delta S^* = -16.60 \pm 0.04$ e.u. at 50°

TABLE 55 : Rates of Hydrolysis of N-(p-Chlorophenyl and m-Chlorophenyl 4-Hydroxybutyramides in Aqueous Perchloric Acid(1.00M)

Temperature	$10^3 k_{obs}$ p-Cl (s^{-1})	-log k_{obs}	$10^3 k_{obs}$ m-Cl (s^{-1})	-log k_{obs}
45.00°	0.298	3.5360	0.385	3.4142
	0.284			
50.00°	0.533	3.2871	0.605	3.2157
	0.508		0.612	
			0.608	
54.90°	0.707	3.1198	0.970	3.0130
	0.751		0.971	
60.00°	1.199	2.9249	1.398	2.8459
	1.178		1.454	
64.70°	1.747	2.7553	1.868	2.6953
	1.766		2.165	

LLSQ treatments yield

p-Chloro

$\Delta H^* = 18.49$ K cal mol^{-1}

$\Delta S^* = -16.51 \pm 0.031$ e.u.at 50°

m-Chloro

$\Delta H^* = 17.12 \pm 0.04$ K cal. $mol.^{-1}$

$\Delta S^* = -20.42 \pm 0.04$ e.u. at 50°

TABLE 56 : Rates of Hydrolysis of N-(p-Nitrophenyl and m-Nitrophenyl) 4-Hydroxybutyramide in Aqueous Perchloric Acid (1.00M)

Temperature	p-NO_2 $10^3 k_{obs}$ (s^{-1})	p-NO_2 -log k_{obs}	m-NO_2 $10^3 k_{obs}$ (s^{-1})	m-NO_2 -log k_{obs}
45.00°	1.020	2.9859	0.467	3.3328
	1.045		0.462	
50.00°	1.630	2.7872	0.752	3.1244
	1.632		0.761	
54.90°	2.437	2.6019	1.082	2.9457
	2.510		1.184	
60.00°	3.671	2.427	1.724	2.7636
	3.810			
64.70°	5.376	2.2775	2.652	2.5925
	5.178		2.460	

LLSQ treatments yield

p-Nitro

$\Delta H^* = 16.79 \pm 0.04$ K cal.mol.$^{-1}$

$\Delta S^* = -19.46 \pm 0.04$ e.u.at 50°

m-Nitro

$\Delta H^* = 17.39 \pm 0.05$ K cal.mol.$^{-1}$

$-\Delta S^* = -19.16 \pm 0.06$ e.u.at 50°

TABLE 57 : Rates of Hydrolysis of N-(p-Tolyl and m-Tolyl) 5-Hydroxybutyramides in Aqueous Perchloric Acid (1.00M)

Temperature	p-CH_3 $10^3 k_{obs}$ (s^{-1})	p-CH_3 -log k_{obs}	m-CH_3 $10^3 k_{obs}$ (s^{-1})	m-CH_3 -log k_{obs}
45.00°	0.226	3.6642	0.272	3.5566
	0.238		0.279	
50.00°	0.346	3.4546	0.446	3.3507
	0.336		0.442	
	0.331		0.448	
54.90°	0.544	3.2662	0.660	3.1764
	0.540		0.672	
60.00°	0.815	3.0952	1.052	2.9786
	0.791			
64.70°	1.237	2.9093	1.504	2.8227
	1.228		1.504	

LLSQ treatments yield

p-Methyl

$\Delta H^* = 17.70 \pm 0.05$ K cal.mol.$^{-1}$

$\Delta S^* = 19.69 \pm 0.06$ e.u. at 50°

m-Methyl

$\Delta H^* = 17.42 \pm 0.05$ K cal.mol.$^{-1}$

$\Delta S^* = 20.09 \pm 0.04$ e.u.at 50°

TABLE 58 : Rates of Hydrolysis of N-(p-Methoxyphenyl and m-Methoxyphenyl) 5-Hydroxyvaleramides in Aqueous Perchloric Acid (1.00 M).

Temperature	p-OCH_3 $10^3 k_{obs}$ (s^{-1})	p-OCH_3 -log k_{obs}	m-OCH_3 $10^3 k_{obs}$ (s^{-1})	m-OCH_3 -log k_{obs}
45.00°	0.177	3.7528	0.382	3.4651
			0.362	
50.00°	0.284	3.5508	0.549	3.2690
	0.278		0.514	
			0.552	
54.90°	0.439	3.3489	0.814	3.0832
	0.460		0.837	
	0.442			
60.00°	0.648	3.1933	1.253	2.9060
	0.633		1.231	
64.70°	1.067	2.9822	1.871	2.8385
	1.019		1.779	

LLSQ treatments yield

p-Methoxy

$\Delta H^* = 17.98 \pm 0.04$ K cal.$mol.^{-1}$

$\Delta S^* = -19.28 \pm 0.04$ e.u. at 50°

m-Methoxy

$\Delta H^* = 15.40 \pm 0.04$ K cal $mol.^{-1}$

$\Delta S^* = -26.018 \pm 0.05$ e.u.at 50°

TABLE 59 : Rates of Hydrolysis of N-(p-Chlorophenyl and m-Chlorophenyl) 5-Hydroxyvaleramides in Aqueous Perchloric Acid (1.00M)

Temperature	p-Cl $10^3 k_{obs}$ (s^{-1})	p-Cl $-\log k_{obs}$	m-Cl $10^3 k_{obs}$ (s^{-1})	m-Cl $-\log k_{obs}$
45.00°	0.317	3.4991		
	0.318			
	0.316			
50.00°	0.519	3.2869	0.616	3.2152
	0.514		0.604	
54.90°	0.753	3.1165	0.936	3.0212
	0.776		0.969	
60.00°	1.095	2.9624	1.416	2.8536
	1.086		1.386	
64.70°	1.700	2.7605	2.084	2.6962
	1.773		1.944	

LLSQ treatments yield

p-Chloro

$\Delta H^* = 17.04 \pm 0.05$ K cal.mol.$^{-1}$

$\Delta S^* = -20.99 \pm 0.04$ e.u. at 50°

m-Chloro

$\Delta H^* = 16.98 \pm 0.04$ K cal.mol.$^{-1}$

$\Delta S^* = -20.80 \pm 0.03$ e.u.at 50°

TABLE 60 : Rates of Hydrolysis of N-(p-Nitrophenyl and m-Nitrophenyl) 5-Hydroxyvaleramides in Aqueous Perchloric Acid(1.00M)

Temperature	p-NO_2 $10^3 k_{obs}$	p-NO_2 $-\log k_{obs}$	m-NO_2 $10^3 k_{obs}$	m-NO_2 $-\log k_{obs}$
45.00°	0.944	3.0333	0.494	3.3112
	0.908		0.483	
50.00°	1.382	2.8645		
	1.353			
54.90°	2.041	2.6862	1.198	2.9292
	2.078		1.157	
60.00°	2.960	2.5312	1.438	2.8318
	2.929		1.509	
64.70°	4.198	2.3691	2.151	2.6528
	4.352		2.297	

LLSQ treatments yield

p-Nitro

$\Delta H^* = 15.65 \pm 0.05$ K cal.mol.$^{-1}$

$\Delta S^* = -23.34 \pm 0.05$ e.u.at 50°

TABLE 61 : Rates of Hydrolysis of m-Butyranilide and m-Methyl Butyranilide in Aqueous Perchloric Acid (1.00M).

Temperature	Butyranilide		m-Me Butyranilide	
	$10^5 k_{obs}$ (s^{-1})	$-\log k_{obs}$	$10^5 k_{obs}$ (s^{-1})	$-\log k_{obs}$
50.00	1.887	4.7241	1.790	4.7470
	1.869	4.7285	1.789	4.7472
54.90	3.186	4.4963	2.909	4.5361
	3.207	4.4940	2.867	4.5327
	3.210	4.4936		
60.00	5.019	4.3000	4.552	4.341
	4.774	4.3212	4.225	4.374
64.70	7.455	4.1272		

LLSQ treatments yield

Butyranilide

$\Delta H^* =$ 19.709 Kcal mol^{-1}.

$\Delta S^* = -19.301$ e.u. at 50°.

m-Me Butyranilide

$\Delta H^* =$ 18.707 Kcal mol^{-1}.

$\Delta S^* = -22.499$ e.u. at 50°.

TABLE 62 : Rates of Hydrolysis of m-Bromo Butyranilide and p-Bromo Butyranilide in Aqueous Perchloric Acid (1.00M)

Temperature	m-Bromo $10^5 k_{obs}$ (s^{-1})	m-Bromo $-\log k_{obs}$	p-Bromo $10^5 k_{obs}$ (s^{-1})	p-Bromo $-\log k_{obs}$
50.00°	2.651	4.5168	2.434	4.4140
	2.693	4.5860	2.291	4.4400
54.90°			4.006	4.3971
60.00°	7.156	4.1451	6.020	4.1208
	6.769	4.1696		
	6.907	4.1605		

LLSQ treatments yield

m-Bromo

$\Delta H^* = 20.396$ Kcal mol^{-1}.

$\Delta S^* = -16.477$ e.u. at 50°.

p-Bromo

Activation energy = -13.235 Kcal.

TABLE 63 : Rates of Hydrolysis of m-Nitro Butyranilide and m-Methoxy Butyranilide in Aqueous Perchloric Acid (1.00M)

Temperature	m-Nitro $10^5 k_{obs}$ (s^{-1})	m-Nitro $-\log k_{obs}$	m-Methoxy $10^5 k_{obs}$ (s^{-1})	m-Methoxy $-\log k_{obs}$
50.00°	3.8327	4.4162		
	3.8272	4.4172		
54.90°	6.0662	4.2171	3.8772	4.4120
	6.0160	4.2208	4.0498	4.3972
	6.0299	4.2200	5.6071	4.2512
60.00°	8.9557	4.0478	6.0675	4.2169
	10.2735	3.9883		

LLSQ treatments yield

m-Nitro

$\Delta H^* = 17.963$ Kcal mol^{-1}.

$\Delta S^* = -23.291$ e.u. at 50°.

TABLE 64 : Activation Parameters for the Hydrolysis of Aryl-Substituted N-Aryl 4-Hydroxybutyramides in Aqueous Perchloric Acid (1.00M)

Substituent	$-E_A$ k cal	ΔH^* k cal.mol^{-1}.	$-\Delta S^*$ (50°) cal. deg.mol^{-1}.
H	18.716	18.074	18.074
p-Me	19.604	18.962	15.928
m-Me	18.793	18.151	17.952
p-MeO	19.418	18.776	17.274
m-MeO	17.975	17.333	20.071
p-Cl	19.128	18.486	16.506
m-Cl	17.759	17.117	20.416
p-Br	19.376	18.734	15.676
m-Br	19.004	18.362	16.603
p-NO_2	17.436	16.794	19.445
m-NO_2	18.027	17.385	19.145

TABLE 65 : Activation Parameters for the Hydrolysis of Aryl-Substituted N-Aryl 5-Hydroxyvaleramides in Aqueous Perchloric Acid (1.00M)

Substituent	$-E_A$ k.cal.	ΔH^* k.cal.mol^{-1}.	$-\Delta S^*(50^\circ)$ cal.deg^{-1}.mol^{-1}.
H	17.725	17.083	21.190
p-Me	18.345	17.703	19.694
m-Me	18.064	17.422	20.089
p-MeO	18.621	17.979	19.280
m-MeO	16.046	15.404	26.018
p-Cl	17.677	17.035	20.994
m-Cl	17.621	16.979	20.804
p-NO_2	16.295	15.654	23.336
m-NO_2	15.767		

TABLE 66 : Activation Parameters for the Hydrolysis of Aryl-Substituted N-Aryl n-Butyramides in Aqueous Perchloric Acid (1.00M)

Substituent	$-E_A$ k.cal.	ΔH^* k.cal.mol^{-1}.	$-\Delta S^*(50^\circ)$ cal.deg.$^{-1}$mol.$^{-1}$
H	20.352	19.709	19.302
m-Me	19.349	18.707	22.499
m-MeO			
m-Br	21.038	20.396	16.477
p-Br	13.236	—	—
m-NO_2	18.605	17.963	23.291

TABLE 66A : Calculated Rates of Hydrolysis of the Conjugate Acids of Butyranilide, 4-hydroxybutyranilide and 5-hydroxyvaleranilide in Perchloric Acid (1.00M).

Temperature °C	Butyranilide $-\log k_p^3$	4-hydroxy-butyranilide $-\log k_p^3$	5-hydroxy valeranilide $-\log k_p^3$
45.00°		2.5112	2.3046
50.00°	3.478	2.3271	2.1361
54.90°	3.147	2.1104	1.9429
60.00°	2.962	1.9501	1.7632
64.70°	2.779	1.7450	1.5807

LLSQ treatment of data yields:-

Butyranilide	4-hydroxybutyranilide	5-hydroxyvaleranilide	
ΔH_1^*:- 19.71 ;	18.36 ;	17.48 ;	k cal mol^{-1}
$-\Delta S_1^*$:- 13.12 ;	12.51 ;	14.36 ;	e.u. (50°)

TABLE 67 : The Rates of Hydrolysis of Aryl Substituted N-Aryl Butyramides in Perchloric Acid (1.00M) at 50.00°

Substituent	$10^5 k_{obs}$	$-\log k_{obs}$	σ
H	1.8868	4.7287	0.00
	1.8686	4.7241	0.00
m-Me	1.7898	4.7476	-0.069
	1.7886	4.7479	-0.069
m-MeO			0.115
			0.115
m-Br	2.6508	4.5768	0.391
	2.6933	4.5700	0.391
p-Br	2.4337	4.6140	0.232
	2.2910	4.6400	0.232
m-NO_2	3.8327	4.4163	0.710
	3.8272	4.4170	0.710

The ρ value for the hydrolysis of this series of amides in 1.00 M Perchloric Acid at 50° was determined by LLSQ treatment of the above data as 0.423 ± 0.012

TABLE 68 : The Rates of Hydrolysis of Aryl-Substituted N-Aryl 4-Hydroxybutyramides in Perchloric Acid(1.00M) at 50.00°.

Substituent	$10^3 k_{obs}$	$-\log k_{obs}$	σ^{123} ($^+$ or $^-$)
H	0.437	3.3591	0.00
	0.437		
p-Me	0.200	3.6988	-0.170
	0.200		($^+$: -0.310)
m-Me	0.432	3.3619	-0.069
	0.437		($^+$: -0.066)
p-MeO	0.254	3.6513	-0.268
	0.253		($^+$: -0.780)
	0.252		
m-MeO	0.517	3.2866	0.115
	0.515		($^+$: 0.047)
p-Cl	0.533	3.2866	0.226
	0.508		
m-Cl	0.605	3.2154	0.373
	0.612		
	0.609		
p-Br	0.542	3.2733	0.232
	0.521		
m-Br	0.597	3.2248	0.391
	0.595		
p-NO_2	1.630	2.7872	1.270 ($^-$)
	1.632		
m-NO_2	0.752	3.1244	0.710
	0.751		

LLSQ treatments of data gives $\rho = 0.48 \pm 0.04$

TABLE 69 : The Rates of Hydrolysis of Aryl-Substituted N-Aryl 5-Hydroxyvaleramides in Perchloric Acid (1.00M) at 50.00°

Substituent	$10^3 k_{obs}$	$-\log k_{obs}$	σ
H	0.434	3.3622	0.00
	0.436		
	0.428		
p-Me	0.346	3.3555	-0.170
	0.336		(σ^+: -0.310)
	0.330		
m-Me	0.446	3.3507	-0.069
	0.441		(σ^+: -0.066)
	0.448		
p-MeO	0.280	3.5508	-0.268
	0.283		(σ^+: -0.710)
m-MeO	0.549	3.2690	0.115
	0.514		
	0.552		
p-Cl	0.519	3.2870	0.226
	0.514		
m-Cl	0.616	3.2160	0.373
	0.604		
p-NO_2	1.382	2.8645	1.270(σ^-)
	1.535		
m-NO_2			0.710

LLSQ treatment of data gives $\rho = 0.32 \pm 0.03$

TABLE 70 : The Rates of Hydrolysis of Aryl Substituted N-Aryl 4-Hydroxybutyramides in Perchloric Acid (1.00M) at 50.00°

Substituent	$10^4 k_{obs}$	$-\log k_{obs}$	σ^-
H	1.20	3.9191	0.00
p-Me	0.747	4.1221	-0.170
	0.763		
m-Me	0.947	4.0238	-0.069
p-MeO	0.550	4.2580	-0.268
m-MeO	2.110	3.6970	0.115
	1.910		
p-Cl	1.678	3.7305	0.226
	1.800		
	2.090		
m-Cl	3.480	3.4291	0.373
	3.960		
p-Br	2.300	3.6403	0.232
	2.270		
m-Br	3.150	3.5045	0.391
	3.110		
p-NO_2	50.390	2.3089	1.270
	47.810		
m-NO_2	10.070	3.0031	0.710
	9.790		

LLSQ treatment of data gives $\rho = 1.26 \pm 0.04$

TABLE 71 : The Rates of Hydrolysis of Aryl-Substituted N-Aryl 5-Hydroxyvaleramides in Perchloric Acid (9.00M) at 50.00°

Substituent	$10^4 k_{obs}(s^{-1})$	-log k_{obs}	σ
H	4.41	3.5410	0.0
	4.39		
p-Me	0.500	4.3512	-0.170
	0.490		
m-Me	1.110	3.9621	-0.069
	1.060		
p-MeO	0.360	4.452	-0.268
	0.370		
	0.330		
m-MeO	1.660	3.3484	0.115
	1.930		
	1.760		
p-Cl	1.850	3.7300	0.226
	1.860		
	1.880		
m-Cl	3.360	3.4740	0.373
	3.360		
p-NO_2	48.990	2.2960	1.270
	52.150		
m-NO_2	10.570	2.976	.0710
	10.650		

LLSQ treatment of data gives $\rho = 1.34 \pm 0.14$

TABLE 72 : Derived Thermodynamic Dissociation Constants of the Conjugate Acids of Aryl Substituted N-Aryl 4-Hydroxybutyramides at 50°.

Substituent	log K_{AH^+}	σ
H	1.022	0.00
p-Me	1.145	-0.170
m-Me	1.208	-0.069
p-MeO	1.204	-0.268
m-MeO	1.144	0.115
p-Cl	1.458	0.226
m-Cl	1.441	0.373
p-Br	1.502	0.232
m-Br	1.390	0.391
p-NO_2	2.240	1.270
m-NO_2	1.638	0.710

LLSQ treatment of data gives $\rho = 0.71 \pm 0.09$

TABLE 73 : Derived Thermodynamic Dissociation Constants of the Conjugate Acids of Aryl-Substituted N-Aryl 5-Hydroxy-valeramides at 50^{0}.

Substituent	$\log \cdot K_{AH^+}$	σ^-
H	1.230	0.00
p-Me	1.440	-0.170
m-Me	1.338	-0.069
p-MeO	1.150	-0.268
m-MeO	1.095	0.115
p-Cl	1.426	0.226
m-Cl	1.113	0.373
p-Br	1.512	0.232
p-NO_2	2.020	1.270
m-NO_2	1.638	0.710

LLSQ treatment of data gives $= 0.50 \pm 0.14$

Table 74 : Determination of ρ values for the Hydrolysis of the Conjugate Acids of Aryl Substituted 4-Hydroxybutyranilides in Perchloric Acid Solutions at 50° from derived log kp^3 values.

Substituent	-log kp^3 at Acid Molarity M			σ
	1M	5M	9M	
H	2.325	2.558	3.915	0.00
p-Me	2.324	2.719	4.116	-0.170
m-Me	2.156	2.557	4.017	-0.069
p-MeO	2.449	2.866	4.258	-0.268
m-MeO	2.140	2.347	3.691	0.115
p-Cl	1.843	2.272	3.718	0.226
m-Cl	1.788	2.155	3.417	0.373
p-Br	1.787	2.207	3.626	0.232
m-Br	1.846	2.146	3.495	0.391
p-NO_2	0.575	0.978	2.239	1.27
m-NO_2	1.504	1.846	2.984	0.710

The derived ρ values were as follows:

1M : 1.17 ±0.08

5M : 1.16 ±0.05

9M : 1.30 ±0.04

TABLE 75 Rates of Initial Change of Endo Cis 2-(N-Phenylcarbonamide), 3-Hydroxymethyl Norbornane (A) and the Secondary Change of Endo Cis 2-(N-Phenylcarbonamide) 6-Hydroxy-norbornane (B) in Perchloric Acid Solutions at 50°.

Acid Molarity	A $10^3 k_{obs} s^{-1}$	B $10^3 k_{obs} s^{-1}$
1.0	6.629	1.852
	7.045	1.840
2.0	18.056	0.923
	18.502	0.924
3.0	35.344	0.492
	36.305	0.494
	35.233	

TABLE 76 Rates of Initial Changes of Endo Cis 2-(N-Phenyl Carbonamide), 3-Hydroxymethyl (A) and 2(N-Phenylcarbonamide) 6-Hydroxy Norbornane (B) and 4-Hydroxy Cis Crotonanilide (C) in Aqueous Perchloric Acid Solutions at 25°C.

Acid Molarity	A $10^3 k_{obs} S^{-1}$	B $10^3 k_{obs} S^{-1}$	C $10^3 k_{obs} S^{-1}$
1.0	0.519	99.66	1.767
	0.540	98.01	1.783
2.0		212.21	4.117
		216.69	4.099
3.0	2.753	291.55	6.889
	2.916		
4.0	5.497	342.62	9.901
	5.267	336.40	9.928
5.0		291.29	10.345
		285.33	10.381
6.0		173.16	6.706
		161.40	6.898
7.5		51.38	1.827
		53.67	1.757
9.0		9.85	0.257
		9.81	0.252

TABLE 77 Rates of Initial Changes of Endo Cis 2-(N-Phenylcarbonamide 3-Hydroxymethyl Norbornane (A), Endo Cis 2-(N-Phenylcarbonamide) 6-Hydroxy Norbornane (B) at several temperatures in 1.0 M Perchloric Acid.

Temperature	A		B	
	$10^3 k_{obs} s^{-1}$	$-\log k_{obs}$	$10^3 k_{obs} s^{-1}$	$-\log k_{obs}$
25°	0.519	3.2855	99.66	1.0014
	0.540	3.2682	98.01	1.0088
30°	0.947	3.0235	145.00	0.8386
	1.108	2.9558	144.23	0.8416
50°	6.630	2.1792		
	7.045	2.1530		
60°	15.565	1.8084		
	10.054	1.8228		

	A		B
ΔH^* k cal mol^{-1} :	18.17	;	13.11
$-\Delta S^*$ e.u. (25°) :	12.57	;	19.14

TABLE 78 Rates of Initial Changes of 4-Hydroxy Cis Crotonanilide at several Temperatures in 1.0 M Perchloric Acid.

Temperature	$10^3 k_{obs}$ s^{-1}	$-\log k_{obs}$
25°	1.767	2.7531
	1.783	2.7490
30°		
50°	30.817	1.5104
	30.326	1.5181
60°	35.715	1.4471
	36.469	1.4381

$\triangle H^*$ k cal mol^{-1}	:	17.08
$-\triangle S^*$ e.u. (25°)	:	13.82

TABLE 79 Rates of Secondary Changes of Endo Cis 2-(N-Phenyl-carbonamide) 3-Hydroxymethyl Norbornane (A), Endo Cis 2-(N-Phenylcarbonamide) 6-Hydroxy Norbornane (B) and 4-Hydroxy Cis Crotonanilide (C) in 1.0 Molar Perchloric Acid at several Temperatures.

Temperature	A $10^4 k_{obs} s^{-1}$	A $-\log k_{obs}$	B $10^4 k_{obs} s^{-1}$	B $-\log k_{obs}$	C $10^4 k_{obs} s^{-1}$	C $-\log k_{obs}$
25°			2.037	3.692		
			2.074	3.684		
30°			3.006	3.522		
50°			1.852	2.732		
			1.840	2.735		
60°	0.261	4.583	3.407	2.468	1.066	2.972
	0.235	4.628	3.673	2.436		

	B
ΔH^* k cal mol^{-1} :	15.73 ;
$-\Delta S^*$ e.u. (25°) :	22.61 ;

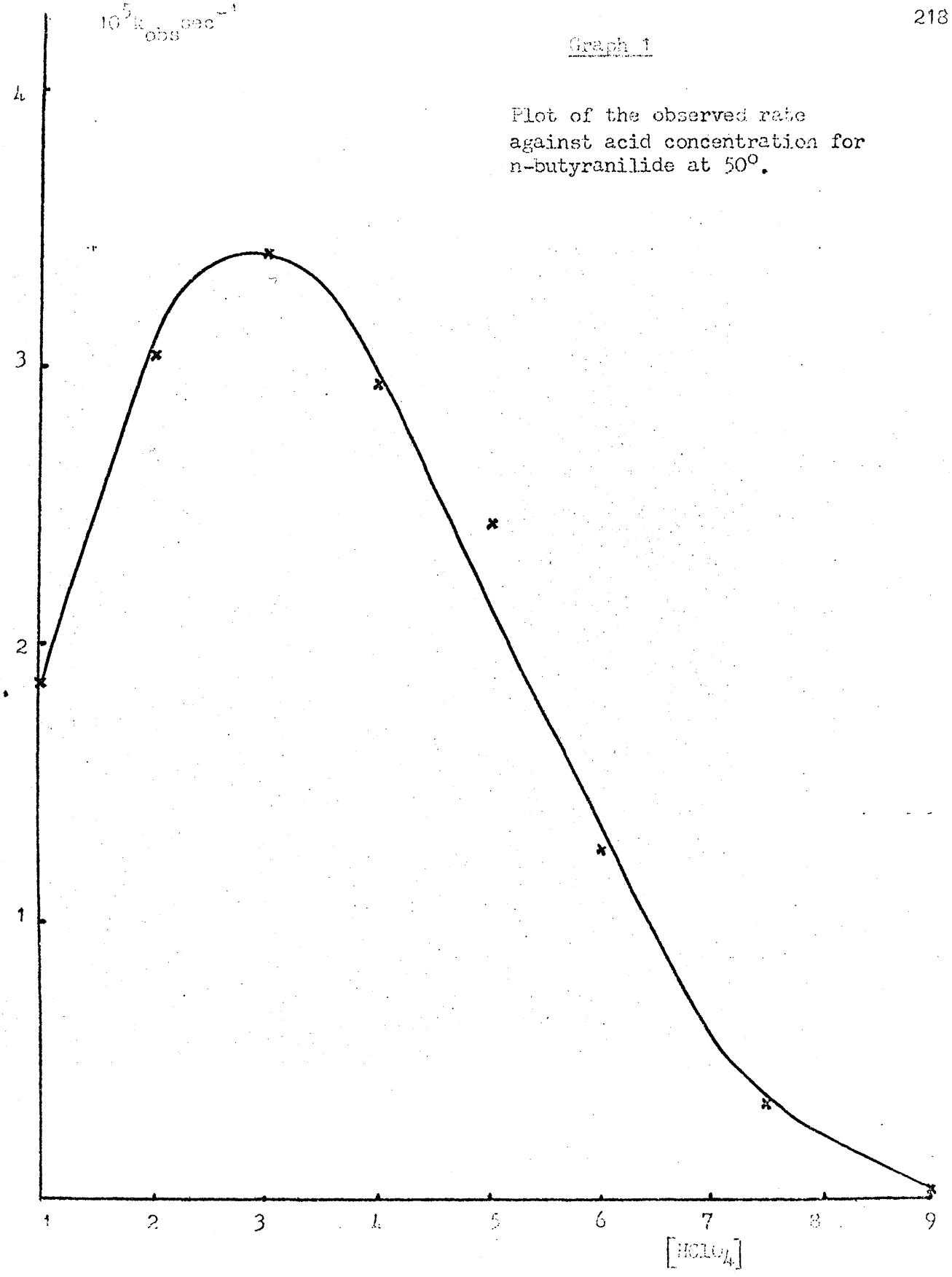
TABLE 80 Activation Parameters for the Initial (I) and Secondary (II) Changes Observed in the Hydrolysis of Endo Cis 2-(N-Phenylcarbonamide) 3-Hydroxymethyl Norbornane (A), Endo Cis 2-(N-Phenylcarbonamide) 6-Hydroxy Norbornane (B) and 4-Hydroxy Cis Crotonanilide (C) in 1 M Perchloric Acid Solutions.

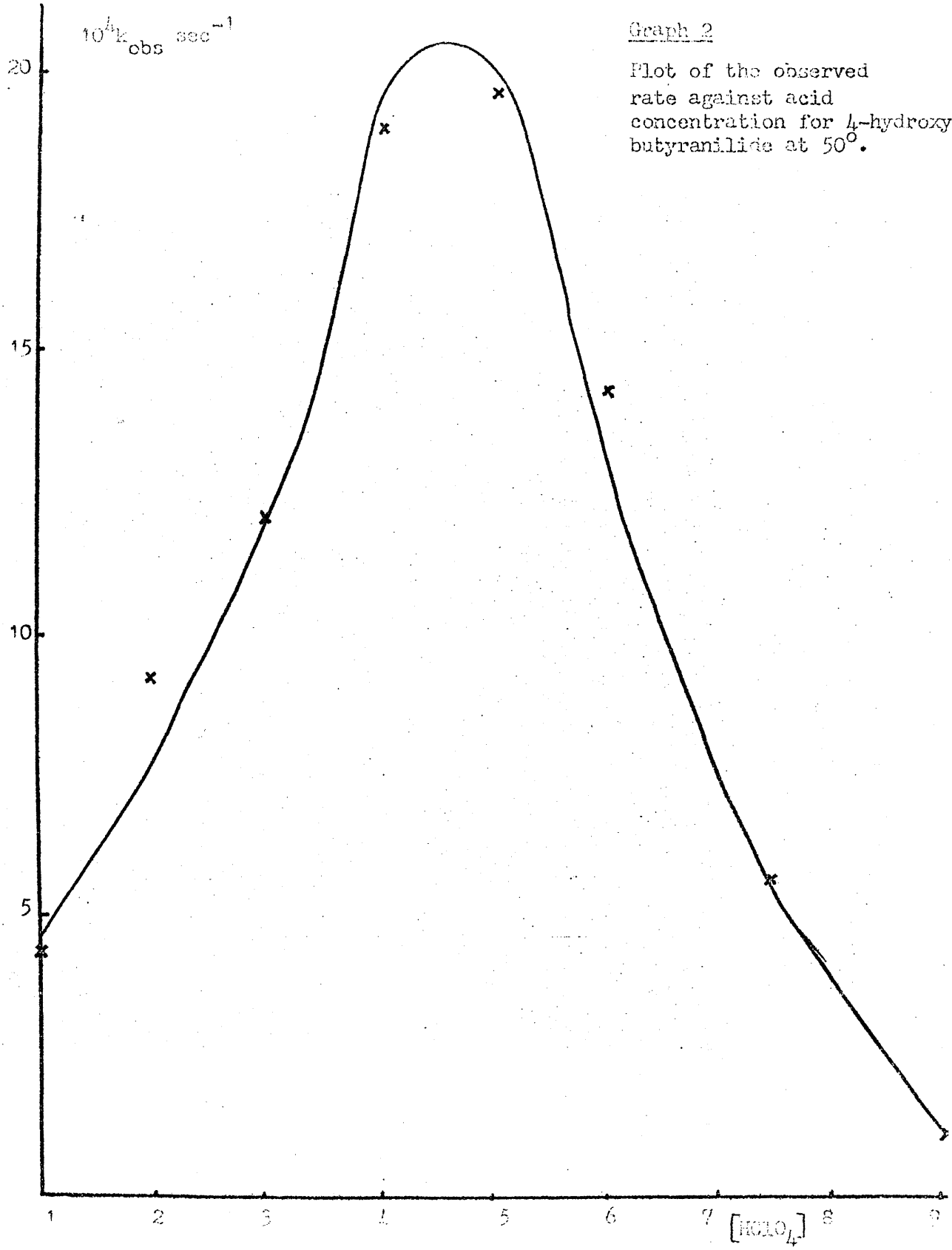
Compound and Change	$-E_A$ k cals	ΔH^* k cal mol^{-1}	ΔS^* cal deg^{-1} mol^{-1}
A I	18.76	18.17	-12.57(25°)
A II			
B I	13.70	13.11	-19.14(25°)
B II	16.32	15.73	-22.61(25°)
C I	17.67	17.08	-13.82(25°)

GRAPHS

Graph 1

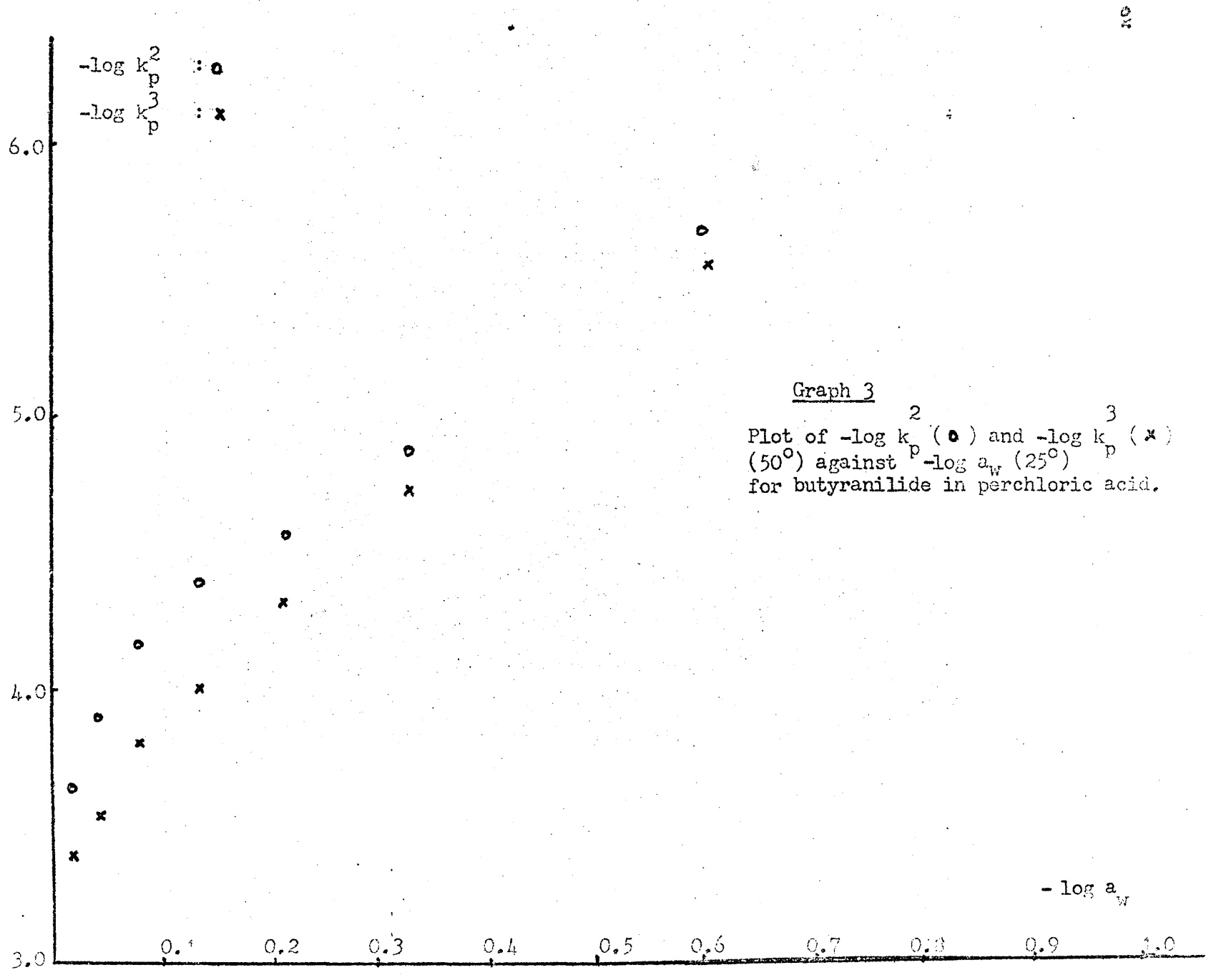
Plot of the observed rate against acid concentration for n-butyranilide at 50°.





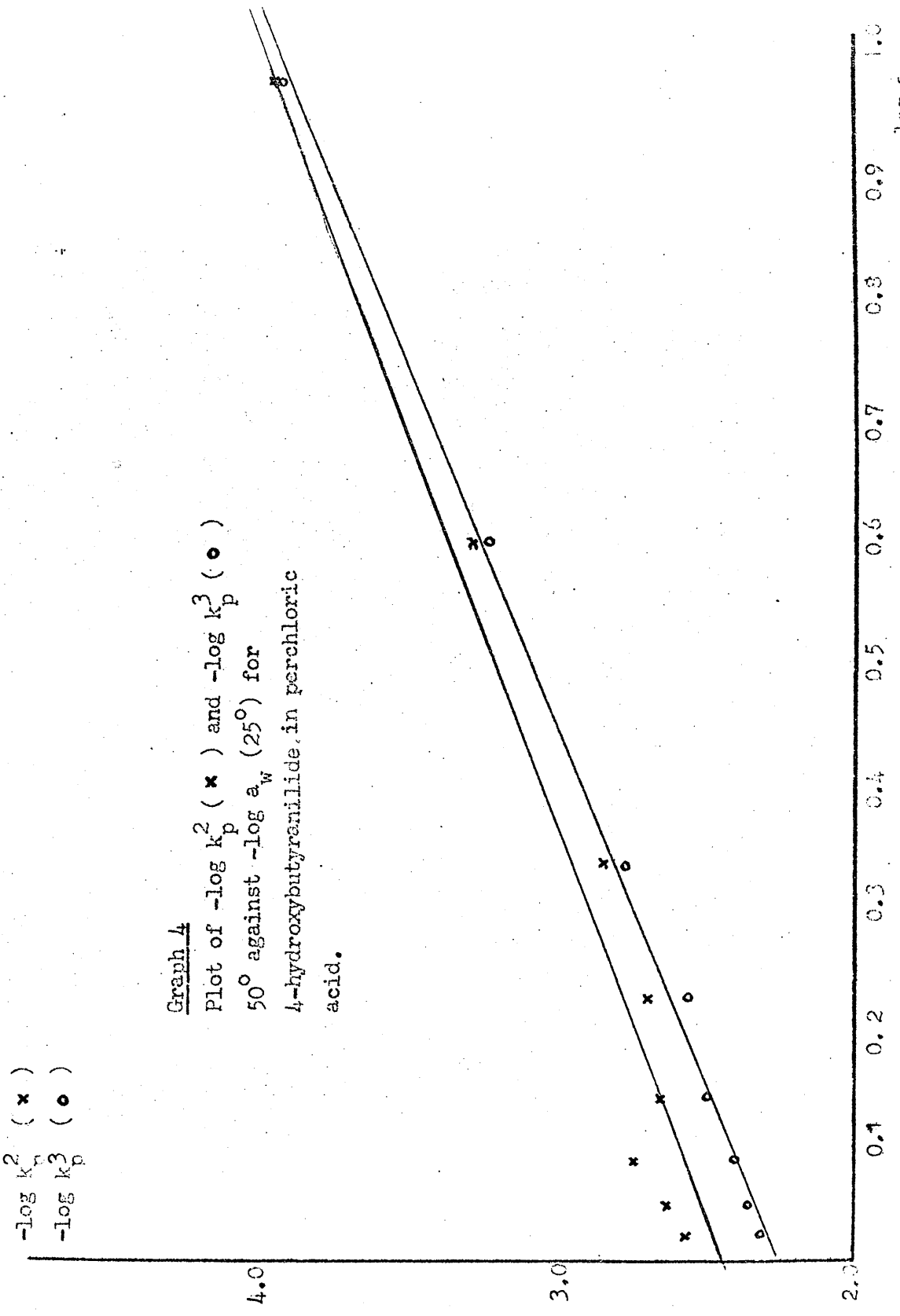
Graph 2

Plot of the observed rate against acid concentration for 4-hydroxy butyranilide at 50°.



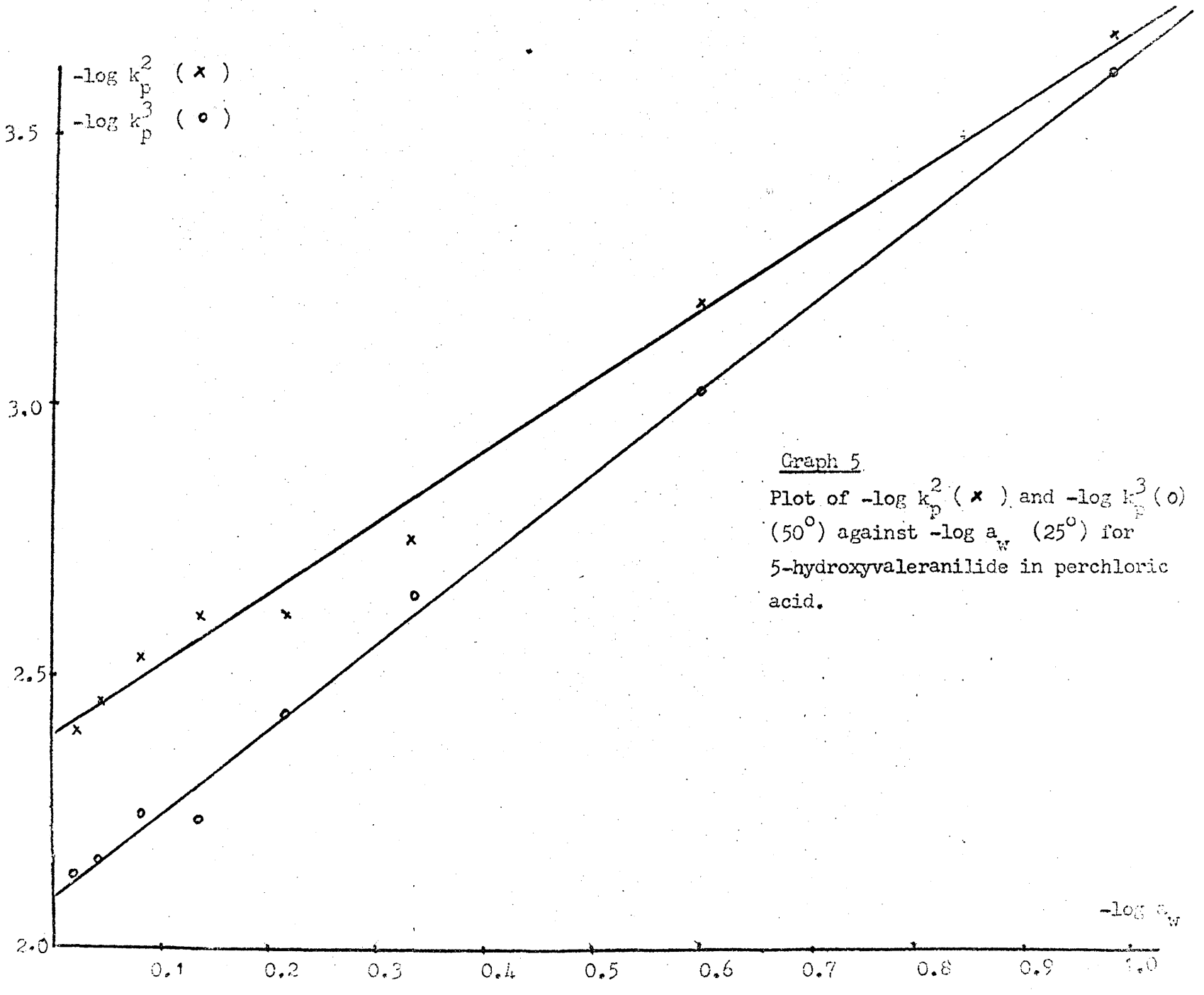
Graph 3

Plot of $-\log k_p^2$ (o) and $-\log k_p^3$ (x) (50°) against $-\log a_w$ (25°) for butyranilide in perchloric acid.



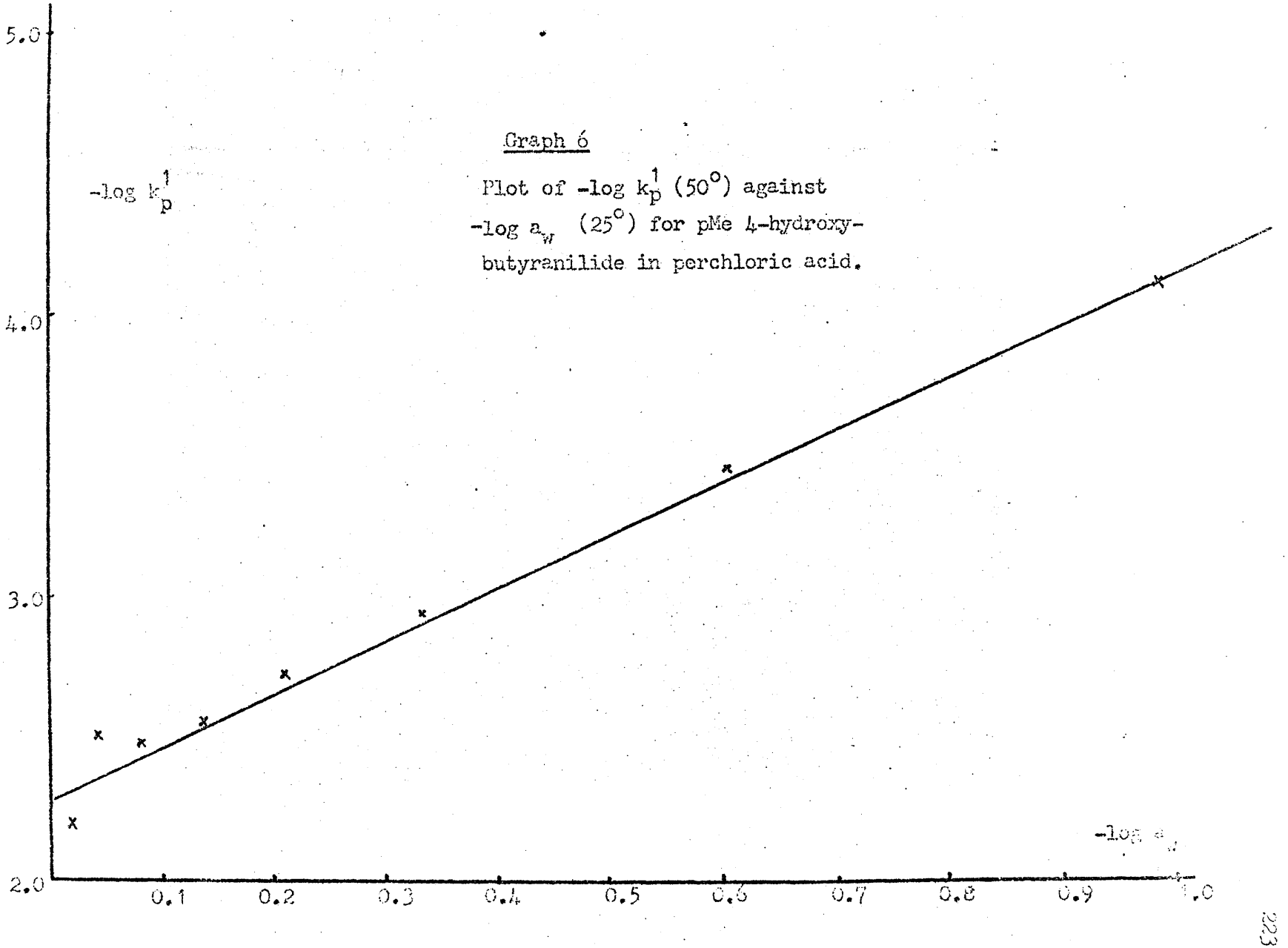
Graph 4

Plot of -log k_p^2 (×) and -log k_p^3 (o) 50° against -log a_w (25°) for 4-hydroxybutyranilide in perchloric acid.



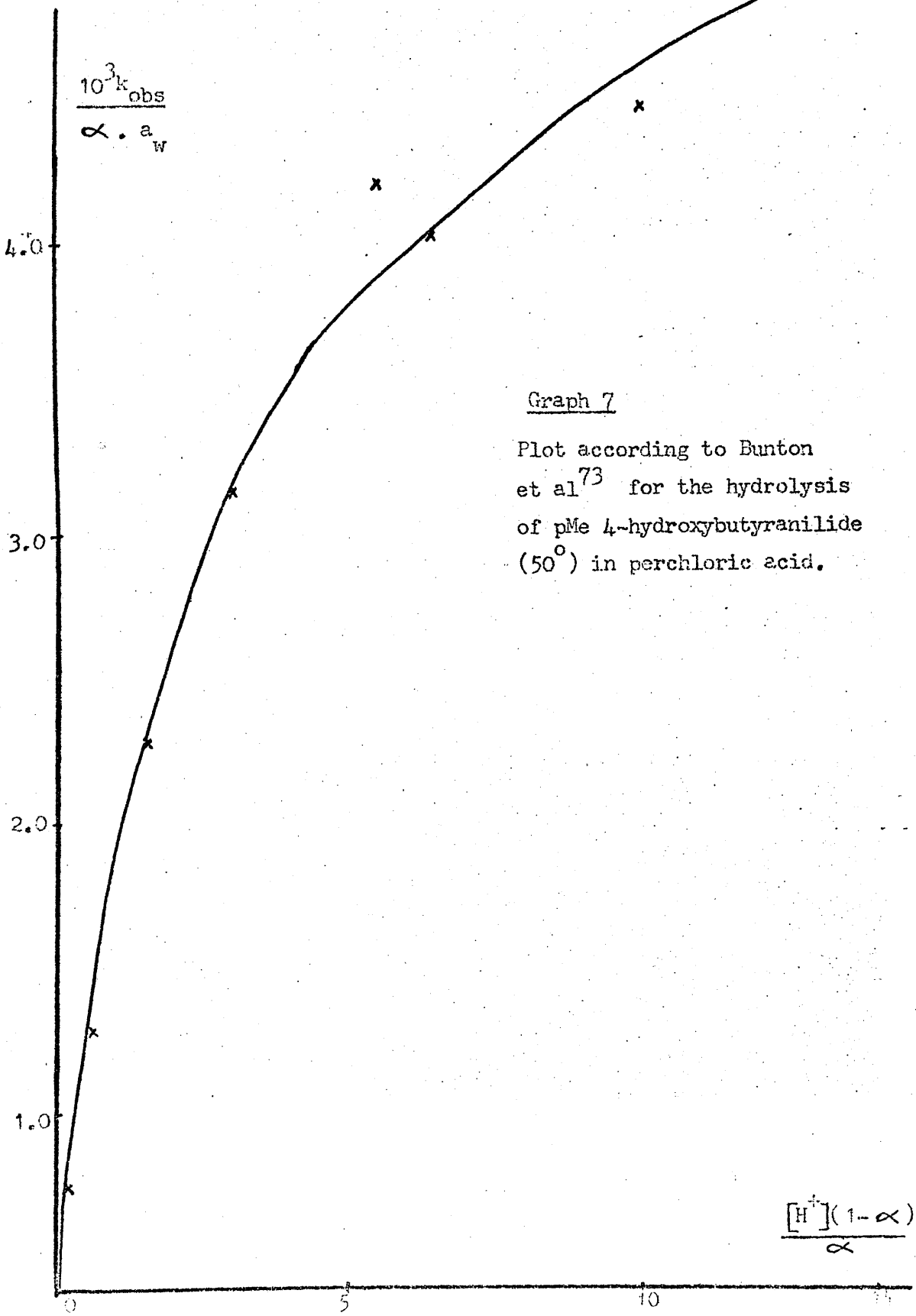
Graph 5

Plot of -log k_p^2 (×) and -log k_p^3 (o) (50°) against -log a_w (25°) for 5-hydroxyvaleranilide in perchloric acid.



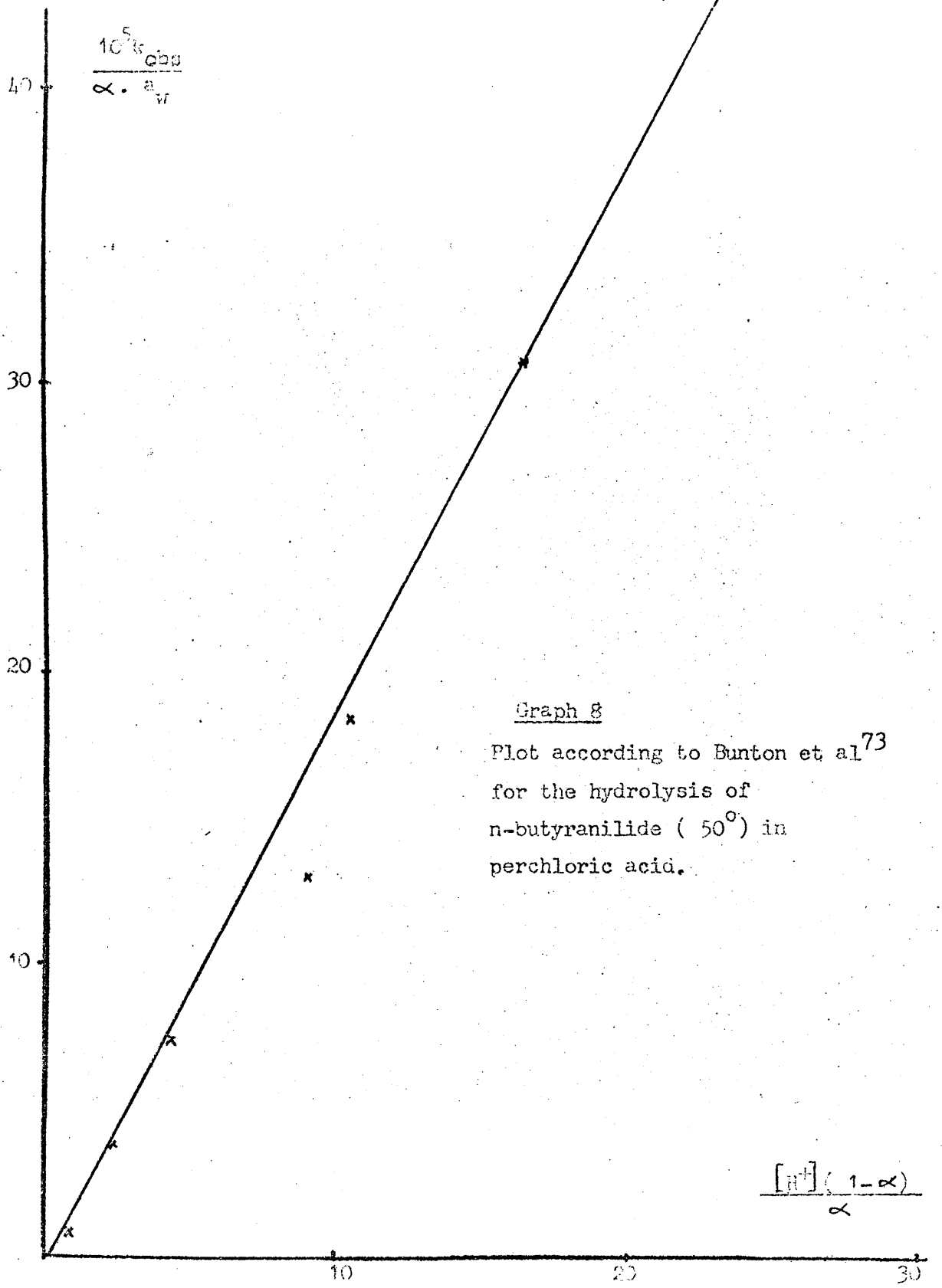
Graph 6

Plot of $-\log k_p^1$ (50°) against $-\log a_w$ (25°) for pMe 4-hydroxybutyranilide in perchloric acid.



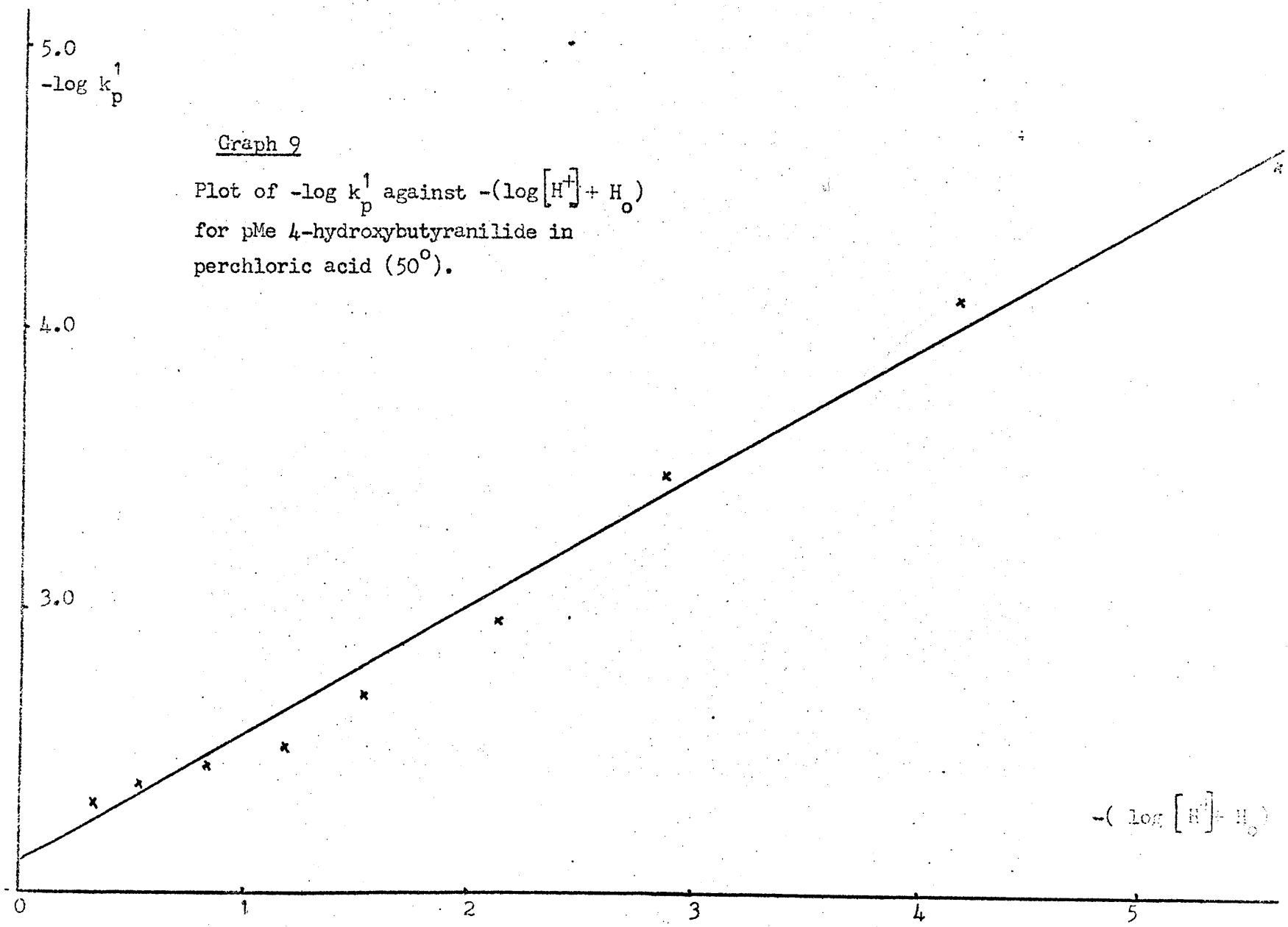
Graph 7

Plot according to Bunton et al[73] for the hydrolysis of pMe 4-hydroxybutyranilide (50°) in perchloric acid.



Graph 8

Plot according to Bunton et al[73] for the hydrolysis of n-butyranilide (50°) in perchloric acid.

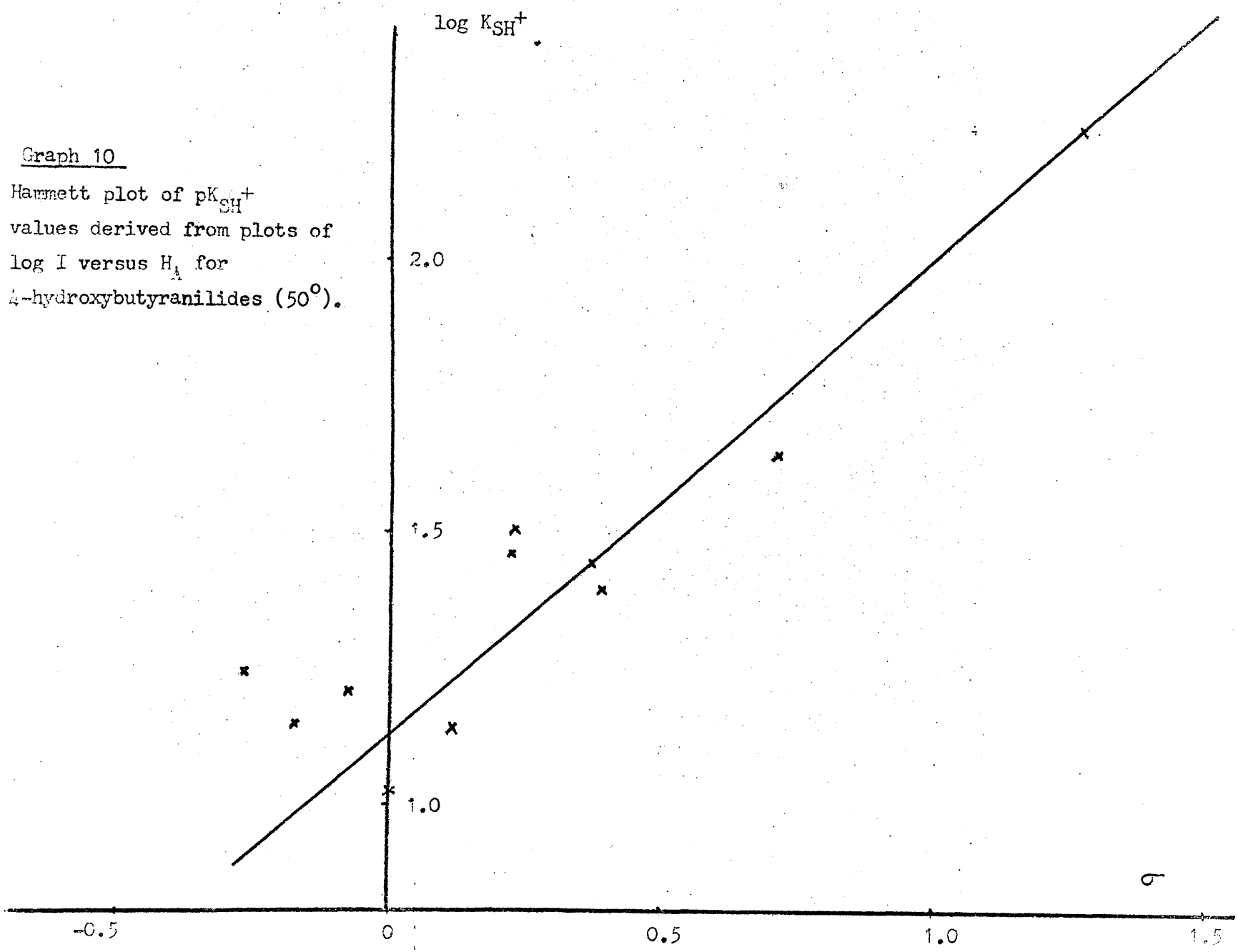


Graph 9

Plot of $-\log k_p^1$ against $-(\log[H^+] + H_o)$ for pMe 4-hydroxybutyranilide in perchloric acid (50^o).

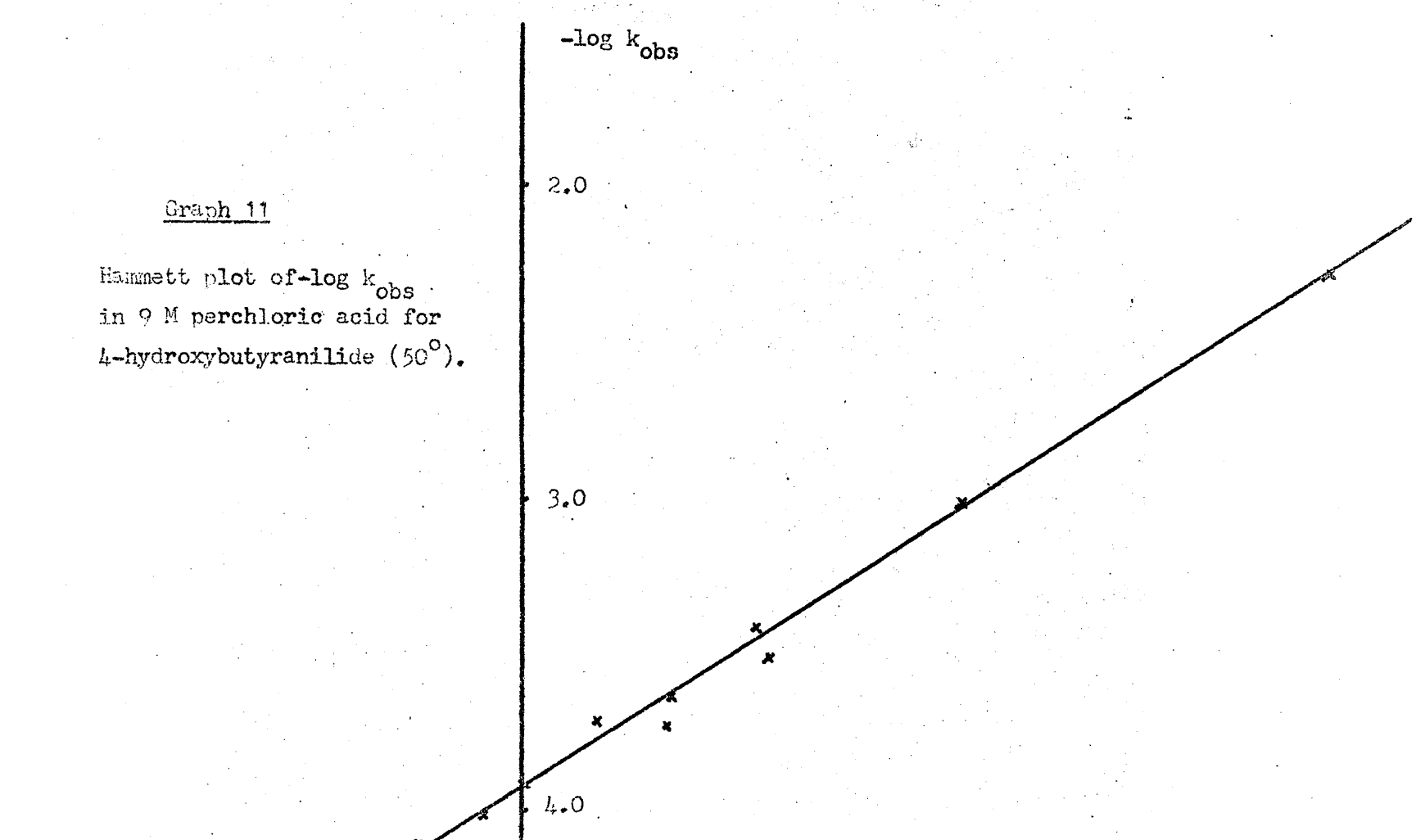
Graph 10

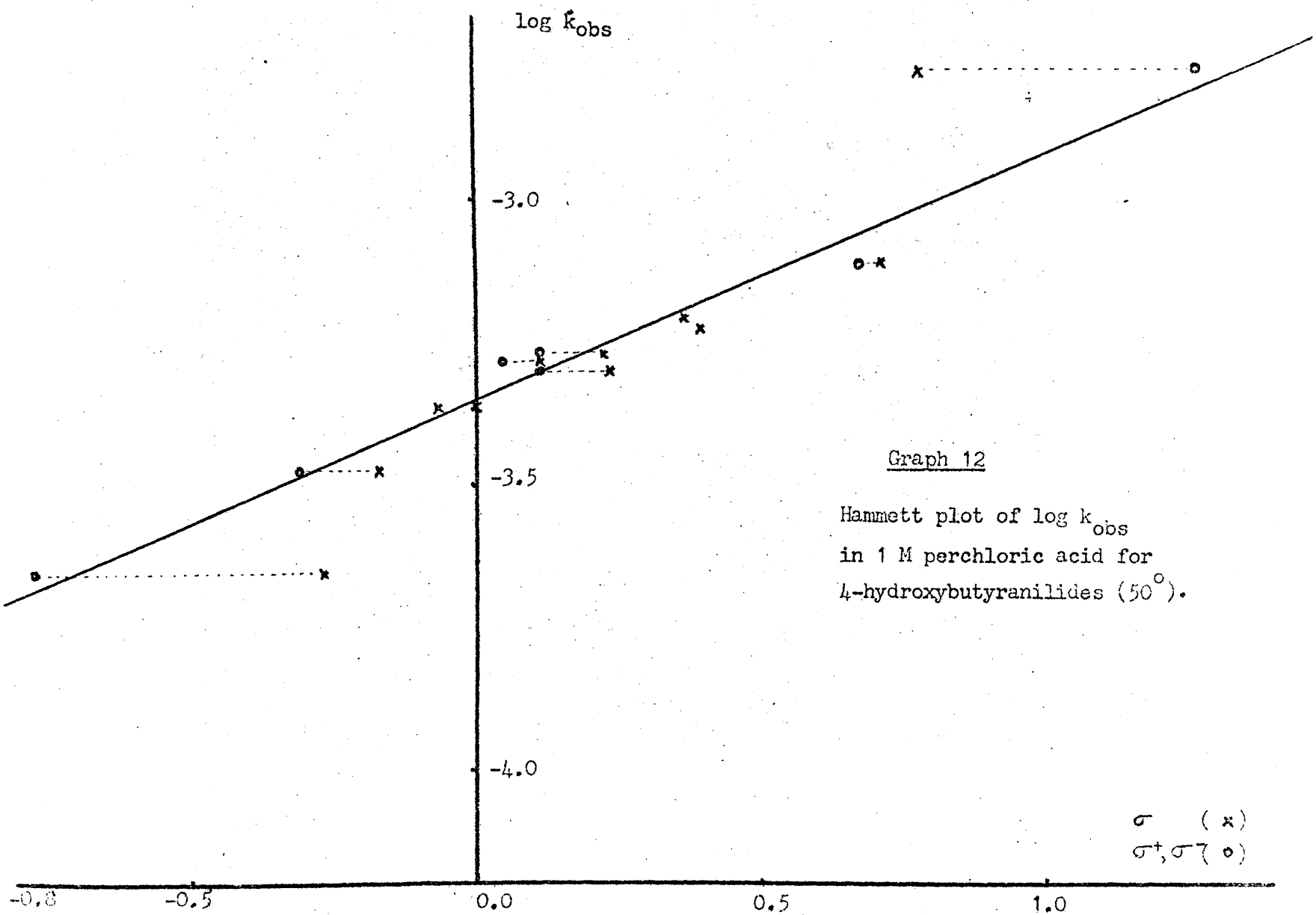
Hammett plot of pK_{SH^+} values derived from plots of log I versus H_A for 4-hydroxybutyranilides (50°).



Graph 11

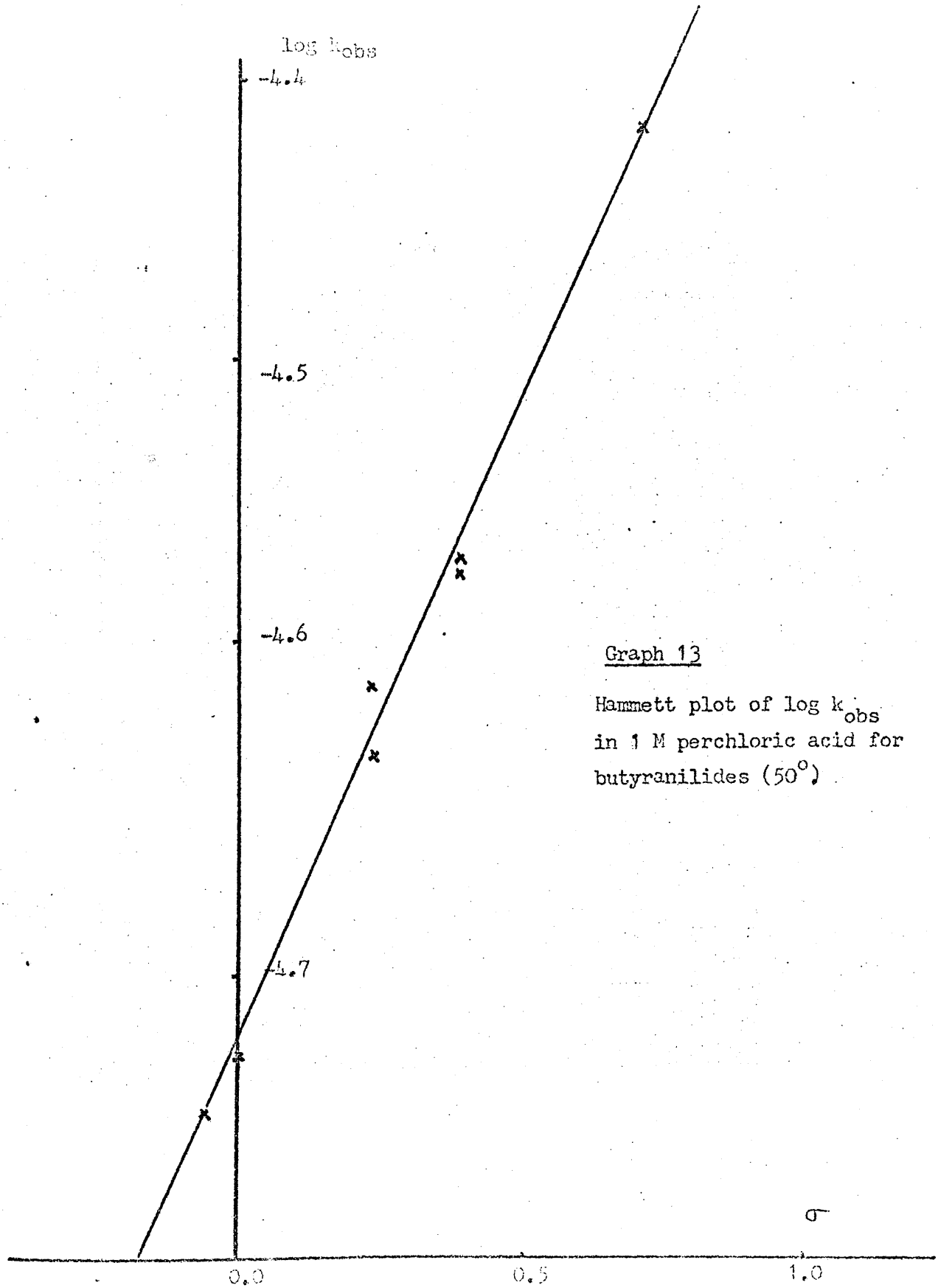
Hammett plot of -log k_{obs} in 9 M perchloric acid for 4-hydroxybutyranilide (50°).





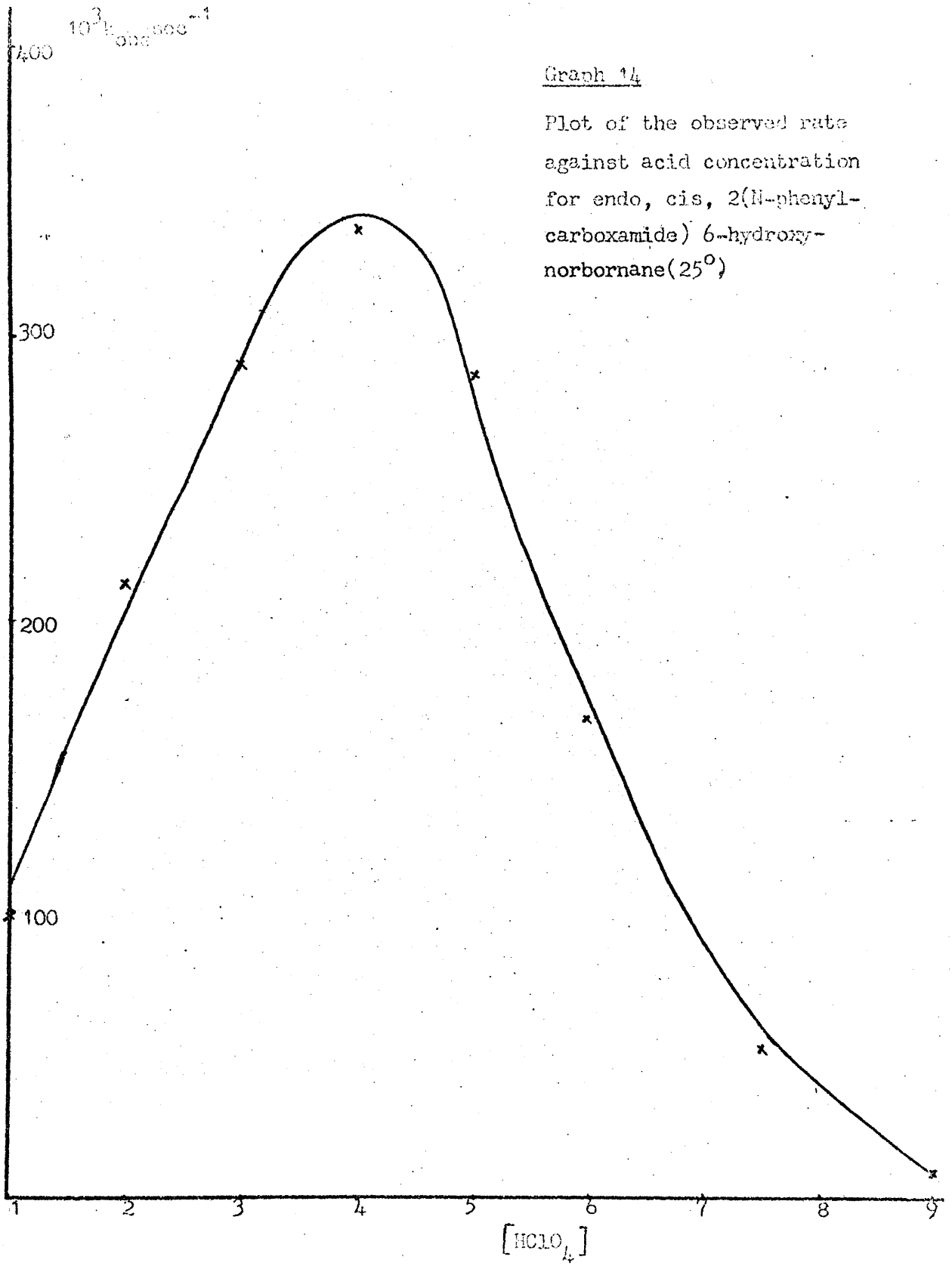
Graph 12

Hammett plot of log k_{obs} in 1 M perchloric acid for 4-hydroxybutyranilides (50°).



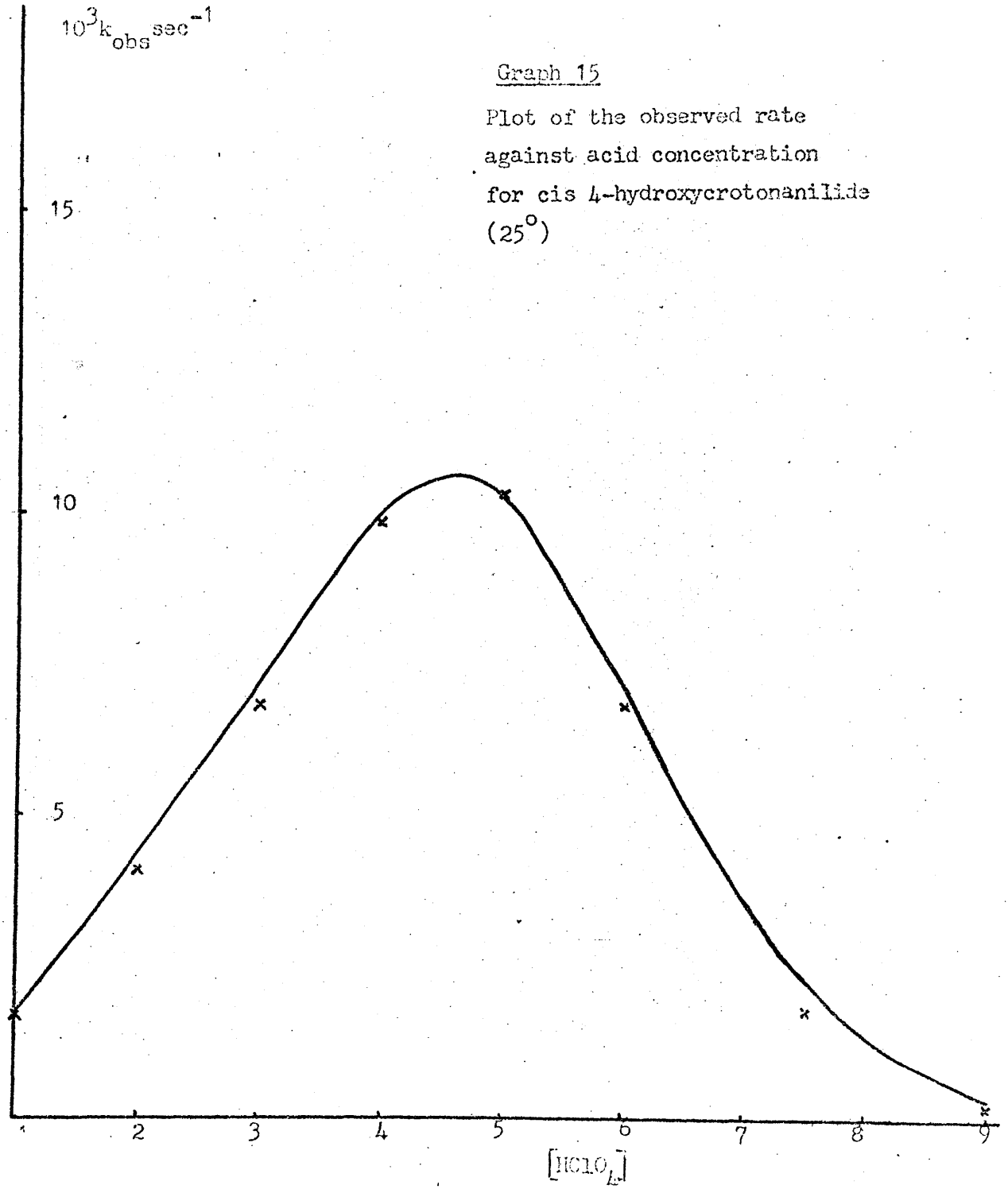
Graph 13

Hammett plot of log k_{obs} in 1 M perchloric acid for butyranilides (50°)



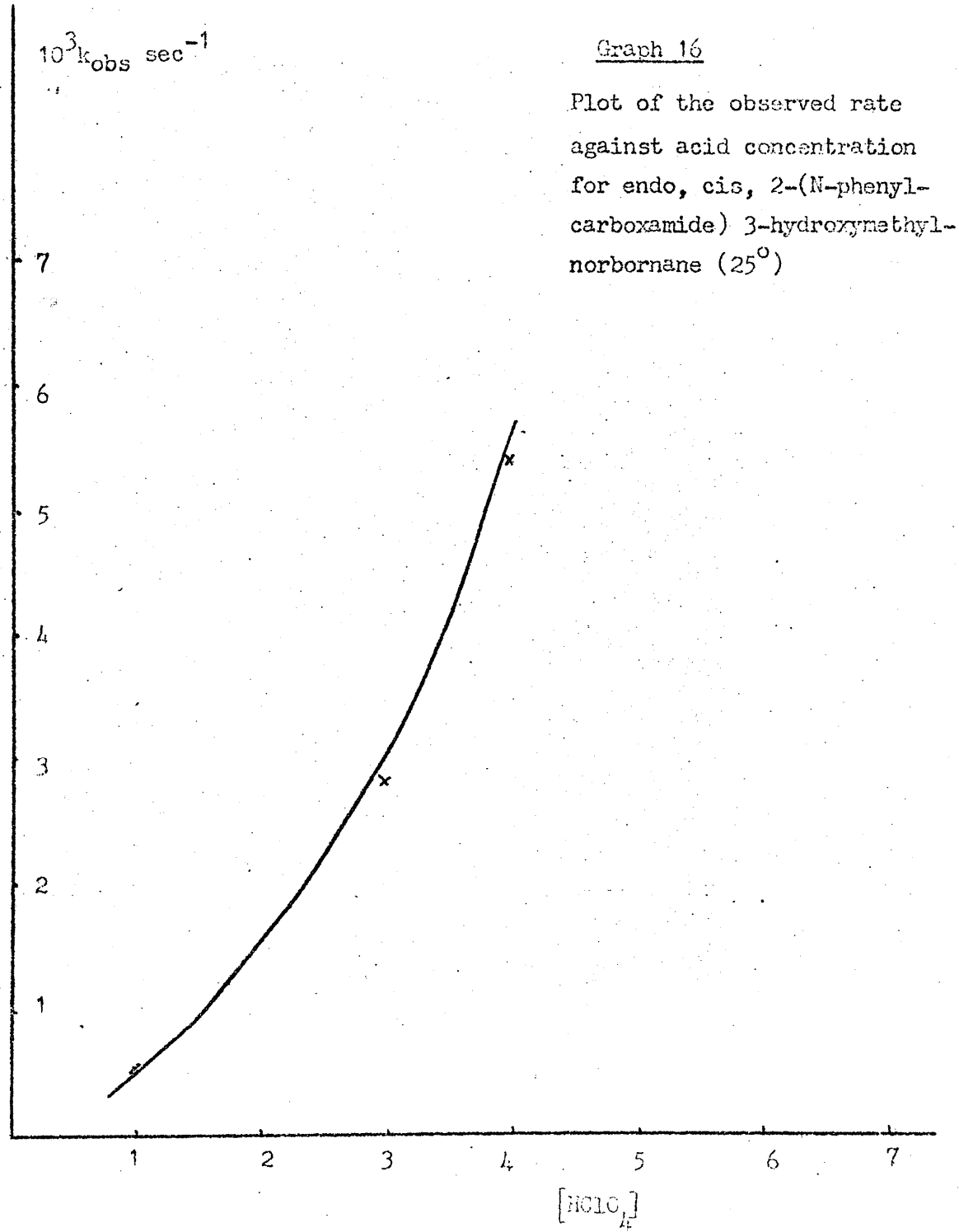
Graph 14

Plot of the observed rate against acid concentration for endo, cis, 2(N-phenyl-carboxamide) 6-hydroxy-norbornane(25°)



Graph 15

Plot of the observed rate against acid concentration for cis 4-hydroxycrotonanilide (25°)



Graph 16

Plot of the observed rate against acid concentration for endo, cis, 2-(N-phenyl-carboxamide) 3-hydroxymethyl-norbornane (25°)

DISCUSSION

The Acid Catalysed Hydrolysis of Anilides

The hydrolysis of a series of substituted anilides of 4-hydroxybutyric acid, 5-hydroxyvaleric acid and n-butyric acid in moderately concentrated perchloric acid solutions at 50° have been studied in order to observe the effect of an adjacent hydroxyl group, suitably situated for intramolecular participation, upon the characteristics of amide hydrolysis under such conditions.

The effects of increasing the acid concentration, from 1 Molar to 9 Molar, upon the observed rate constants of the anilides are listed in tables 27, 28 to 39 and 39 to 48 respectively. From this data it is observed that these anilides exhibit a maximum in the plot of rate against acidity, a feature observed for all amides.

A comparison of the observed rate constant for butyranilide at 50°in 1 M perchloric acid with the observed rate constants for 4-hydroxybutyranilide and 5-hydroxyvaleranilide under the same conditions yields the following relative rate ratio :-

1 : 23.3 : 23.2

This compares with the relative rate ratio determined by Zurn[9]

for the hydrolysis of n-butyramide, 4-hydroxybutyramide and 5-hydroxy-valeramide at 30° in hydrochloric acid:-

1 : 17.7 : 46

This notably different ratio determined for these anilides in comparison with analogous amides is maintained throughout the whole series of substituents and will be discussed later.

The A2 Mechanism

On the basis of the A2 reaction scheme, Edward and Meacock[61c] and Martin[124] derived semi quantitative relationships which describe the effect of increasing acid concentration upon the observed rate constant. Whereas an expression for the observed rate constant derived by application of the steady state principle to a hydrolysis step intermediate would predict an initial slope then a plateau, these relationships predict a maximum in the plot of observed rate versus acidity, the position of the maximum being determined by the opposing effects of increasing acid concentration, decreasing acidity and the magnitude of the equilibrium constant for dissociation of the protonated amide. On this basis and on premise that the intramolecular hydroxyl group acts as a nucleophile or in some other way performs the function of a water molecule which would normally be required in non-hydroxylated anilides to promote the formation of the transition state, it is reasonable to assume that the effect of decreasing acidity will be less significant in the hydrolysis of the hydroxyanilides compared with the intermolecular reaction.

The above premise is substantiated by the observation that the maxima for butyranilide and the unsubstituted hydroxybutyranilides occur at 2.8 Molar and 4.5 Molar $HClO_4$ respectively (graphs 1 and 2). Since $pK_{SH}+$ values are approximately equivalent (1.36, 1.02 and 1.23 respectively) and all other factors are equal, and since it is observed that the ratio for the hydrolysis rates of the protonated anilides, 4-hydroxybutyranilide and butyranilide, increases as acid concentration increases (12.3 to 1 in 1 Molar, 60.2 to 1 in 5 Molar 327 to 1 in 9 Molar perchloric acid from k_p^3 values, (tables 27 and 28) it is obvious that the presence of a constant concentration of potential nucleophile becomes increasingly important as the concentration of water decreases.

The Protonation Pre - equilibrium.

Based on the A2 mechanism, the rate of the slow step in amide hydrolysis depends upon the concentration of protonated amide present, this concentration dependimg upon the acid concentration and the dissociation constant of the amide conjugate acid, $K_{SH}+$.

Methods for determining $K_{SH}+$ for any amide depend initially upon an estimation of the ionization ratio I, which in turn depends upon a determination of the amounts of protonated and unprotonated amide in any acid solution. The method of determining these concentrations is described in the kinetic experimental section.

The method of Stewart and Granger[111] was used in the

determination of I from the plot of ϵ against H_A. This method attempts to eliminate or minimize medium effects by making an arbitrary choice of ϵ_B and ϵ_{BH^+} approximately $\pm$1.5 log units on the H_A scale, relative to the estimated point of inflection. If no spectral shifts are produced by the solvent, errors of approximately 3% can be introduced by this method but this arbitrary choice of limits generally falls close to the graphical values and so was employed.

The largest source of error in determination of I values is probably the observetion of ϵ values at intermediate acidities (5M $\pm$2M) perchloric acid solutions. In these solutions, at 50°, the hydrolysis of hydroxyanilides with electron withdrawing substituents becomes quite rapid and could have been a fertile source of error had the rapid observation technique described previously not been employed. Even this technique was not sufficient however to deal with the rate of hydrolysis of some of the anilides and a rather approximate graphical estimation of the extinction coefficient of the species at time zero had to be employed which was probably accurate to $\pm$5%.

The extinction coefficients, the ionization ratios I and the logarithm of I for each anilide in a series of perchloric acid solutions are displayed in tables 3 to 24.

As described in the introduction a plot of log I versus H_o, if linear with unit negative slope, will indicate that the

substrate behaves as a Hammett base over the range of acid used.

When this test was applied to the log I values determined for eleven aryl substituted 4-hydroxybutyranilides, ten aryl substituted 5-hydroxyvaleranilides and n-butyranilide, the plots, although linear, had negative slopes whose magnitudes ranged between 0.45 and 0.73, the negative slope for butyranilide being 0.612 ± 0.032 (tables 25 and 3 respectively). Thus none of the anilides studied approximated to the criteria required in order that their protonation in perchloric acid solutions could be described by H_o thus indicating a differing effect of the changing medium on the activity coefficient ratios of the substrate and of the bases used to define the acidity function.

When similar correlations of log I were performed with the H_A function for perchloric acid solutions[120] linear plots were generally obtained with thirteen out of twenty one hydroxyanilides having negative slopes in the range 0.90 to 1.10. This correlation when performed for butyranilides gave a linear plot of slope -0.999.

Thus, although a few widely varying results were obtained, the activity coefficient ratio implicit in this correlation,

i.e. $\dfrac{f_A \cdot f_{BH^+}}{f_{AH^+} \cdot f_B}$ (where B and BH^+ represent the amide bases used to construct the H_A function) obviously approximates much more closely to unity than the previous ratio. The

resultant slopes of these correlations are listed in tables 26 and 3.

Aromatic amides have been found to be adequately described in their protonation equilibria by the H_A function whereas alkyl carboxamides such as propionamide have not[55] and it seems likely that changes in activity coefficient behaviour must contribute largely to the observed deviation.

The structure of the base types being implicitly compared in these correlations has been recognised as being of great significance.[55] Thus, in the case in hand, it would seem that anilides approximate more closely in the behaviour of their activity coefficients in a changing medium to the activity function behaviour of the aromatic amides used to define the acidity function H_A than does the activity function behaviour of alkylcarboxamides.

It therefore follows that the protonation equilibria of anilides can be more adequately decribed by an acidity function based upon aromatic amides.

Treatment of Data from Strong Acid Kinetics

The rate and protonation data obtained by studies of n-butyranilide, aryl substituted 4-hydroxybutyranilides and aryl substituted 5-hydroxyvaleranilides in aqueous perchloric acid solutions was used to correlate the observed rate constants for acid-catalysed hydrolysis of the above anilides with measured water activity data according to the methods of Bunnett[46], Bunnett and Olsen[57], Moodie et al[49], Bunton et al[73] and Yates et al[60].

Bunnett's Hydration Parameter Treatment

It has been mentioned previously that ω and ω^* values derived by application of this treatment to the reaction of organic bases in concentrated acid solutions can be a useful criterion for the classification of the reaction according to the mode of involvement of water in the transition state of the rate determining step.

The significance which can be attached to ω and ω^* values derived from any study has been shown to depend upon the medium invariance of the activity coefficient ratios

$$\frac{f_{s(H_2O)_s} \cdot f_{BH(H_2O)_a^+}}{f_{B(H_2O)_b} \cdot f^*_{(H_2O)_t}} \text{ and } \frac{f_{s(H_2O)_s} \cdot f_{H(H_2O)_n^+}}{f^*_{(H_2O)_t}}$$

in equations (19) and (22) respectively.

If these requirements are met then the significance of ω and ω^* can be related to the general mode of action of water

by a correlation with data for other reactions of known mechanism or alternatively in terms of the extreme hydration parameter interpretation which, based on the nomenclature of equations (16) and (17), defines ω^* as the hydration of the transition state less the total hydration of substrate plus proton (t-s-n) and was a measure of the transition state hydration requirements on a scale relative to the difference in hydration changes between protonating a substrate molecule and a Hammett indicator base. The assumption inherent in this interpretation is that the activity coefficient ratios of species of like charge are medium independent but as demonstrated generally for amides[46], and, in the case in hand, by plots of log I versus H_o, this assumption is not valid.

Thus, the significance of ω values for acid catalysed hydrolysis of amides in general cannot be described in these simple terms but must be viewed as indications of the deviation from "ideal" unit slope of the plot of log k_{obs} versus $-H_o$ as the logarithm of the activity of water decreases with increasing acid concentration.[46]

Thus, in this case, these parameters lose much significance as simple criteria of mechanism. Although this difficulty of interpretation exists, ω values or their observed deviation from expected values have been used as mechanistic criteria for the hydrolysis of amides[122] and hydroxyamides[14].

In the case of butyranilide and the hydroxyanilides studied,

the degree of protonation became extensive as acid concentration was increased as can be observed by consideration of I values (tables 3 to 24). The anilides were generally more than 90% protonated in 9.0 Molar acid. Thus these hydroxyanilides are considered as moderately weak bases and the appropriate form of the Bunnett equation is used to correct the observed rate constant, over the acid concentration range, for degree of protonation. Thus the logarithm of the hydrolysis of protonated amide is denoted log k_p^2 (tables 27 to 48)

i.e. $$\log k_p^2 = \log k_{obs} - \log \frac{h_o}{h_o + K_{SH^+}}$$

Where data for ω^* plots was calculated the appropriate equation was used and the left hand side is denoted log k_p^4 (tables 27 to 48)

i,e, $$\log k_p^4 = \log k_{obs} - \log \frac{[HX]}{h_o + K_{SH^+}}$$

The equilibrium constants used in these correction factors were those derived from plots of log I against H_A, the H_A value at 50% protonation being equivalent to the ionization ratio where H_A is zero under the condition of invariance of the aforementioned activity coefficient ratio with change of medium (tables 3 and 26).

In general, in the cases of the hydroxyanilides studied, plots of log k_p^2 were linear, or nearly so, in log a_w to the limit of acid concentration studied (9 M $HClO_4$). The values of ω derived from these plots extended from 1.01 to 2.08 with 14 out of 21 ω values being in the range 1.5 ± 0.3 and are listed in

tables 49 and 50. In comparison, the ω value calculated for butyranilide was 2.66 ± 0.18 whereas the ω values derived for 4-hydroxybutyranilide and 5-hydroxyvaleranilide were 1.34 ± 0.12 and 1.18 ± 0.06 respectively.

Only in the case of butyranilide did any tendency toward curvature of the ω plot appear (graph 3) but this did not seem to be the normal type shown by aromatic amides[60] which appears at higher acid concentrations and is probably due to errors of determination of K_{SH^+} for butyranilide. The plots for the hydroxyanilides did not show any tendency to curvature as evidenced by the typical plots for 4-hydroxybutyranilide and 5-hydroxy-valeranilide displayed in graphs 4 and 5.

The fact that $\log a_w$ varies with temperature and will have an effect upon the magnitude of hydration parameters derived using rate constants obtained at another temperature has been demonstrated[60] but has not been taken into account in consideration of ω values since the absolute values of ω appear to have little significance and it is the difference between the values obtained for the hydroxylated and non-hydroxylated alkylcarboxanilides which is of interest. In general an increasing temperature of determination of rate constant produces a decreasing value of hydration parameter for water activity values measured at constant temperature[60].

Martin et al[14] obtained ω values for the hydrolysis of

4-hydroxybutyramide in sulphuric acid of 0.37, 0.55 and 0.30 at 15, 25 and 30° respectively. Also a value of 0.65 for ω was determined for the hydrolysis of the same substrate, in perchloric acid at 25° using a kinetically determined acid dissociation constant. These ω values for hydroxyamides may be compared with representative literature values of ω values for some alkylcarboxamides. Acetamide in hydrochloric acid[46] gave values of 5.04 and 4.78 at 50° and 61°, and 1.60 in perchloric acid at 95.° Propionamide[46] gave values of 2.69 and 2.50 in HCl at 40.5° and 59.6° respectively.

Thus, although it is obvious ω varies with temperature and between different acids, the same trends in values between hydroxyamides and non hydroxyamides as found between the corresponding anilides will exist if the factors of acid type and temperature are taken into account.

This common trend in ω value from hydroxyanilides to alkylcarboxanilides can only be construed as an artifact of the variation of the behaviour of the activity coefficient ratio of the hydrated substrate and transition state caused by the inclusion of a hydroxyl group in the molecule, as a change in the absolute ω value, with the attendant hydration connotations, or as a mixture of the two effects. It is probable that the latter case pertains.

Although, in general, ω plots had a high degree of linearity,

the data for ω^* plots, log k_p^4 gave curved plots, in all cases with, log a_w .

The Modified Hydration Parameter Treatment

The modified hydration parameter treatment was applied to the hydrolysis of butyranilide and the series of hydroxyanilides yielding the parameter r which was suggested to have more significance in amide hydrolysis[55] since the H_A acidity function, based on amides and therefore more appropriate, was incorporated in the factor correcting the observed rate constant for degree of protonation. This log k_p^3 was plotted against log a_w in the equation

$$\log k_{obs} - \log \frac{h_A}{h_A + K_{AH^+}} = r \log a_w + \log \frac{k^1}{K_a} + \log \frac{f_{SH^+p}}{f^*}$$

$$= \log k_p^3 \qquad (51)$$

based on the equations

$$S_s + H_n^+ \underset{K_{SH^+}}{\rightleftharpoons} SH_p^+ + (s+n-p)\ H_2O \qquad \text{(fast)}$$

$$SH_p^+ + rH_2O \underset{K_a}{\rightleftharpoons} \left[TS^*\right] \xrightarrow{k^1} \text{products} \quad \text{(slow)}$$

where the subscripts refer to the hydration number of the species[60].

A similar derivation produced an equivalent form of this equation, as described in the introduction

$$\text{i.e. } \log k_{obs} - \log \frac{h_A}{h_A + K_{SH^+}} = r + (b-a) - (s-p) \log a_w + \log \frac{k}{K_{SH^+}}$$

$$+ \log \frac{f_{S_s}\ f_{BH_a^+}}{f_t^*\ f_{B_b}}$$

This equation is derived from the above representation of the A2 mechanism in which the slow stage is represented as

$$SH_p^+ + rH_2O \underset{}{\overset{k}{\rightleftharpoons}} [TS]^* \longrightarrow \text{products}$$

Thus it is clear that the same basic problems pertain to this treatment as pertained in Bunnett's initial treatment.

Since there is no possible way of measuring terms like f^* directly, their medium dependence must be taken into account by assuming some form of cancellation with another activity coefficient term in the rate equation. To minimize the seriousness of the approximation the usual approach is to select a reasonable model for the indicator conjugate acid BH^+ and hope that, because of the similar structure and charge of the two species, the ratio f_{BH}^+ / f^* will be fairly insensitive to medium changes, or, on the basis of equation (5'), which assumes this cancellation, that the charge and structure of the transition state and the conjugate acid of the amide substrate are sufficiently similar that the ratio $f_{SH_p}^+ / f^*$ will be medium insensitive.

The observation of curvature in r plots for aromatic amides and the non coincidence of r plots in different acid solutions even upon extrapolation to dilute acid has led several authors to the conclusion that the activity coefficient ratios are not medium independent. None of the aforementioned hydration parameter treatments, however, takes into account the counterion of the catalysing acid. Although it is unlikely that the presence of

different counterions could affect the critical role of water in the A_2 type hydrolysis of carboxylic acid derivitives in converting the conjugate acid to the transition state, there remains the possibility that the presence of, or an increasing concentration of a specific counterion could stablize a slightly different transition state or alter the structure or number of water molecules in the immediate region of the transition state since the solvent properties of water depend upon its hydrogen bonded structure. Irrespective of the model used to account for the properties of water, this structure should be affected by added ions.[140-145]

The catalytic effectiveness of a series of acids in the hydrolysis of a series of esters was compared by Bunton et al[139] who arranged the second order rate constants in series. Studies of the variation of the activity coefficients of each ester with the nature of the counterion showed that they decreased in accordance with the general pattern found for polar non-electrolytes so that at any concentration of acid, log f_s is in the sequence $H_2SO_4 > HCl > HClO_4$. If only initial state effects were of importance in the hydrolysis reaction this order would be transmitted into any comparison of reaction rates. Although this order does obtain in $A_{AC}2$ ester hydrolysis, the reverse order, $HClO_4 > HCl \doteq H_2SO_4$, is found for A_1 ester hydrolysis. This suggests that the differential kinetic effects of strong acids must depend to some extent upon the reaction mechanism in that

the large, low charge density perchlorate ion appears to be more effective in those reactions (A1) where the transition state would have a high degree of carbonium ion character and to be less effective in the A2 reaction where the transition state is considered to have large amounts of charge localized upon centres with acidic protons which can hydrogen bond strongly to water. The degree to which, and sense in which any initial state and transition state effects exerted by the counterion influence the activity coefficient ratios and hydration numbers in hydration parameter treatments could therefore be at least in part responsible for variation in hydration parameters over a series of acids. Although this variation is frequently small, or somewhat obscured by changes due to other factors, it is usually significant[46,53]. Suitable data for amides unobscured by such factors as temperature changes is rather limited but the variation of r values with counterion is well illustrated by ethyl acetate hydrolysis in H_2SO_4 and $HClO_4$ at constant temperature which gives initial r values of 2.10 and 1.63 respectively[127]. Martin et al[14] quote ω values for the hydrolysis of 4-hydroxybutyramide at 25° in H_2SO_4 and and $HClO_4$ of 0.55 and 0.65.

Notwithstanding the effect of the counterion in concentrated solutions, all strong mineral acid solutions eventually exhibit the same activity coefficient behaviour at high dilution which would imply that ω or r plots for a given hydrolysis reaction

in different acids should extrapolate to the same point in dilute acid. This condition however is not generally obeyed and differences of more than 0.5 log unit are sometimes obtained.[7]

These presently non-quantifiable discrepancies remain as deficiencies of any simple hydration model which neglects the role of the counterions and hence reduce any significance which might be afforded to the hydration parameter treatments.

It is a common feature of rate - water activity correlations in strong acid examined in the literature that, although the acidity function and water activity data are determined at 25°, the rate and equilibrium data for the substrate being studied are generally determined at the most convenient temperature across a broad range. Initially this practice was justified for the case where E_A (or ΔH^*) is effectively constant over the range of acid studied[54] but it has recently demonstrated[60] that the apparent variacid studied[54] but it has recently demonstrated[60] that the apparent to a variation of a_w with temperature. Thus the consequence of using water activity data for 25° in a correlation of the rate of amide hydrolysis at some higher temperature with water activity data is to introduce a linearly increasing error in log a_w, since log a_w^T is linear in log a_w^{25}, which results in a fixed error in the r value for that particular temperature. The shape of the r plot will not change because of the linearity of the introduced error over the range of acid considered but the magnitude of r will

change by a fixed amount depending upon the acid used and upon the temperature at which the kinetic studies were performed. Yates et al[60] observed in the hydrolysis of benzamide in H_2SO_4 that the r value can change by up to 0.5 unit over a 60°range, positive increases in temperature producing negative changes in the derived r value. When the temperature variation of a_w is taken into account the enthalpy of activation is seen to be medium invariant across the acid concentration range.

In the present work, no data was available in order that the magnitude and sense of the variation of a_w for $HClO_4$ solutions with temperature could be calculated. That such calculations would be relevant was, however, considered doubtful in the light of the limitations, enumerated above, on the significance of hydration parameter values. In view of the level of significance of the absolute values of the r parameters, it is reasonable to assume that the sense and magnitude of the variation of a_w with temperature for $HClO_4$ solutions will be directly comparable with that of H_2SO_4 solutions[60], that the effect on the derived r values would be negative and would be in the order of 10% for the 25° difference in temperature. Since this medium effect will be equally active both in the case of butyranilide hydrolysis and in the case of the hydrolysis of aryl substituted 4-Hydroxy-butyranilides, such corrections need only be applied if any significance is to be given to the absolute values of the

hydration parameter derived from the plots of log k_p^3 against log a_w^{25}.

Plots of log k_p^3 against log a_w^{25} produced in general, graphs which were close to linearity (eg graphs 4 and 5). The slope of this plot for each anilide was calculated by linear least squares treatments by the data (tables 27-48) and are listed in tables 49 and 50.

Butyranilide gave an r value of 3.04 ± 0.16. The series of aryl substituted 4-hydroxybutyranilides gave r values in the range 1.95 to 1.52 with ten out of eleven of these values in the range 1.8 ± 0.2 (table 49). The series of aryl substituted 5-hydroxyvaleranilides gave values of r over a larger range and are displayed in table 50.

Thus, initially, it is interesting to note that these values appear to be numerically similar to values derived for other amides, that the difference in value between the hydroxylated and non-hydroxylated compounds is of the expected order in view of the proposed role of the terminal hydroxyl group in the hydrolysis reactions.

Although the linearity of these plots is good it could be argued that the range of acidity (or range of water activity) studied is rather limited i.e. 1 to 9 M H ClO_4, ($-\log a_w^{25}$ values: 0.018 to 0.981 [121]) since, over a similar range in $HClO_4$, the plot of log k_p^3 against log a_w (present notation) for the hydrolysis

of butyramide is fairly linear but shows definite curvature toward higher acidities[87].

If these results were numerically significant they would imply that the hydration number for amide hydrolysis was indeed 3 as has been suggested[49,55] provided that the intramolecular hydroxyl group assumes the role fulfilled by only one water molecule in intramolecular reaction. However, in the light of the enumerated limitations of this treatment it is sufficient at this point to say that the values of these parameters provide interesting data which could perhaps be shown to be of greater significance than can at present be afforded to them.

Moodie's Hydration Parameter Treatment[49].

Amide hydrolysis may be formulated as follows:

$$SH^+(H_2O)_a + bH_2O \xrightarrow{k} (H_2O)_{a+b}$$

Thus, Rate $= k_{obs}\left([SH^+] + [S] \right) = k\ SH^+\ a_w^b\ f_{SH^+} / f^*$

where k_{obs} is the observed first order rate coefficients, the activity coefficients referring to hydrated species.

Thus

$$\log k_{obs} - \log [SH^+] / ([S] + [SH^+]) = \log k.f_{SH^+}/f^* + b \log a_w$$

or $\log k_p^1 = \log k.f_{SH^+} / f^* + b \log a_w$

Thus this equation does not depend upon estimates of pK_{SH^+} or upon an acidity function and thus the assumptions made previously as to the similarity of indicator bases and the amides in protonation are not required. Thus a plot of $\log k_p^1$ against $\log a_w$ will give, if the activity coefficient ratio is assumed constant, the value of b, the number of water molecules in addition to the hydration sheath of the protonated amide needed to form the activated complex.

However this dependence for linearity on the medium invariation of the kinetic activity coefficient ratio makes the same type of profound assumptions about the nature of the amide transition state and about the behaviour of its activity coefficient in mineral acid solutions of changing concentration as other hydration parameter treatments.

Plots of $\log k_p^1$ against $\log a_w$ for the series of anilides under consideration in this work were linear but with a slightly

higher degree of scatter of points than observed in treatments where the value of the correction factor involved a single assessment of a value for K_{SH}^{+}. This is typified by graph 6. The data for these plots for the hydroxyanilides and for butyranilide are listed in tables 27 to 48. The values of the derived 'b' parameters for the series of 4-hydroxybutyranilides range from 2.09 to 1.27 and are listed on table 49 with the value obtained for butyranilide (3.05 ± 0.25). The values of b obtained for the series of 5-hydroxyvaleranilides ranged, with the exception of two compounds, from 1.27 to 2.22. In both the series of hydroxyanilides the large majority of the b values obtained were in the range 1.9 ± 0.3 with those values outside the range tending to be the more reactive compounds which were more susceptible to experimental error in determination of the correction factor $[SH^{+}] / ([S] + [SH^{+}])$.

However it is notable that this closely related hydration parameter treatment gives very similar values for the resultant parameter as have been obtained in the other treatments in that there is approximately unit difference between the derived results for the hydroxyanilides and the single butyranilide, as would be expected if these treatments gave a reasonable approximation of the hydration change occurring in the reaction, provided the hydroxyl group is playing the expected role.

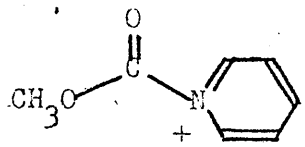
This treatment is subject to the uncertainties listed in the

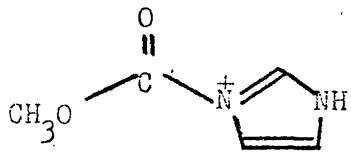
case of the related hydration parameter treatments. The significance of the results cannot therefore be regarded as being quantitative but the qualitative importance of the results remains relatively unimpaired.

The Dual Meachanism Postulate

The postulate by Bunton et al[73] (to account for observed curvature in hydration parameter plots) that acid-catalysed amide hydrolysis occurs by way of two mechanisms involving N- and O-protonated species in concurrent steps was examined. A plot of $k_{obs} / \propto .a_w$ against $[H^+](1- \propto)/(\propto)$ would be expected to be linear if the postulate was valid and if the equation derived from the postulated mechanism was also valid. Accordingly, such plots for some members of the series of hydroxyanilides under study were drawn from calculated data (tables 27-48) but found in all cases to be non linear. A typical example of this plot is displayed in graph 7.

This result is in accord with that of Barnett et al[94] who found, upon a general application of the equation[73] to acid-catalysed amide hydrolysis, that linear plots were only obtained in the case of aromatic amides, all other types of amides producing non linear plots. The criticisms of this postulate and the assumptions involved in the derivation of the equation have been enumerated in the introduction. These criticisms and the results obtained tend to lend low significance to this postulate. It has been demonstrated that a dual mechanism involving both N and O protonation need not, in all cases, be postulated to account for curvature in hydration parameter treatment plots





since, in the systems shown, which are models for carbamates protonated only on Nitrogen, curvature in the plot of log k_p against log a_w is observed.[126] Thus, in these systems and perhaps in general, the existance of competing mechanisms based on different sites of protonation as an explanation of observed curvature in hydration parameter treatment plots would seem to be unfounded.

However when the alkylanilide, butyranilide was considered, a linear plot of $[H^+](1-\alpha)/\alpha$ was obtained (graph 8). This observation is unusual since it has been observed that pseudo aromatic amides such as anilides do not normally give linear plots, and since no other treatment applied gives such an apparently clear indication that the acid catalysed hydrolysis of alkyl anilides differs fundamentally from the hydrolysis of hydroxyanilides. However, in view of the low significance and harsh criticism[60,87] attributed to this treatment, the implications of this result will be treated with caution.

Linear Free Energy Relationships

The changes in rate or state of equilibrium brought about by systematic variation of reactant structure or reaction conditions in chemical reactions are often found to be linearly related, other variables being kept constant. Since the logarithm of an equilibrium constant is proportional to the standard free energy change accompanying the reaction and the logarithm of a rate constant is proportional to the standard free energy of activation (according to transition state theory[125]), these linear relationships are linear free energy relationships (l.f.e.r.). All such linear free energy relationships are based on the criterion that the free energy changes produced by a systematic variation of the reactant structure or reaction conditions of a particular reaction are linearly related to the free energy change that those variations bring about in another reaction. This topic has been thoroughly reviewed[128] and analysed[128,129] but a recent addition to these empirical correlations are the linear relationships which have been shown to exist between the logarithms of equilibrium quotients and (or) second order rate coefficients for diverse reactions as these quantities vary with acid concentration in solutions of moderately concentrated mineral acid.

L.F.E.R. in Concentrated Solutions of Mineral Acids.

The l.f.e.r. treatment of reactions in solutions of mineral acids was applied to the protonation and hydrolysis reactions of the anilides under consideration in solutions of perchloric acid at

50° ranging from 0.01 Molar to 9.0 Molar.

Application of the L.F.E.R. treatment to Protonation of Anilides.

The protonation of the anilides under consideration was observed to follow the l.f.e.r. treatment of Bunnett and Olsen[56] in that plots of $(H_o + \log I)$ against $(H_o + \log [H^+])$ proved to have a high degree of linearity. The data for each anilide for the left hand side of equation (30) which was being tested for linearity is listed in tables (27) to (48). The data for the right hand side of this equation is listed in table (2). Graph (9) is example of the degree of linearity obtained in these plots.

The slopes of these plots give the parameter ϕ_e the interpretations of which have been listed above. Generally, these parameters are considered useful in characterizing the response of the equilibrium quotients of the bases under consideration to changing acid concentration in relation to the specified standard base but can be shown to be the proportionality constants between logarithms of activity coefficient ratios (equations 33 and 34). However, as previously mentioned, these parameters, in an extreme interpretation in which hydration change is considered to be the only significant factor affecting ratios of formal activity coefficients, can be equated with the ratio of average hydration change in the hypothetical reaction

$$SH(H_2O)_p^+ + B(H_2O)_b \rightleftharpoons S(H_2O)_s + BH(H_2O)_a^+ + (p-s-a+b)H_2O \qquad (44)$$

to that in the protonation of an aromatic primary amine indicator base.

Irrespective of the interpretation given to this parameter ϕ_e, since it is unlikely that the hydroxyl group of the hydroxylated anilides plays any part in the protonation reaction and since the presence of the hydroxyl group in the protonated and unprotonated hydroxyanilides is likely to have have the same effect on the activity coefficients of both species thereby leaving the relevant activity coefficients ratio unchanged, the value of the ϕ_e parameter would be expected to be similar for the protonation of both butyranilide and the hydroxylated anilides.

The values of the ϕ_e parameter for the protonation reactions of the anilides under consideration are listed in tables 49 and 50. For the series of 4-hydroxybutyranilides these values fall in the range 0.40 to 0.76 whilst the values for the series of 5-hydroxyvaleranilides fall in the range 0.36 to 0.68. For butyranilide the value obtained for the ϕ_e parameter, 0.48 ± 0.06, thus falls well within the range determined for the hydroxylated compounds. These values of ϕ determined for the aryl substituted anilides are approximately of the same magnitude as those values determined for aryl substituted benzamides[56]. The ϕ_e values for the benzamides are however spread over a considerably narrower range than the hydroxy anilides. This spread of ϕ_e values obtained for the series of hydroxyanilides would seem to be the result of experimental errors

introduced during the determination of the ionization ratios of these relatively reactive compounds.

If these figures are considered in terms of the hydration change hypothesis in its extreme form, the hydration of the conjugate acid of the anilide is seen to be greater than that of the unprotonated anilide by a quantity $4.5\phi_e$ (ω'_e) which is approximately in the range 1.8 to 3.4 with the majority of values centred around 2.5.

The utility of this relationship is much enhanced by the fact that if infinite dilution in water is taken as the standard state for all activity coefficients, the intercepts of these plots can be taken to represent the pK_{SH^+} for the real base referred to infinite dilution in water as standard state. This may be compared with the pK_{SH^+} value derived from plots of log I against H_A which merely represents the value of the logarithm of the ionization ratio at zero H_A. This is not normally zero acid concentration and since activity coefficient ratios can differ appreciably from unity at zero H_A, the pK_{SH^+} at infinite dilution is not immediately accessible.

It has been pointed out that l.f.e.r. estimates of pK_{SH^+} of a base depend upon the assumption that the straight line established by the experimental points in linear to infinite dilution in water. Any inconsistancy in this assumption or any experimental error will introduce error into the derived pK_{SH^+} value which will be magnified by extrapolation.

The pK_{SH}^+ values for the anilides under examination derived from the l.f.e.r. treatments are listed in table 26A. These values when compared with the values of pK_{SH}^+ obtained by the acidity function method, as listed under the heading $H_A(50\%)$ in table 26 are observed to be of the similar magnitude and differing in a random fashion from the acidity function derived pK_{SH}^+ values.

In view of the uncertainty of the determined I values it was considered that the errors introduced by taking the value of H_A at 50% protonation (equivalent to the value of log I when H_A is zero) as the pK_{SH}^+ of the anilides, thereby using approximately 1Molar $HClO_4$ as the standard state (see table 2) and introducing a small deviation from infinite dilution as standard state, would be preferred to a lengthy extrapolation to infinite dilution of plots which, from the scatter of ϕ_e values, have been shown to be subject to error.

Application of L.F.E.R. treatment to Hydrolysis of Anilides.

The l.f.e.r. treatment for reactions in moderately concentrated mineral acids[57] was applied to the hydrolysis reactions of the anilides under consideration by plotting $\log k_{obs} - \log ([SH^+] / [S] + [SH^+])$ against $H_o + \log [H^+]$. The data for the left hand side of equation 31, from which these terms are derived, is listed, for each anilide, in tables 27 to 48 under the heading $\log k_p^1$. The values of $(H_o + \log [H^+])$ for perchloric

acid solutions at several concentrations are listed in table 2.

Plots of log k_p^1 against H_o + log $[H^+]$ for butyranilide and the two series of hydroxyanilides were found, in general, to show a tendancy towards nonlinearity of the type displayed in graph 9. Since these plots are derived from data incorporating ionization ratio data in which one type of experimental error is known to be subject to a directional increase such that the value of I and hence of I/I+1 tends to be larger in magnitude than would be expected at certain intermediate acid concentrations ($[SH^+]$ / $[S]$ + $[SH^+]$ calculated as I/I+1), it is not immediately obvious whether the nonlinearity of these plots is due to some factor other than experimental error. If log k_p^3 is substituted for log k_p^1 in these plots that element of error in I which is dependent upon acid concentration is effectively eliminated in that a fixed value of K_{SH^+} is used in the correction factor. This substitution when carried out in a number of cases did not serve to eliminate the curvature in these plots although it did reduce it.

Apart from systematic errors, Bunnett[57] lists abnormal variation in activity coefficient ratios or the inception of a second reaction mechanism as possible sources of nonlinearity in these plots. Curvature exhibited by these plots because of the existance of two mechanisms having non-equivalent ϕ values would tend to be of the opposite type to that exhibited by these

compounds since the reaction of lower ϕ would go relatively faster at higher acid concentration leading to a decreasing (not increasing) overall l.f.e.r. plot slope.

Departure from the usual linear relations between the logarithms of activity coefficient ratios is another condition which could lead to nonlinear plots. However there is no evidence to support these possible sources of curvature in these systems. From the nature of the curvature it is thought that the source resides in experimental error.

Although this curvature is exhibited by a number of the anilides under study, it is not a completely general feature and in no case is it so pronounced as to render the estimation of the ϕ r parameter irrelevent. Accordingly, these parameters were calculated and are listed in tables 49 and 50. The values of the ϕ r parameters for the series of aryl substituted 4-hydroxybutyranilides are spread over a narrow range all values between 0.36 and 0.55. The ϕ r values for the series of 5-hydroxyvaleranilides are spread over a slightly greater range, all values but one being within the limits 0.31 and 0.63. These values can be compared with the value obtained for n-butyranilide of 0.79.

The possibility that an increasingly important intermolecular hydrolysis with a relatively high ϕ r value (butyranilide : 0.79; 4-hydroxybutyranilide: 0.38) could be the source of the curvature

in these plots is rejected when the nature of the probable catalytic action of the hydroxyl group and the effect upon water activity of increasing acid concentration is considered. This intermolecular reaction will obviously become less important at higher acid concentrations, as is confirmed by a consideration of the relevant rate ratios, which would again lead to a curvature inverse to that observed.

When the various interpretations placed upon ϕ_r values are considered it is obvious that, as would be expected, the kinetic effect of changing the reaction medium by increasing acid concentration and thereby reducing water activity is greater in the compound where there is no intramolecular hydroxyl group. These parameters can, in a similar manner to the previously considered case, be taken as proportionality constants, expressive of the relative variation in terms log (f_{SH^+} /f^*) and log (f_{BH^+} / $f_B \cdot f_{H^+}$) as the medium changes.

In terms of the extreme hydration hypothesis, these variations of activity coefficient ratios are entirely due to hydration changes between initial and final or transition state so that the ϕ_r parameter can be interpretated as a proportionality constant between the average hydration change of the reaction under study and the average hydration change in equilibrium protonation of a primary aromatic amine indicator base. The value of the latter change can, as described, be approximately quantified as $4.5\ \phi_r$ over the range.

3.5 to 7 M mineral acid which enables the hydration change in the reaction under study to also be approximately quantified as $4.5\ \phi_r$ or ω_r^1, thus giving a means of estimating the average hydration change in the reaction of interest, should the extreme hydration hypothesis apply.

The values of ω_r^1 were calculated from the ϕ_r^1 values for each anilide and are listed in tables 49 and 50. As probable indications of average hydration change in this reaction in the event of this hypothesis being correct, these values are remarkable consistant with the values obtained for the hydration parameter r. These ω_r^1 values fall in the range 1.58 to 2.19 for the series of 4-hydroxybutyranilides and all members of the series of 5-hydroxyvaleranilides but one have ω_r^1 values in the range 1.41 to 2.84. These values can be compared with the ω_r^1 value obtained for butyranilide of 3.55. Also, as rough estimates, which is all they purport to be, these values fit in well with the general picture of amide hydrolysis transition state hydration requirements previously evolved[49,55] in that they would seem to indicate that the number of water molecules required in going to the transition state in amide hydrolysis has to be one unit greater in the absence of a suitably situated intramolecular hydroxyl group(in the presence of which the number required is approximately two.) The utility of this approximation is obviously limited to this level of estimation in that there is no method of

determining the factors affecting the critical activity coefficient ratio. Also the omission of such factors as the nature of the counterion in mineral acid solution seem to play a role in limiting the significance of hydration parameter treatments, and these factors have not been taken into account in this treatment.

Three categories of reaction mechanism were delineated by Bunnett, with respect to ω values, on the basis of empirical correlations with calibration reactions of known mechanism. On the same basis these categories were expressed in terms of ϕ values (table 1) and from tables 49 and 50 it can be seen that the ϕ r values for most of the hydroxyanilides tend to fall into the category in which water acts as a nucleophile but that like other series of amides they tend to straddle the 2nd and 3rd mechanistic categories, with butyranilide falling into the third category in which water acts as a proton transfer agent.

The Hammett Structure - Reactivity and Related Correlations.

The Hammett $\sigma\rho$ relationship[130] equates the change in the logarithm of rate or equilibrium constants of aromatic side chain reactions due to a substituent to the corresponding change in the logarithm of the acid dissociation constants of benzoic acid as standard. The electronic and inductive effect requirements of the latter process lead to a series of values of the logarithmic ratio which have been tabulated as the parameter sigma (σ)[123].

The proportionality constant between these changes, rho (ρ), on the above definition of σ, can be considered as representing the susceptibility of the reaction series being considered to the electronic and inductive effect of the substituent relative to the corresponding effect in the standard reaction.

The relationship is thus expressed as

$$\log k/k_o = \sigma\rho$$

where k and k_o represent either equilibrium or rate constants for the substituted and unsubstituted reactants.

The Hammett equation has been extensively reviewed[128,131] since its presentation[130]. Re-examinations of the relationship have led, within this particular type of l.f.e.r., to a proliferation of σ values based on the varying types and degrees of susceptibility to reaction-centre interaction.

Hammett[130] first suggested that enhanced σ values might be required for all substituents in the para position capable of

direct resonance interaction with reactions involving negative charge or unshared electron pairs on an atom next to a benzene ring. The substituent parameters for this type of group are currently denoted σ^- [137].

The relative importance of resonance and inductive effects peculiar to electrophilic aromatic substitution reactions led Brown et al[132] to define a parameter σ^+ which is also applicable to a variety of aromatic side chain reactions in which a positive charge capable of direct resonance interaction with the ring is generated. The standard process for defining σ^+ is the solvolysis of substituted 2-phenyl, 2-propylchlorides in 90% acetone[132c].

The concept of three distinct σ scales has been seriously questioned[134] and it has been argued that a continuous range of σ values corresponding to a range of conjugation and polarization is to be expected for substituents capable of direct conjugation with reaction sites. A continuous range of substituent constant values in cases where conjugation can occur have been observed in a re-examination of Hammett equation correlations[133]. This it is suggested that σ^+ and σ^- values are simply limiting cases of these ranges[133,138].

Several approaches to the problem of varying conjugative effects have been taken in correlation of reactivity data[134]. That many types of reactions can be correlated by the Hammett ρ constants to a fair degree of accuracy is an experimental fact[128] which

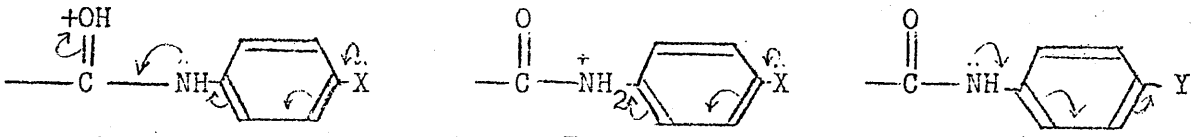
must result from a fortuitous coincidence that, in a great many aromatic side chain reactions, the relative importance of inductive and resonance effects is relatively constant.

The hydrolysis reactions of certain carboxylic acid derivatives, including anilides, which are thought to follow an A2 mechanism, will be expected, from a consideration of the equilibrium and kinetic characteristics of the bimolecular reaction, to show only weak polar effects overall[135]. This expectation has been borne out in the studies performed on the acid catalysed hydrolysis of substituted benzamides in N/2 hydrochloric acid which produced a ρ value of 0.118[62]. A consideration of the conjugate acids of benzamides and anilides on the A2 mechanism shows, irrespective of the nature of the conjugate acid, that the conjugate acids will be both destablized with respect to the amide and rendered more susceptible to attack by a nucleophile by an electron withdrawing substituent. Thus both the hydrolysis step of the conjugate acid and the acid dissociation equilibrium should have ρ values of the same sign (positive).

A consideration of benzamides and their conjugate acids show that para substituents capable of conjugative interactions would only be able to conjugate with the reaction centre in the protonation equilibrium if the centre of protonation were the carbonyl oxygen. However it was shown that a better correlation in the application of the Hammett equation to the basicities of benzamides was obtained

with σ values rather than σ^+ values[136] suggesting that the amide nitrogen was the centre of protonation.

A consideration of the possible anilide conjugate acids suggests that σ^- and σ^+ values will be



required for good correlation. Thus the logarithms of the dissociation constants of the conjugate acids of the series of hydroxyanilides, determined from plots of log I against H_A, were plotted against σ (e.g. graph 10). The introduction of σ^+ values[137] for those substituents capable of conjugate interaction with the side chain appeared to do nothing to improve the correlation while the use of the σ^- value[137] for the p-nitro substituent seemed to be necessary for improved correlation. However, in view of the uncertainties in the magnitudes of the pK_{SH}^+ values, no conclusions can be drawn from this result.

The electronic requirements of the hydrolysis reaction of the amide conjugate acid can be considered by examining the hydrolysis in solutions of perchloric acid in which the amide is completely protonated[68]. This condition pertains in 9 Molar acid. Plots of log k_{obs} in this acid correlated well with σ values apart from the p-nitro derivative which required the σ^- parameter for correlation. The substitution of σ^+ values for the appropriate para substituents considerably reduced the correlation (e.g. graph 11).

The overall reaction for each series of anilides was considered by plotting the logarithm of the rate constants observed for hydrolysis in 1 Molar perchloric acid against σ values. The correlation was poor in this case and was considerably improved by the use of σ^- and σ^+ values for the appropriate substituents (e.g. Graph 12). The observation that σ^+ values do not correlate the logarithms of the rate constants in 9 Molar acid suggest, on the basis of O-protonation, that the reaction centre must conjugate with the appropriate para substituents in the transition state as well as in the conjugate acid.[134] Although expected, no improvement in correlation was obtained by the introduction of σ^+ values in the Hammett plot for the dissociation of the amide conjugate acid due to experimental uncertainty. Since the hydrolysis reaction does not correlate with σ^+ and since the overall reaction does correlate with σ^+ it can be deduced that the acid dissociation reaction should correlate with σ^+.

Since ρ values for the development of a positive charge adjacent to a benzene ring are normally[128] much greater in magnitude than those ρ values determined for the amide conjugate acid dissociation reactions[123] (0.71 ± 0.09 for 4-hydroxybutyranilide and 5-hydroxyvaleranilide respectively, tables 72 and 73) it would seem that the positive charge does not develop to any great extent on the nitrogen atom. Thus these facts would seem to point to O-protonation with conjugative interaction with the positive charge

by the nitrogen lone pair, but to a very small degree. Previously, ρ values determined for aromatic amide protonation have all had similar magnitudes to those determined in this work. Yates and Stevens[55] considered that a ρ value of -0.92 for the protonation of a series of benzamides was a reasonable value for an ionization in which unit positive charge is developed and essentially localized at a distance of two atoms from the benzene ring. These low ρ values also suggest that, in anilides, a conjugate interaction of the N lone pair with a positive charge on the carbonyl oxygen, which would produce a partial positive charge on the N atom, is not essentially part of the equilibrium process.

The ρ values determined for the reaction in 9 Molar perchloric acid which closely approximates to a consideration of the hydrolysis reaction of the amide conjugate, were 1.26 $\pm$0.04 and 1.34 $\pm$0.14 tables(70,71)for the 4-hydroxybutyranilide and 5-hydroxyvaleranilide series respectively. Thus the anilide conjugate acids are fairly susceptible to polar interactions in the hydrolysis reaction and these values suggest that the electron density is increasing in the transition state and that this change is localized probably on the atom adjacent to the nitrogen or on atoms once removed from this but probably not on the nitrogen atom itself unless the change is small. Since the percentage amide protonated and thus the rate constant for the hydrolysis of the protonated amide have been previously calculated, determinations of the reaction constant

ρ for the hydroxyanilide series using this data (table 74) were carried out and found to be in good agreement with the "approximate value".

Based on the A 2 mechanism, it can be shown that the overall value of 0.40 ± 0.02 and 0.32 ± 0.03 for 4 and 5-hydroxyanilides (tables 68 and 69 respectively) is the sum of the values for the equilibrium protonation (or dissociation) and the hydrolysis reaction.[69] In this case where the dissociation constants were considered the relationship would be

$$\rho_{\text{overall}} = \rho_{\text{hydrol}} - \rho_{\text{diss.}}$$

This relationship was found to approximately hold for the hydroxyanilide series the variance probably being a result of the uncertainties in ρ for conjugate acid dissociation.

The hydrolysis of a series of meta substituted n-butyranilides in 1 Molar perchloric acid at 50° was also examined via the Hammett equation. The overall ρ value determined for the plot of the logarithm of the observed rate constants versus σ (table 67, graph 13) was 0.42 ± 0.01 which is in good agreement with the values determined for the intramolecular reaction in 4-hydroxybutyranilide and 5-hydroxyvaleranilide. It is unlikely that the presence of a terminal hydroxyl group will alter the electronic requirements of the protonation equilibrium as evidence presented earlier suggests. Thus on the basis of the additivity of the component ρ values[69] it can be deduced that, since the ρ values for the

protonation equilibrium will be similar, that the ρ values for the hydrolysis steps will be similar. Thus it can be suggested that since the electronic requirements of the intermolecular and intramolecular reactions will be similar, that the gross mechanistic features of the reaction mechanisms will be comparable.

Activation Parameters

The pseudo first order rate constants for the acid catalysed hydrolysis of series of aryl substituted butyranilides, 4-hydroxy butyranilides and 5-hydroxyvaleranilides were determined at several temperatures in aqueous solutions of a mineral acid (1 M $HClO_4$) (tables 51-66). From the slopes of plots of the logarithm of the observed rate constant against the reciprocal of the temperature on the Absolute scale, the energy of activation E_a and hence the enthalpy of activation for the hydrolysis of each anilide was determined.

If these hydrolysis are considered to proceed by $A_{AC}2$ type mechanisms, or by any process involving a pre-equilibrium protonation the observed rate will depend on the equilibrium constant for the first step and upon the rate constant for the second step.

Consequently the calculated enthalpies and entropies of activation (ΔH^*, ΔS^*) must be the sum of the enthalpy and entropy changes for the protonation step (ΔH^o, ΔS^o) and the enthalpies and entropies of activation for the second step (ΔH_1^*, ΔS_1^*).

i.e. $\Delta S^* = \Delta S^o + \Delta S_1^*$

Available evidence from the study of the $\underline{\omega}$ -hydroxy and $\underline{n}$ alkyl anilides suggests that the mechanism of the protonation step is not affected by the incorporation of a terminal hydroxyl group in the alkyl anilide. A protonation step common to

all series will thus contribute equal ΔS^{o} and ΔH^{o} values to ΔS^{*} and ΔH^{*} so that these parameters for the same number of each series can be directly compared in the knowledge that the source of any changes in these parameters between series will reside in ΔS_{1}^{*} and ΔH_{1}^{*} .

On this basis the magnitude and signs of the activation parameters are, as a first approximation, relevant. It is generally accepted that there is an empirical correlation between entropy of activation and reaction order for acid catalysed reactions[145]. On a simple basis, ΔS_{1}^{*} should be positive for an A1 reaction and negative for an A2 reaction mechanism. When the parameter ΔS^{*} is determined the accepted procedure is to assume ΔS^{o} as small and probably positive; then a positive value of ΔS^{*} should indicate an A1 mechanism while a negative value will indicate an A2 mechanism.

The values of ΔS^{*} determined were all strongly negative thus indicating an A2 type mechanism or a hydrolysis step involving a process which carries a large negative entropy of activation. In specific terms, the ΔH^{*} values determined for the series of aryl substituted n-butyranilides in aqueous perchloric acid solutions ranged from 18.0 to 20.4 k cal per mol whilst the ΔS^{*} values (50^{o}) for this series were in the range -16.5 to 23.3 e.u. (table 66). When the values of ΔH^{*} and ΔS^{*} determined herein for the hydrolysis of butyranilide in aqueous perchloric acid

(19.7 k cal per mol, -19.3 e.u.) are compared with recorded[146-152] activation parameters for the acid catalysed hydrolysis of analagous aliphatic amides, they are found to agree well. Thus for aliphatic amides ΔH^{*} is found to be in the range -18 to -22 e.u. Although these values are largely calculated from second order rate constants, provided the correct choice of standard state is made they can be compared directly with those determined herein for butyranilide. Thus on this piece of evidence it would appear that the replacement of one amide N-bound proton by a N-phenyl substituent has little effect upon the activation parameters. It would be expected that the effect of such a substitution would be to produce a more negative ΔS^{*} value since increased steric effects should lead to an increased loss of vibrational and rotational freedom in an A2 transition state. Also as the A2 transition state is approached, irrespective of the nature of the conjugate acid, the amount of positive charge sited on the N atom will reduce whilst increasing upon the incoming nucleophilic oxygen atom. Thus the removal of a hydrogen bonding site on N and its replacement by a phenyl group should reduce the possibility of decreasing solvent electrostriction at N whilst the solvent electrostriction at O is increasing. This effect is observed when acetamide[152] and benzamide[60] undergo progressive methyl substitutions on nitrogen.

The effect of introducing a hydroxyl group in the γ position

in butyranilide to produce 4-hydroxybutyranilide is an approximate twenty fold rate enhancement indicating, since the polar effect of this group would be negligible[71], that intramolecular participation takes place in the acid catalysed hydrolysis. Evidence so far presented suggests that the reaction mechanism has not altered and that a more favourable free energy of activation is the source of the rate enhancement.

The loss of three transitional and up to three external rotational degrees of freedom and the accompanying unfavourable free energy change incurred at the formation of the transition state of the bimolecular reaction is eliminated on going to a unimolecular reaction. It has been estimated[39] that these entropic losses could be expected to be of the order of 40 to 50 e.u. for many bimolecular reactions in solution, but that other factors such as residual freedom of internal motions, differential solvation of polar or hydrophobic groups in the reactants, products or transition state reduce these losses to the more commonly found values. Thus these losses are not incurred in intramolecular reactions but are replaced by other unfavourable entropy changes such as restriction of internal rotations and by favourable factors such as low frequency motions in the product or transition state.

Thus the participation of a hydroxyl group in the acid

catalysed hydrolysis of amides would, on a simple model, be expected to leave ΔH^{*} essentially unaffected, a small favourable change, probably as a result of the increased nucleophilicity of the oxygen, being anticipated. The negative ΔS^{*} term would be changed to a more favourable value. However it has been noted in the introduction that this is an oversimplified picture and that for an intramolecular reaction the reduction in the number of species present in the transition state does not always reflect uniquely in the entropy of activation but that the activation enthalpy can play a decisive role even where the intramolecular and intermolecular reactions have the same mechanistic features[153].

The activation parameters for the hydrolysis of the series of 4-hydroxybutyranilides in 1 M perchloric acid (tables 51-56, 64) are not found to differ greatly in either the activation enthalpy or entropy from the values derived for the butyranilides (tables 61-63, 66). The activation entropy for 4-hydroxybutyranilide (-18.1 e.u.) is slightly more favourable than that for butyranilide (-19.3 e.u.). This slightly more favourable activation entropy (ΔS^{*}) is found to be almost general throughout the series and falls within the range -20.4 e.u. to -15.6 e.u., these figures being on average 3.3 e.u. less negative than the non-hydroxylated alkyl anilides. The activation enthalpies for the series of 4-hydroxybutyranilides are, as might be expected on a simple model, slightly more favourable than those of the n-butyranilides and range between the limits

16.7 and 18.9 k cal per mol, the comparative values of the unsubstituted members of the series being 18.07 and 19.71 k cal per mol respectively. A comparison[154] of the activation parameters derived from second order rate constants for the hydrolysis of a series of γ-hydroxy alkyl amides in dilute HCl solutions with reported activation parameter values for alkyl amide hydrolysis under similar conditions showed that in these compounds the change from inter- to intra-molecular reactions brought the results which would be expected on the simple model defined above. Thus the activation enthalpies for 4-hydroxybutyramide (19.9 k cal /mol) was similar but slightly less favourable than the literature value (18.9 k cal/mol)[147] for butyramide whilst the activation entropy for the hydroxyamide (-12.9 e.u.) was considerably less negative than the literature value for the butyramide (-19.5 e.u.).

Thus the introduction of a N-phenyl substituent in the 4-hydroxybutyramide series appears to produce a pronounced loss of activation entropy (5.2 e.u.) with a slight increase in activation enthalpy. This could be rationalized in terms of increased losses of rotational and vibrational freedom in the transition state due to an increase in steric compression over the simple amide case upon introduction of the aromatic residue. Entropies of internal rotations in the gas phase determined by experiment and from theory are in good agreement and are not appreciably

changed in solution[155,156]. Entropy losses as a result of restriction of internal rotations of about 12 e.u. have been tabulated, and small orientational restrictions are sufficient to cause the almost complete loss of the entropies of internal rotation of up to 7 entropy units[39].

That this more negative activation entropy is not observed when the non-hydroxylated analogues are considered could be a result of only the total increase of steric requirements of the transition state (N-phenyl substitution plus conversion of the nucleophile to an effective primary alcohol) being significant.

It has been estimated that the entropy loss upon restriction of rotation about a saturated carbon-carbon single bond, after correction for low frequency motions in the incipient ring, is 3.7 to 4.9 e.u.[39]. The inclusion of further CH_2 group in the alkyl chain of 4-hydroxybutyranilide to form 5-hydroxyvaleranilide result in more negative activation entropies over the series of on average 3.6 e.u. . The activation enthalpies for this series are overall slightly more favourable by approximately 1k cal mol^{-1} than those of the 4-hydroxybutyranilide series (tables 57-60, 65).

In the hydroxyanilide series, increasing the length of the alkyl chain incurrs an additional entropy loss. This entropy loss is presumably due to restricted internal rotation about the additional carbon-carbon bond in the transition state and this suggests that this rotation is in no way frozen out in the initial amide.

Recently it has been demonstrated[167] in hydroxyamides

that the amide function and the hydroxyl group form a 1:1 complex in non-polar solvents in which a hydroxyl proton to carbonyl oxygen hydrogen bond has been suggested. Such a demonstration however merely indicates that the δ hydroxyamides have the geometric ability to form such complexes but offers no evidence as to the structure in highly polar aqueous solvents. Thus, in hydroxyanilides, the additional loss of entropy observed in going from 4-hydroxy to 5-hydroxy anilides precludes the possibility of initial state hydrogen bonding. No such entropy loss is observed in hydroxyamides,[154] the corresponding change being a favourable one of 1.4 e.u. . Thus, in the case of the hydroxy amides, the extension of the alkyl chain by one unit serves to reduce the activation entropy while in the hydroxyanilides it serves to increase the activation entropy and only hydroxyamide initial state internal hydrogen bonding would seem to serve as an explanation of this anomaly at this point.

In the hydroxyanilide series the additional losses of activation entropy are offset by a slightly more favourable activation enthalpy. This lower activation enthalpy must be assumed to be the source of the general overall 10% rate enhancement of the 5-hydroxyvaleranilides over the 4-hydroxy-butyranilides since the activation entropies are less favourable. The sources of enthalpic advantage as they depend on ring size have been considered[153] and it seems likely that the source of

this more favourable enthalpy must be in the relative numbers of eclipsed and of skew butane interactions as the particular transition states are approached.

Thus in the 5-hydroxyvaleranilide series it is the enthalpy of activation ΔH^{*} which appears to give the intramolecular reaction an energetic advantage over the intermolecular reaction. The hydrolysis of the hydroxyamide analogue has been studied in dilute acid[154] and in this case the activation parameters determined are similar to those determined by the same authors for 4-hydroxybutyramide. The activation entropy and enthalpy are respectively -11.5 e.u. and 20.0 k cal mol. Thus in this case the inclusion of another CH_2 group in the chain does not serve to produce a more negative activation entropy but produces the opposite effect whilst the activation enthalpy remains effectively constant.

The effect upon the activation parameters, ΔS^{*} and ΔH^{*}, of changing the substituent on the aryl residue of the series of anilides studied appears to be significant(tables 64-66) and, in that the standard deviations for the observed rate constants are generally much less than 1%, are outwith the level of uncertainty expected from experimental error[145]. Also, without reference to any particular mechanism, the parameters form a self consistant series based upon the expected electronic and inductive effects of substituents. The sense of the change which substituents effect upon ΔS^{*} and ΔH^{*} values could be of significance in any

determination of the nature of the transition state of the reaction but a consideration of this change would be of value only if the sense of the change was identical for all steps of the reaction. A determination of the magnitudes of the individual effects would otherwise be necessary to determine the sense of the change in the slow step.

A source of change in ΔS^{o} which could be influenced by substituents on the aryl residue would be a variation in solvent restriction via hydrogen bonding to the acidic protons in the reactant and product. Since this electro-striction would be increased by electron withdrawing and decreased by electron releasing substituents, a consideration of probable factors affecting ΔS^{o} suggests that the sense of any change would be the same as that observed overall. These effects would be more important in the conjugate acid irrespective of its nature. However this is complicated by the suggestion[156] that the degree of total solvation or the total ordering and disordering effect about any species is composed of effects upon a tightly bound inner solvation shell and on a subsequent solvation layer. These layers are thought to be more structured and less structured respectively than bulk water, and so will register opposite entropic changes upon variation in the acidities of the protons involved in solvent binding processes.

A consideration of the effect of the introduction of an

aromatic substituent upon processes such as solvation and charge delocalization in the conjugate acid and the postulated hydrolysis step transition state tends to suggest that an electron withdrawing group will be more effective in creating initial state instability by charge separation and would thus give more favourable activation enthalpy changes and more negative activation entropy values due to relatively greater increases in transition state solvent electrostriction.

Thus entropy differentials between members in anilide series will be a result of differential solvation due to electronic and inductive effects of the substituents.

In each series the electrophilicities of the conjugate acids of the anilides vary according to the substituent which would account for variance in activation enthalpy (ΔH^{*}) values. Thus electron withdrawing substituents in any series would lower the activation enthalpy, as is observed (tables 64-66). However electron withdrawing substituents are observed to enhance the dissociation constants of the conjugate acids of the anilides thereby having the opposite effect on the standard enthalpy change for the protonation than is observed overall. Thus it can be assumed that the enthalpy change for the hydrolysis reaction becomes more favourable upon substitution of an electron withdrawing substituent.

Direct calculations of the activation parameters for reaction of the conjugate acids of several amides have been carried out.

Martin et al[14] plotted the logarithm of the observed first order rate constant for the hydrolysis of the conjugate acid of 4-hydroxybutyramide against the logarithm of water activity and determined the first order rate constant for the reaction at unit water activity by extrapolation, the rate constants for the hydrolysis of the conjugate acid having been determined by correcting the observed first order rate constants for degree of protonation in the normal manner, the ratio $h_o/(h_o+K_a)$ being taken to represent the fraction of protonated amide. The assumptions made in these determinations and in the subsequent determination of activation parameters by repeating the above calculations at several temperatures are the assumptions that the amide behaves as a Hammett base and that the equilibrium constant K_a does not vary over the temperature range 15 to 35°. From this work, but subject to the above uncertainties, the authors determined ΔS^*, as -28e.u. .

Yates and Smith[60] used an experimental determination of the protonated amide concentration in the acid catalysed hydrolysis of benzamides in H_2SO_4 and so produced values for the first order rate coefficient for hydrolysis of the amide conjugate acid, k_p. These authors, as mentioned previously, also demonstrated that at any concentration of acid, the water activity (and hence the activity of acidic species) is not temperature independent. Thus an error factor is introduced into activation parameter determinations in that an acid concentration, standardized at

one temperature, will vary with temperature. In their calculation of the protonization correction factor these authors assumed no significant change with temperature, thus making the assumption that the dissociation constant of the amide conjugate acid was temperature independent. This assumption was justified to a degree by a demonstration that the logarithm of the protonation correction factor for N-methylbenzamide, over large temperature and concentration ranges varied by a maximum of 1.5%. Moreover pK_a values are in general fairly insensitive to temperature[168].

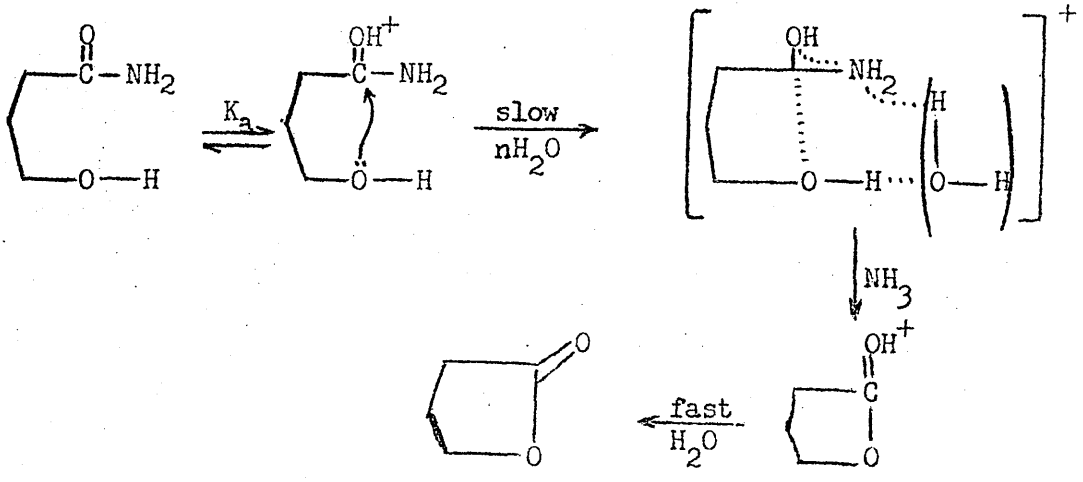
If this is applied to the present work then it is assumed that the conjugate acid dissociation constsnts for the anilides studied are invariant over the range 45° to 65°. Thus ΔS^{*}, and ΔS° can be separately determined.

This procedure was applied to the non-substituted members of the anilide series. The first order rate constants for the hydrolysis thus determined were used to obtain values for ΔS^{*}, for each series (table 66A).

From the results, ΔH_o appears to be small while ΔS_o appears to be negative and of a similar magnitude for each compound so that the magnitudes of ΔH_1^{*} and ΔS_1^{*} bear the same relative relationship within the series as do the ΔH^{*} and ΔS^{*} values.

Mechanisms of Intramolecular Amide Hydrolysis

Previous studies[10,12,13,14,154] of acid catalysed intramolecular hydroxyamide hydrolysis have suggested, when the hydroxyl group has the appropriate disposition to the amide function, that the mechanism is essentially a slow nucleophilic attack on the amide conjugate acid by the hydroxyl group. Concerted proton transfer and nucleophilic attack in the rate determining step was proposed[13] and extended[14,154] to incorporate a role for water in the slow step to give the following mechanism :-



Yamana et al[154] provided evidence of the overall mechanistic features of the hydrolysis reaction of simple hydroxyamides when the reaction product was shown to be mainly lactone by thin layer chromatography, and when the rate of lactone production was shown to fit the theoretical rate according to the scheme:

amide $\xrightarrow{k}$ lactone $\rightleftharpoons$ acid

These observations eliminated the possibility of a neighbouring

group effect increasing the rate of the bimolecular reaction. The same method offered proof that γ ,δ dihydroxyvaleramide hydrolyses by different routes to give the lactone and hydroxy acid.

Thus, the accumulation of experimental evidence(see introduction) obtained indicates nucleophilic attack by solvent water in simple amide acid hydrolysis while experimental evidence obtained in this work and in the literature indicates that the most logical explanation for the enhancement of rate of hydroxy amide hydrolysis is nucleophilic participation by the hydroxyl group. Evidence[154] to support the proposed mechanisms for hydroxyamide hydrolysis includes the observation that the effect of phosphate buffer concentration on the acid hydrolysis of 4-hydroxybutyramide is the same as observed in the acid hydrolysis of acetamide[12] suggesting that the reasonable mechanism of amide hydrolysis by general acid BH is one insensitive to the pK_a of BH as proposed by Bruice et al [12]. This indicates[12] that the processes of proton transfer and nucleophilic attack are concerted in the hydrolysis of amide.

Yamana et al [154] observed the deuterium isotope effect k_{D_2O} / k_{H_2O} on the hydrolysis of 4-hydroxybutyramide at 20° in dilute HCl to be 1.19 which compares with the value determined for acetamide[74], under similar conditions, of 1.45, these values being compatible with the proposed proton transfer mechanism.

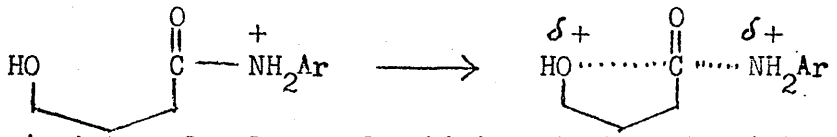
Under these conditions the observed rate constant is controlled to a large extent by the K_a value of the amide which produces, in presence of the weaker base D_2O, the rate ratios observed. It would be of interest to determine this ratio in concentrated acid where the relative rates observed would be those of the hydrolysis reaction alone.

If the slow step includes deuterium transfer to amide nitrogen as suggested it would seem that its effect would be illustrated to greater advantage by this rate ratio since the hydrolysis reaction should be subject to a large primary deuterium effect because a proton transfer is occurring in a concerted rate limiting process. However whether this effect would be manifested in the D_2O/H_2O rate ratio is uncertain since in some reactions where proton transfers between O atoms are thought important, deuterium isotope effects are observed to be small[160-164].

Zimmermann[165-6] has suggested that proton transfer to amides might be concerted with attack of water in the intermolecular reaction because the proton could be moving very rapidly back and forth between substrate and solvent and therefore would remain on the substrate for only 10^{-3} to 10^{-11} seconds. This can be extended to suggest that the attacking water molecule in the intermolecular reaction could come from the immediate hydration sphere of the proton.

However, from the Hammett correlations, the protonation and

and hydrolysis reactions do not appear to be concerted. The ρ value for the acid dissociation reactions when compared with reaction constants for acid dissociation such as the dissociation of the anilinium ion ($\rho = 3.186$ in 30% ethanol[138]) indicates that the positive charge is not located on the nitrogen atom, thereby suggesting O-protonation. There is strong evidence from activation parameters in the anilide series that the slow step is normally A2 in that it involves another species either intramolecular in ring formation or intermolecularly. The sources of entropy losses probably change on going to the intramolecular reaction from loss of translational and overall rotational freedom to loss of freedom of internal rotational and vibrational motions, but the fact that they are observed eliminates unimolecular reactions in the slow step. The magnitude and sign of the ρ value obtained for the intramolecular hydrolysis step of an O-protonated amide conjugate acid reduces the number of possible slow steps. The nucleophilic substitution reaction at the amide carbonyl, if such a reaction were to occur, would possibly produce a similar ρ value but would probably require an N-protonated species for a concerted reaction.



An intramolecular nucleophilic attack by the intramolecular hydroxyl group on the O protonated anilide conjugate acid to

produce a reaction intermediate which breaks down rapidly to produce the lactone and aniline thus seems the most logical process, although a substitution step on an N-protonated amide with concerted loss of aniline has been considered[60] as a possible mechanism in amide hydrolysis to explain the lack of observation of O^{18} exchange.

That some process involving water molecules takes place in the transition state of amide hydrolysis has been indicated by the hydration parameter treatments in this work and in the literature (see introduction). That an intramolecular hydroxyl group, suitably placed, reduces this requirement has again been demonstrated[154] in hydroxyamides and in hydroxyanilides but the work herein and in the literature tends to show that a requirement still exists.

The numerical magnitude of this requirement and the shortcomings of the hydration parameter treatment in predicting this and the role played by the participating water molecules has been discussed. The evidence available for the proposed[14] proton transfer through solvent water molecule(s) to the amide nitrogen being concerted in the transition state has been stated and no new evidence to confirm or disprove this suggestion has arisen herein. However a proton transfer to nitrogen atom well advanced in the transition state would impart a partial positive charge to this atom which, it would appear, could not be compensated for by a suitable

reduction in the suspected minimal conjugative interactions of the nitrogen lone pair to the prospective reaction centre and the reaction centre, respectively in the O-protonated conjugate acid and in the transition state, in order that the observed magnitude of ρ value be produced. Thus this proton transfer process should not be fully concerted with nucleophilic attack although such a process which has not significantly proceeded at the transition state but which has the required water molecules correctly structured in this state, could be suggested to retain a role for water in the transition state. Thus water molecule(s) in the transition state could be acting as a general base, enhancing the nucleophilicity of the oxygen atom by hydrogen bonding.

A further consideration of activation parameter results has shown that the introduction of an N-phenyl group apparently produces significant changes in the constituent activation energy and enthalpy changes. The presence of an N-phenyl group appears to supply a source of entropy loss in the intramolecular reaction. It has been suggested that the presence of an aromatic nitrogen substituent and a primary alcoholic group acting as a nucleophilic in combination are the source of sufficient steric restriction of transition state vibration and rotation to cause the observed entropy losses.

The steric sensitivity of the intramolecular amide hydrolysis transition state can be illustrated by a consideration of

determined activation parameters of 4-hydroxybutyramide and 4-hydroxyvaleramide. The hydrolysis rate is reduced upon the introduction of a 4 methyl substituent[154]. The factors operating to produce this rate reduction should be steric effects and strain effects at the reaction centre in the transition state. Thus further steric interactions in the transition state, upon the introduction of a methyl group, would result in a more negative entropy of activation due to increased restrictions to internal rotational and vibrational motions and in a higher activation enthalpy due to increased strain in the transition state. An increase in nucleophilicity of the secondary alcohol over that of the primary alcohol would be expected to counteract the above effects and tend to enhance the rate with an accompanying more favourable activation enthalpy. These predictions are borne out when the activation parameters are determined[154]:

	4 hydroxybutyramide	4 hydroxyvaleramide
ΔS^{*} e.u. :	-12.9	-13.3
ΔH^{*} k cal mol^{-1}:	19.9	18.4

The entropy losses which result from increased nucleophilic bulk can be taken as further indication that the ring closure by nucleophilic attack is the slow step. Thus steric restrictions would seem to be most important in the transition state.

Another difference which is seen to arise is the change in rate ratio between 4-Hydroxy and 5-Hydroxy amide series upon the

introduction of an N-phenyl substituent.

Although the rate ratio for the anilide series indicates that the rates are essentially equal in 1 Molar perchloric acid the rate constants in general indicate that the hydrolysis rates of the 5-hydroxyvaleranilide series are 10 to 20% greater than the corresponding rates of hydrolysis of the 4-hydroxybutyranilide series. This small increase appears to be a result of slightly more favourable activation enthalpy changes since the activation entropy changes are distinctly unfavourable. In this comparison the source of the more favourable activation enthalpy factors must be a decrease in strain and interaction factors arising on changing from a five membered to a six membered incipient ring in the respective transition states.

Conclusion.

The experimental facts in the acid catalysed hydrolysis of hydroxyanilides and hydroxyamides in mineral acids seem to be consistant with a nucleophilic attack of the intramolecular hydroxyl group upon the O-protonated amide conjugate acid with water molecule(s) acting as general base as the rate determining step.

Not quite concerted with this step, but proceeding to some degree as the transition state decays to the addition intermediate, a rapid proton transfer from hydroxyl oxygen to amide nitrogen seems to be indicated. This would be followed by an elimination

of aniline to form the lactone.

This sort of mechanism in amide hydrolysis explains all experimental observations as long as the slow nucleophilic attack is more than 100 times slower than the elimination reaction since this is the limit of sensitivity of isotopic O^{18} analysis which shows no exchange in amide hydrolysis.

The overall similarities of the intramolecular and intermolecular reactions tends to suggest that the rate enhancements observed are the result of a simple concentration effect with slight energetic favourability being secondary. In this context it was thought to be of interest to study the hydrolysis of hydroxyanilides in which the positions of the reacting groups have been adjusted so that they closely resemble the positions they are thought to assume in the transition state for lactonization.

The Acid Catalysed Hydrolysis of Olefinic and Bicyclic Hydroxyanilides

The most favoured mechanisms for the acid catalysed hydrolysis of amides in the literature (see introduction) involve, as the principle steps, a slow nucleophilic attack by solvent water on the O-protonated amide conjugate acid and a relatively fast breakdown of the addition intermediate to produce an acid and amine.

If the proposed tetrahedral addition intermediate exists as a discrete species in acid catalysed amide hydrolysis, the lack of O^{18} exchange[170,171] suggests that the breakdown of the intermediate to products is at least one hundred times faster than the return to reactants.

In the 4-hydroxybutyranilide and 5-hydroxyvaleranilide series, the γ or δ hydroxyl function produces approximate twenty - fold rate enhancements apparently as a result of a higher effective nucleophile concentration.

It is obvious that the effective concentration of nucleophile can be increased by positioning the hydroxyl group and the anilide function in a suitably rigid structure in order that the two

functions are in constant close proximity to one another. Although the precise relative locations and orientations of these groups could be of importance[110,111] it would seem that endo, cis 2-(N-phenylcarbonamide) 6-hydroxynorbornane and endo cis 2-(N-phenylcarbonamide) 3-hydroxymethyl norbornane would have increased rates of nucleophilic attack of the hydroxyl function on the amide conjugate acid due to an increased effective concentration over both the simple anilides and simple hydroxyanilides.

Characteristics of Acid Hydrolysis.

Thus these bicyclic hydroxyanilides were prepared and characterized as detailed in the preparative experimental section. Also, an olefinic hydroxyanilide 4-hydroxy - cis crotonanilide, was prepared and characterized. These compounds were hydrolysed in several moderately concentrated solutions of perchloric acid at a series of temperatures and the reaction was followed by the normal procedure (kinetic experimental section), the rate of disappearance of the anilide being monitored. In each case, the anilide had an ultra-violet spectrum which had a maximum at 242.0nm, this band being expected to disappear upon hydrolysis since both of the expected products, the lactone and aniline have no effective absorbance at this wavelength in moderately concentrated perchloric acid solutions at this substrate concentration (1×10^{-4} mol litre^{-1}.).

However, this behaviour, which is observed under these conditions for the alkylanilides and simple hydroxy anilides studied, was not

observed in the cases of these rigid hydroxyanilides.

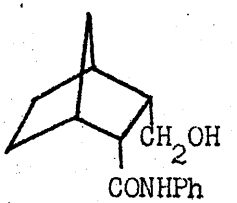
The absorbance changes observed for the bicyclic compounds were an initial rapid absorbance decrease then a relatively slow decrease, to approximately zero absorbance (Figs. 1 and 2).

The first order rate constants for these changes were determined in the normal fashion (see kinetic experimental section), the infinity value of absorbance being estimated for the initial change.

In the case of the bicyclic compounds, under standard conditions of 1 Molar perchloric acid at 25°, the rapid initial reaction had an absorbance change of approximately 30% of the total absorbance decrease. The olefinic hydroxyanilide seemed to exhibit a normal absorbance change in 1 Molar acid (Figure 3). However, in more concentrated acids, it was thought that a change was observed similar to that described above, but in which the initial change was 85% of the total (Figure 4).

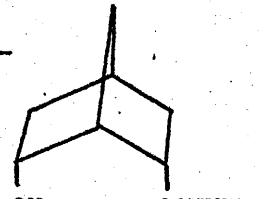
When the initial reactions were followed in a series of acid solutions of increasing concentration the rates were found to increase to approximately 4.5 Molar perchloric acid and then decrease to the upper limit of concentration series used (9 Molar).

Figure 1



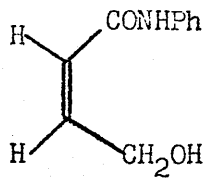
A 1.0×10^{-4} molar solution in 0.5 Molar perchloric acid at 50°. Absorbance change followed at 242.0nm.

Figure 2



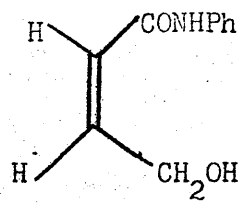
A 1×10^{-4} molar solution in 1.0 M perchloric acid at 25°. Absorbance change followed at 242.0nm.

Figure 3



A 1×10^{-4} molar solution of 4-hydroxy-cis-crotonanilide in 1.0 molar perchloric acid at 25°C. Absorbance change followed at 242.0nm.

Figure 4



A 1×10^{-4} molar solution of 4-hydroxy-cis crotonanilide in 6.0 Molar perchloric acid at 25°C. Absorbance change followed at 242.0nm.

In following the initial reaction in the case of the 2,6 substituted bicyclic hydroxyanilide, the estimated endpoint was found to occur at a progressively lower absorbance value for each acid concentration (1 to 9 Molar) (eg. Figures 2 and 5).

Conversely,the absorbance endpoint to which the initial reaction tended, in the case of the 2,3 substituted bicyclic hydroxyanilide, increased with increasing acid concentration. Thus, although the rate of this initial reaction increased with increasing acid concentration over the range 1 to 4 Molar perchloric acid (Tables 75,76,Graph 16), the above tendancy of the initial reaction endpoint reduced the absorbance decrease observed in 1 Molar acid (Figure 1) until at 5 Molar acid little or no initial change was observed (Figure 6). This trend continued so that at 9 Molar acid an initial rapid increase in absorbance at 242.0nm of approximately 0.2 absorbance units for a 10^{-4} Molar solution of hydroxyanilide was observed.

In the case of the olefinic hydroxyanilide the effect of an increasing acid concentration upon the endpoint of the suspected first stage reaction could not be determined.

All of the initial reactions were observed over the range of acidities at 25^{o}whereas the relative slowness of the secondary changes meant that they were more easily observed at higher temperatures. The extreme rapidity of the initial change of the 2,6 substituted hydroxyanilide meant that even in the most dilute solutions used

(1 Molar acid)the rate of change of absorbance was too rapid to be followed by the method used at temperatures above approximately $40^{o}C$.

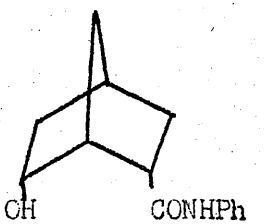
Thus the effect of increasing the acid concentration on the observed rate of the initial change for the 2,6 substituted bicyclic and the olefinic hydroxyanilides is observed to be similar to the effect upon the observed hydrolysis rate of simple amides and simple hydroxyamides in that the rate-acid concentration profile includes a maximum (table 75, graphs 14 and 15). The rate of the initial change of endo cis 2-(N-phenylcarbonamide) 3-hydroxymethyl norbornane was observed to increase with increasing acid concentration to the limit of observation (tables 75,76 and graph 16).

The effect of increasing the acid concentration on the observed rate of the secondary change for the 2,6 substituted bicyclic hydroxyanilide was seen to be a rate decrease (table 76).

A similar decrease for the 2,3 substituted bicyclic hydroxyanilide was observed in 0.5, 1.0 and 1.5 Molar perchloric acid solutions from absorbance versus time plots but rate constants were not calculated to quantify the rates.

From rate constant determinations at various temperatures the activation parameters for several of the observed changes in absorbance for these compounds were calculated (tables 77,78) and are listed in table 79.

Figure 5



A 1×10^{-4} molar solution
in 7.5 molar perchloric acid at 25°.
Initial change followed at 242nm.

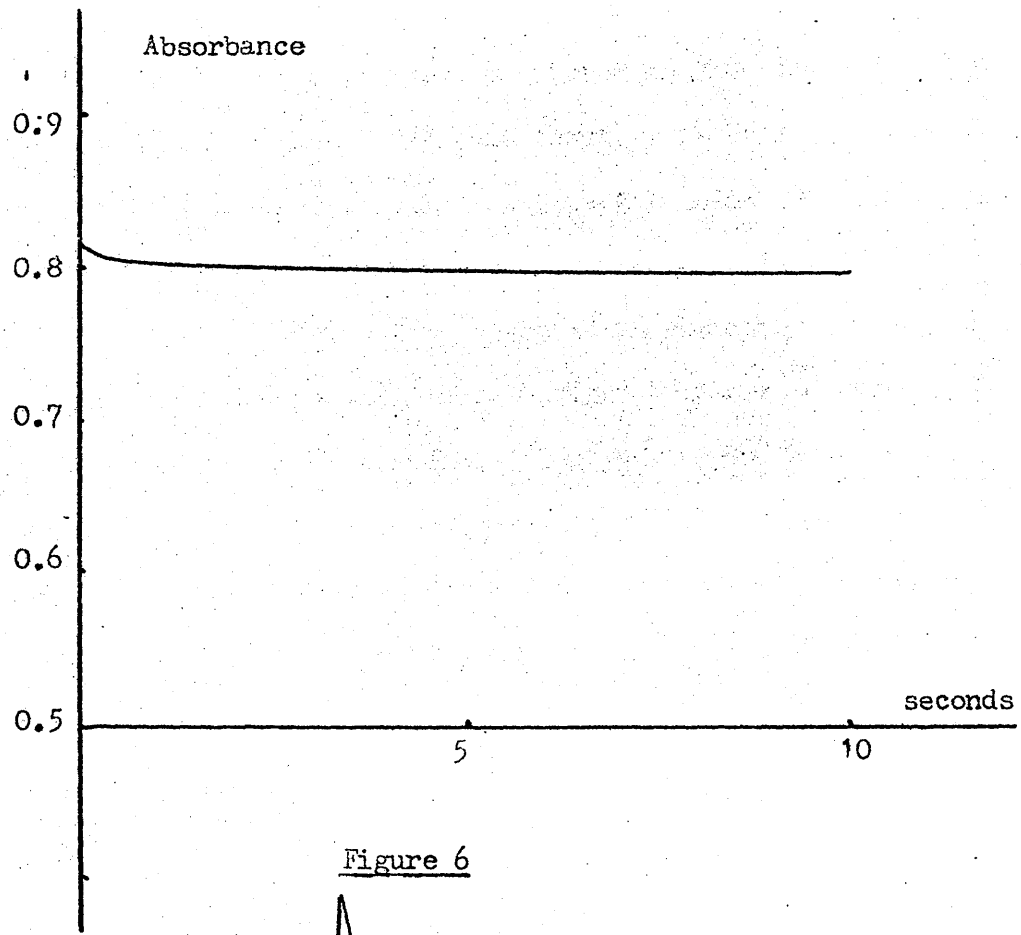
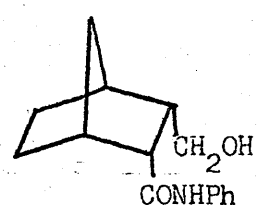


Figure 6



A 1×10^{-4} molar solution in 5.0 molar perchloric acid at 25°. Absorbance monitored at 242.0nm.

Discussion

Since the absorbance changes in the case of the rigid hydroxyanilides are not the same as those monitored in the simple hydroxyanilides, it appears that a different reaction is being observed.

The first consideration which must be taken into account is the nature of the materials the hydrolyses of which are being studied. The bicyclic hydroxyanilides were prepared as described in the experimental section from well characterized lactones by reaction with an anilinium Grignard reagent. The hydroxyanilides were characterized by the normal methods giving all the expected elemental analysis, infra-red, n.m.r. and ultra-violet spectroscopic data. The t.l.c. data showed the 2,6 substituted hydroxyanilide to be pure within the limits of detection although the 2,3 substituted compound had some minor impurities at lower R_f. Hydrolysis of these compounds in 0.5 Molar perchloric acid produced dark oils the R_f's of which (0.68,$CHCl_3$) were identical with the parent lactones and which were produced in close to theoretical yields.[159] One feature of the solution infra-red spectra of the bicyclic hydroxyanilides was that the amide I,amide II regions differed from that observed in the nujol mull spectra, the bands appearing to be shifted or at least the amide II band being shifted to approximately 1770 cm^{-1}. Hydrogen bonding effects in non polar

solutions, to which these types of compounds have been shown to be susceptible[167], are known to give rise to considerable shifts of the frequency of the amide I, II bands[169].

The olefinic hydroxyanilide was prepared by a series of well tested, stereoselective procedures, each stage being characterized by the normal methods and thus the hydroxyanilides which were subjected to hydrolysis conditions are confirmed as the desired materials.

As can be seen from the tables of results,(tables 75-80) in data accumulated to characterise the hydrolyses of these species is rather limited, the most data being available for the absorbance changes observed for the 2,6 substituted bicyclic hydroxy anilide.

Endo Cis 2-(-N-Phenylcarbonamide) 6-Hydroxy norbornane

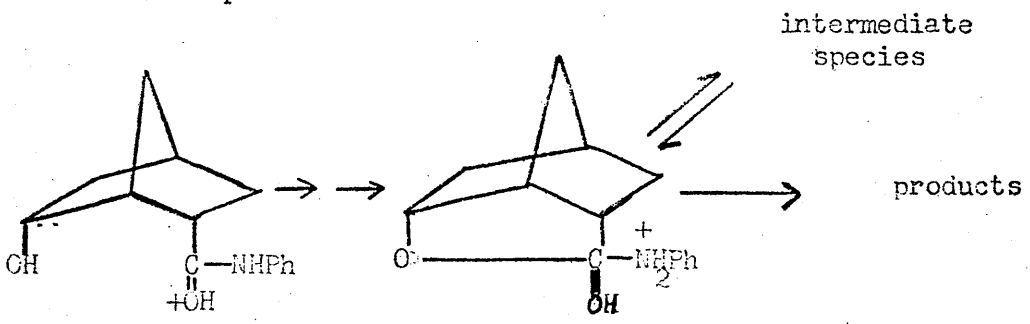
The form of the absorbance versus time plots for the acid catalysed hydrolysis of these rigid hydroxyanilides suggests that some type of intermediate compound is formed which slowly hydrolyses to produce the lactone and aniline.

If the expected mechanism of hydroxyanilide hydrolysis is first considered, other possible changes being ignored, a logical explanation of the abnormal absorbance changes can initially be presented.

If the rigid juxtaposition of the hydroxyl and carboxanilide groups increases the rate of the proposed rate determining nucleophilic attack by intramolecular hydroxyl group to a sufficiently large extent, the rate determining step of the reaction will change

to become the rate of the next slowest step in the reaction.

If a fairly stable reaction intermediate forms, the breakdown of this intermediate could be observable. The probable nature of the initially formed intermediate in hydroxyanilide acidic lactonization is depicted below

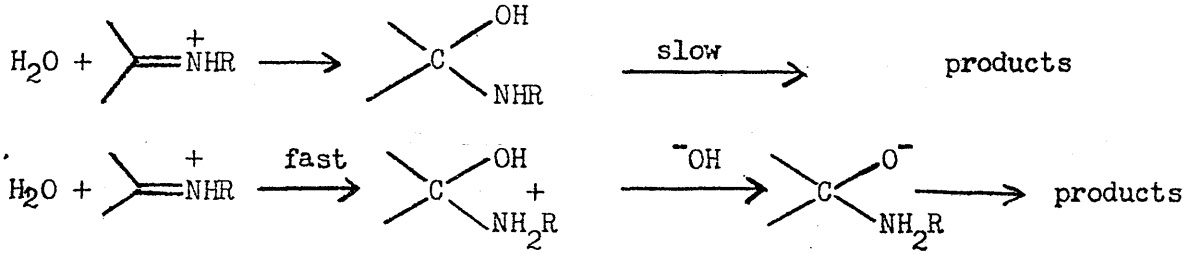


Since the formation of the intermediate will occur at a greatly enhanced rate irrespective of the nature of the slow step, the initial absorbance change must be attributable to the rate of disappearance of the hydroxyanilide functional group combination. In one possible scheme (shown above) the transformation to intermediate is considered irreversible. If the rates of the subsequent reactions are very slow, then the rate of hydroxyanilide lactonization can be determined. In this case it has to be assumed that the ultra-violet spectrum of an intermediate is somewhat similar to that of the hydroxyanilide in that it contains a band at similar wavelength in 1 Molar perchloric acid (but of lower extinction coefficient.) As acid concentration increases, the intensity of this absorption band decreases considerably.

The nature of the ultra-violet spectrum of such an intermediate species tends to suggest that it would not be of the form thought

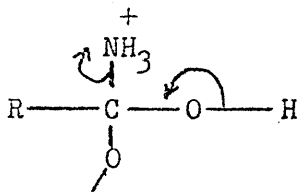
to be a probable tetrahedral intermediate structure since such a structure would be essentially anilinium-ion like and thus would give an almost featureless spectrum under these conditions.

The presence of a species which could form, by reversible addition of water, a similar tetrahedral intermediate to that thought to be present in amide hydrolysis and which would have a suitable ultraviolet spectrum is a possibility in this case. A prominant feature of the rate of disappearance of the intermediate species in the case of the 2,6 norbornane was the decrease in rate with increasing acid concentration. This same feature is observed in such compounds as Shiff bases[167] and iminolactones[172] which are thought to proceed through similar intermediates to those suggested for amide hydrolysis. Thus the acid catalysed hydrolysis of benzylidene-anilines in acid solution is thought to involve the decomposition of the protonated amino alcohol intermediate or of the neutral species in its zwitterionic form



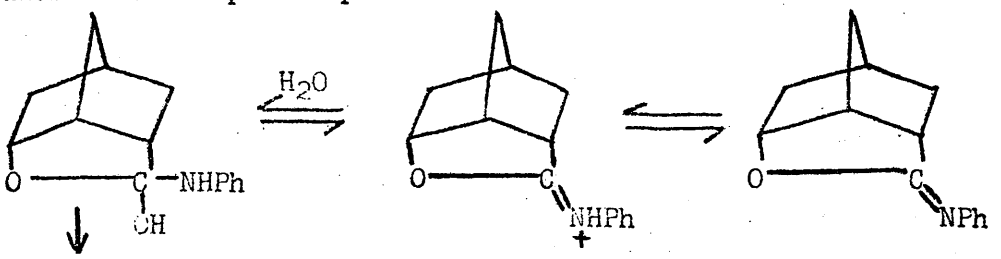
The decrease in the rate of this reaction in strongly acid solutions is thought to be a result of the fact that these reactions require general base catalysis to remove the proton from the amino alcohol intermediate[173]. Similar behaviour in the acid catalysed hydrolysis

of iminolactones has been observed[172,174] these compounds being thought to produce the same intermediate as that produced by the acid catalysed lactonization of hydroxyanilides[172]. The kinetic behaviour of 2-phenyliminotetrahydrofuran was shown by Schmir et al to be similar to that found in imine hydrolysis and the hydrolysis of related compounds, the common mechanism which appears to encompass such compounds being thought applicable[172]. Thus, in acidic media, the reaction of water with the protonated iminolactone leads to a neutral tetrahedral intermediate, breakdown of which in its zwitter-ionic form allows for the expulsion of the neutral amine. The much more rapid hydrolysis of this iminolactone in acid solution than the hydrolysis of 4-hydroxybutyranilide was demonstrated as was the complete partitioning of the intermediate species to lactone and aniline. The non observance of isotopic O^{18} exchange in amide hydrolysis can therefore be explained by the existance of such an intermediate that allows the more favourable release of a neutral amine.



The iminolactone studied by Schmir et al had a rate maximum at approximately pH5, increasing acid concentration causing a rate decrease, the behaviour which is displayed by the intermediate species in the reaction presently under consideration. Thus, if as proposed for reactions involving intermediates of the above type, the breakdown of the tetrahedral intermediate is the slow step in

moderately concentrated acid solutions, then equilibria with the iminolactone and its conjugate acid, as shown below, could account for the observed spectral changes. This would depend upon the magnitudes of the extinction coefficients and/or the relative amounts of each species present



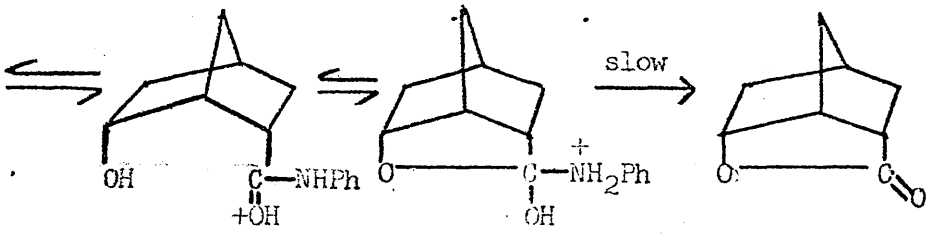
products

The extinction coefficients for these or related species in 1 M perchloric acid are not available. However, in ethanol, the extinction coefficients[172] of 2-phenyliminotetrahydrofuran and 4-hydroxybutyranilide are 6900 at 243 nm and 15000 at 242 nm respectively. Also, the decay to lactone and aniline of 2-phenyliminotetrahydrofuran is calculated to be 2.5 times faster than the dehydration to iminolactone conjugate acid[172]. Thus it would seem that, for the proposed existance of iminolactone intermediates to be possible, either some factor favouring the partitioning to iminolactone is present or the extinction coefficient of the iminolactone or its conjugate acid is of sufficient magnitude in moderately concentrated acid to produced the observed spectral changes.

A kinetic determination[172] of the pK for the protonation equilibrium of 2-phenyliminotetrahydrofuran gave a value of 5.06

suggesting that the major species present throughout the acid concentration range used in the study of this essentially similar compound would be the unprotonated iminolactone. Thus this species would be required to be present in large concentrations or to have a larger extinction coefficient than the hydroxyanilide. The observation that an increasing acid concentration increases the fraction of the total absorbance change attributable to the initial reaction (Figs. 1,5) could be accounted for by an accompanying decrease in the rate of iminolactone conjugate acid formation.

In another reaction scheme (shown below) the observed spectral changes are accounted for by the reversible formation of the tetrahedral intermediate. In this case the rapid formation of an equilibrium amount of tetrahedral intermediate would account for the initial rapid absorbance decrease, while the slow breakdown of intermediate to lactone and aniline would provide the second absorbance change.



As acid concentration increases, the decrease in the rate of the second reaction could be accounted for by a decrease in the concentration of a basic species required to catalyse the breakdown

of an amino alcohol intermediate to products or by a reduction in the degree of proton transfer, as water concentration decreases, to create the intermediate form most favourable for aniline elimination.

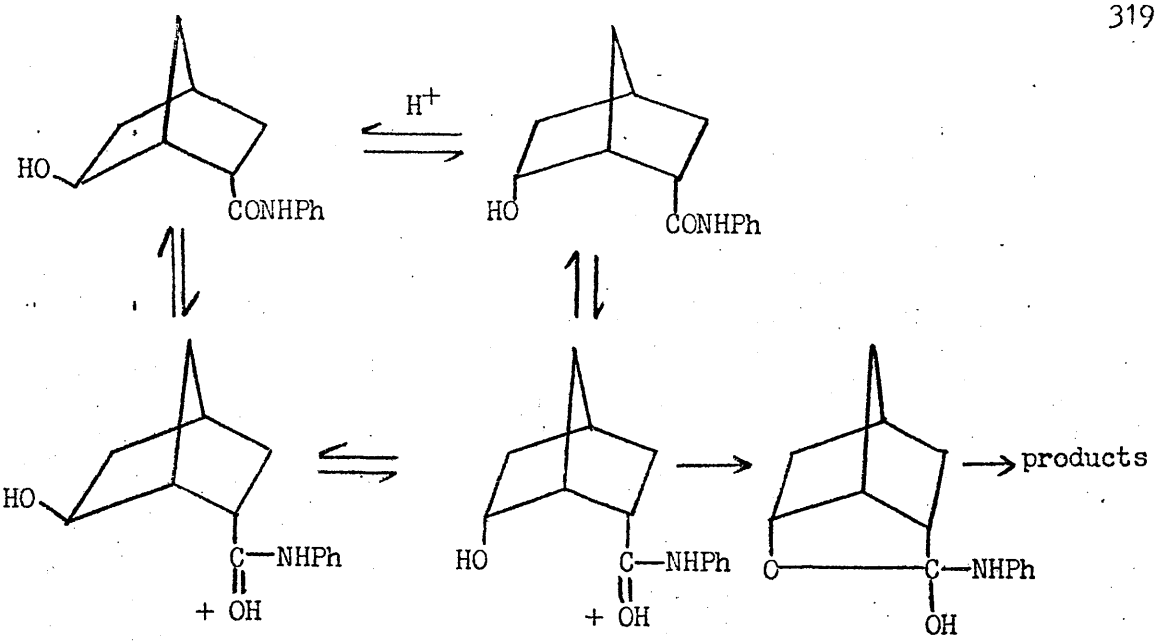
The activation parameters which would be expected on the basis of the postulated schemes can be compared with the parameters derived from the initial and secondary changes. The parameters derived from the intial change would consist of different combinations of parameters if either of the hypothetical schemes obtained. This would also be true for the second reaction.

The activation entropy (table 77) for this compound's initial change was -19.4 e.u. and the activation enthalpy was 13.11 k cal mol^{-1}. The corresponding values of these parameters for the secondary change were -22.61 e.u. and 15.73 k cal mol^{-1} respectively. When the activation parameter values obtained for the initial change are compared with the corresponding parameters for the hydrolysis of 4-hydroxybutyranilide under the same conditions(-18.11e.u.and18.07 k cal mol^{-1} respectively) it is seen that the initial reaction is mainly characterized by a lowered activation enthalpy. Empirically, on the basis of the suggested mechanisms, the activation entropy would be expected to be less negative since freedom of internal rotation about two C-C bonds has been eliminated in the intial and transition states, but factors such as transannular non-bonded interactions causing rotational restrictions in the transition state of this sterically compact system could, with other factors such as the

presence of a nucleophile with greater steric requirements, be the sources of the entropic losses. The lowered value of the activation enthalpy appears to be the source of rate enhancement in energy terms and is considered to derive from a high enthalpic initial state in which steric compression is important and from the more nucleophilic secondary hydroxyl function.

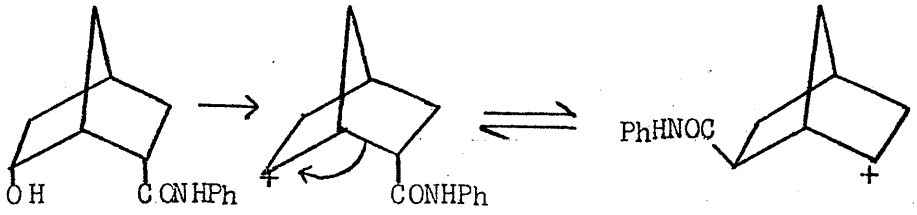
The activation parameter values for the secondary change suggest a bimolecular reaction and would be in accord with the slow step being the attack of water on the protonated iminolactone or a base catalysed hydrolysis of an amino alcohol intermediate. The complex nature of the probable composition of these parameters as derived from any of the suggested mechanisms suggests caution in any interpretation of their overall magnitudes.

Another apparently acceptable mechanism to account for the observed changes could be written as shown below. Thus a rapidly achieved equilibrium mixture of exo and endo alcoholic anilides could possibly explain the spectral observations. In this mechanism the reversion of the exo species to endo could be the slow step, and would be required to be retarded by increasing acid concentration. If the achievement of equilibrium was also retarded by increasing acid concentration all the observed changes would seem to be accounted for.



This scheme would involve epimerization at the carbon to which the hydroxyl group is attached. These changes are thought unlikely since they would not be a possible explanation of the very similar changes observed in the case of endo-2(N-phenylcarbonamide)-endo-3-hydroxymethyl norbornane.

The use of the norbornane ring raises the question of non-classical ion rearrangements as exemplified below:



Such rearrangements would probably produce the same results as above and so would not be an explanation in the 2,3 substituted norbornane case.

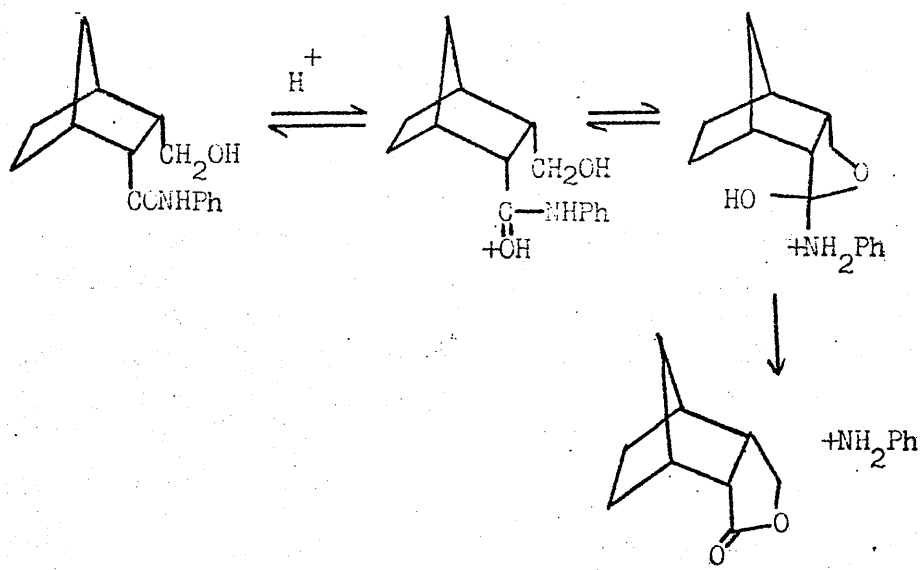
Endo-Cis 2-(N-Phenylcarbonamide) 3-Hydroxymethyl Norbornane and 4-Hydroxy-Cis-Crotonanilide.

Consideration of kinetic and spectral data obtained from a study of the acid hydrolysis of the 2,3 substituted bicyclic hydroxyanilide and of 4-hydroxy-cis-crotonanilide provides evidence which supports the suggestion that these rigid hydroxyanilides proceed, in their acid hydrolysis, via intermediate species, the breakdown of these species being the slow step in the overall reaction. Some indication is given that the same mechanisms need not be present throughout the series.

At low, fixed acid concentration (1.0 Molar perchloric acid) the same characteristic spectral changes are clearly exhibited by both bicyclic species (Figures 1 and 2 respectively). It is thought that similar changes can be detected in the plots of absorbance versus time for the olefinic hydroxyanilide (Figure 4). However the response of these spectral characteristics of the bicyclic species to an increasing acid concentration differ markedly as described earlier. In the case of the 2,6 substituted hydroxyanilide, on the basis of the proposed scheme, the spectral changes would seem to indicate that either a combined concentration increase of anilide conjugate acid plus tetrahedral intermediate (anilinium-ion like) or a similar concentration change of iminolactone type species was occurring with increase in acid concentration.

As described previously, the effect of increasing acid concentration, in the case of the 2,3 substituted bicyclic compound, is the reverse of that exhibited by the 2,6 substituted bicyclic hydroxy-anilide.

It would appear, on the basis of generally observed spectral behaviour of anilides in acid solutions, that the exclusive presence of the system, depicted below, is ruled out in the case of the 2,3 substituted bicyclic compound since superficially it seems that a species of a greater extinction coefficient than the anilide or its conjugate acid is formed.



However, in the absence of spectral data for the relevent imino-lactones, no further conclusions can be drawn.

The spectral changes observed in the acid hydrolysis of the

olefinic hydroxyanilide in 1 Molar perchloric acid appeared to be no different from those obtained for 4-hydroxybutyranilide. However, when the absorbance versus time curves for hydrolysis in stronger acid solutions were examined, the same general changes as found in the bicyclic compounds were thought to be exhibited (Fig. 4).

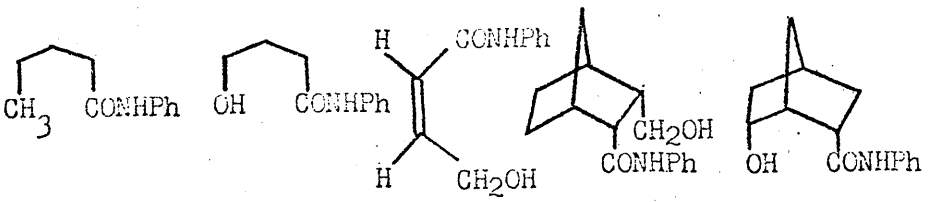
Activation parameters were determined in 1 Molar perchloric acid for the initial change for the 2,3 substituted compound and compared with similar parameters determined for the 2,6 substituted compound thus -12.52 e.u. and 18.2 k cal mol^{-1} were the values determined at 25° for ΔS^{*} and ΔH^{*} for the 2,3 substituted compound. These do not compare closely with the corresponding values determined for the 2,6 substituted hydroxyanilide (-19.14 e.u. and 13.11 k cal mol^{-1}) but are similar to those determined for the reaction of 4-hydroxy-cis-crotonanilide (-13.82 e.u. and 17.08 k cal mol^{-1} for ΔS^{*} and ΔH^{*} respectively). These values of ΔS^{*} , for the bicyclic, 2,3 substituted and olefinic hydroxyanilides are in line with the expected ΔS^{*} values when the reactions of butyranilide and 4-hydroxybutyranilide are considered (-19.30 e.u. and -18.07 e.u. respectively), since the 'freezing out' in the initial state of an internal rotation about a carbon to carbon σ bond by the introduction of a rigid structure or a π bond would be thought to lead to a lower activation entropy. In the case of the 2,6 substituted compound, two internal rotations about carbon to carbon single bonds are 'frozen out' in the initial state, but the

expected entropy gain appears to be compensates by some other source of entropy loss.

These activation parameters, depending upon the scheme or schemes by which initial reaction proceeds, could be a complex combination of several constituent parameters so that the relative magnitudes of a parameter for each compound need not be significant. Moreover, the relative magnitudes of ΔS^{*} values determined in the butyranilide and 4-hydroxybutyranilide cases did not seem to be adequately predicted by the simple principles described above. It would therefore seem, in these more complex systems, that any conclusions drawn from these activation parameter magnitudes should be treated with caution.

If the same unusual spectral changes thought to be observable in the lactonization reaction of the olefinic hydroxyanilide are indeed present, then the constituent absorbance changes are different in magnitude from those observed in the bicyclic cases. In this case the secondary change would only be accounting for approximately 15% of the total in 6M perchloric acid (Fig.4). The mechanism involving the equilibrium formation of a tetrahedral intermediate is not ruled out but no conclusions can be drawn in the absence of spectral data for the relevant iminolactones.

A consideration of rates of the initial changes of the complete series of hydroxyanilides at 50° in 1M perchloric acid solution relative to the rate of butyranilide hydrolysis under the same conditions gives the following relative rate ratios:

Compound: 

$10^5 k_{obs}$ sec^{-1} :	1.877	44.28	3057	683.8	58,900*
k_{rel} :	1	23.2	1628	364	31,400*

(* The reaction of the 2,6 substituted norbornane was too rapid to be followed at 50° and the values shown were estimated from the Arrhenius plot).

Although these figures depend upon the assumption that the change in absorbance being monitored is entirely the result of disappearance of anilide function, the relative rates nevertheless bear a resemblance to relative rates obtained for the lactonization of bicyclic hydroxy acids[175].

It might have been expected that the ability of the π electrons of the olefinic hydroxyanilides double bond to stablize the positive charge of the conjugate acid of the same species by resonance interaction would have resulted in a rate of disappearance of anilide function somewhat slower than in the 2,3 substituted bicyclic hydroxyanilide. However this resonance interaction shows up neither in the relative rate ratios, in that the olefinic hydroxyanilide disappears at a greater rate, or in the activation parameters, in that such an interaction would be expected to raise the activation enthalpy since the electrophilicity of the anilide conjugate acid

would be reduced. It must be assumed that this effect is totally overcome by some other factor which favours cyclization. Factors which could be relevant in this context would be tortional strain effects and angle strain effects in the respective transition states but the features which would control these factors cannot be profitably discussed without some degree of certainty as to the degree of bond formation and hence cyclization which exists in the transition state.

Any discussion of the observed secondary reactions is limited at this stage by the paucity of data. However its bimolecular nature has been indicated in at least one compound this being in accord with the suggestion that the slow step could be the base catalysed conversion to products of the tetrahedral intermediate or the attack of a water molecule on the conjugate acid of the imino-lactone formed by dehydration of the tetrahedral intermediate.

One feature which must be taken into account when considering the manner in which the proposed mechanisms fit experimental observations, both in this work and in the literature, is the observation that no O^{18} exchange is found in amide hydrolysis. In the case of methylated benzamides, no exchange is observed up to 85% sulphuric acid although the corresponding benzimidates exhibit a change of rate determining step within this range to produce considerable quantities of the corresponding amide[116]. If this observation extends to anilides of the type studied herein the existance of the mechanism involving equilibrium between the

anilide conjugate acid and the cyclic tetrahedral intermediate must be in doubt. Also, while imidates can produce amides in strong acid solution, there arises some considerable doubt, at least in the methyl benzamide systems, that amides and imidates proceed in their hydrolysis by way of the same intermediate. If this doubt can be extrapolated to the hydroxyanilide system then the proposal that iminolactones species are intermediates in hydroxyanilide hydrolysis must be examined. It would be useful to critically test these proposals by a synthesis and a study under acid conditions of the relevant iminolactones.

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