A Thesis

entitled

"Spectroscopic studies concerning certain biologically important substances"

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by

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Summary.

The object of the research described in this thesis has been to utilise infrared spectroscopy in the study of the detailed structure and the interactions of some biologically important molecules capable of inter- and intra-molecular hydrogen bonding. Interest has been particularly directed towards the study of a number of salicylates which have been used therapeutically with some degree of success by the late Dr. James Reid and his colleagues of the Medical Research Council, at the Clinical Chemotherapy Research Unit, Western Infirmary, Glasgow. The research falls into five convenient sections. The reasons for undertaking the work in each section, a description of the work and its results are given below.

Section 1. The Ethynyl-Hydrogen Bond. Association in Ether solution. A number of interesting acetylenic compounds were available for study. These acetylenes offered an excellent opportunity to obtain first hand experience of intermolecular associations by proton donating groups where steric interferences were at a minimum. The spectra of these compounds were obtained for liquid or solid state, in hexane, carbon disulphide, and ether

solutions. The effects of self association and association with ether have been evaluated.

Section 2. Infrared Spectra of Aryl Carboxylic Acids and their Esters. As a necessary preliminary to the interpretation of substituted salicylic acid spectra, some substituted benzoic acids and esters were studied. Complex carbonyl absorption in ortho halogeno-benzoic acids and esters was observed and ascribed to conformational isomerism rather than Fermi Resonance. This finding initiated a larger scale investigation into the spectra of substituted benzoic acids, esters, benzaldehydes and acetophenones. Some correlations between relative acidity and infrared spectra have been considered.

Section 3. Infrared Spectra of Substituted Salicylic Acids and their Esters. As mentioned above, the biological importance of some substituted salicylic acids merits detailed investigation into their structures and interactions. Spectra of a large number of substituted salicylic acids and esters in several solvents have been recorded. Marked frequency shifts by 6-alkyl or bulky 3-alkyl groups have been ascribed to steric enhancement of chelation by compression of the phenolic hydroxyl group.

Section 4. Infrared Spectra of Substituted Salicylaldehydes.

The two main objectives of this section were to ascertain (a) if competitive intramolecular bonding existed between a phenolic hydroxyl group and carbonyl or nitro groups as alternative proton acceptor sites, in a series of 3-nitrosalicylaldehydes and (b) if the steric enhancement of chelation, found for substituted salicylic acids and esters, also existed in the corresponding substituted salicylaldehydes. A parallel trend to (b) has indeed been found. However the subject matter of this section is mostly concerned with the competitive intramolecular bonding afforded by the 3-nitro substituents. The character of the hydroxyl, carbonyl and nitro absorptions (in a non polar medium) shows that the phenolic group is bonded principally to the nitro group, but that the chelated o-hydroxy-carbonyl species predominates in 2-hydroxy-3-nitro-acetophenone and methyl 3-nitrosalicylate.

Section 5. Phenol-Ether Association. It is difficult to interpret the true nature of the effects due to bulky alkyl groups ortho to a grouping involved in intermolecular association. Both steric inhibition to association and deactivation of acidic protons by inductive effects are

equally reasonable explanations for the resultant spectral characteristics normally identified with hydrogen bond weakening. Spectroscopically detected entropy effects of considerable magnitude are found in the association of a range of ortho alkyl substituted phenols with a series of dialkyl ethers. This system was chosen for a more detailed quantitative investigation of the problems mentioned above. It has been found that systematic alkyl substitution in the ortho positions of phenols and the α-positions of the ether molecules lowers the equilibrium coefficients for the phenol...ether association. However the strength of the bond, as indicated by the hydroxyl frequency shift, is affected by steric factors due to the phenol, only in solutions of 2,6-di-t-butyl phenol. Of the ethers, di-t-butyl ether shows some bond weakening but only with the ortho dialkyl phenols.

The author wishes to express his gratitude to Professor R.A. Raphael, Regius Professor in Chemistry, University of Glasgow and the late Dr. James Reid, Director, Medical Research Council, Clinical Chemotherapy Research Unit, at the Western Infirmary, Glasgow, for the opportunity to carry out this work and for their guidance. He also thanks Drs. G. Eglinton and C.J.W. Brooks, who jointly directed this research, for their constant help and encouragement.

He thanks Mrs. F. Lawrie and Mr. F. Gisbey for considerable aid and teaching in the technique of infrared measurements, andMisses J. Young, I. Currie and P. Pellit for preparation or purification of some samples. He is grateful for helpful discussions with many members of Glasgow University staff, in particular Dr. J.C.D. Brand and with Dr. L.J. Bellamy of the Ministry of Aviation, E.R.D.E., Waltham Abbey, Essex.

Contents

Page

Introduction.....1

Section 1. - Historical.....10
Results and Discussion...13
Summary.....33
Appendix.....34

Section 2. - Historical.....46
Results and Discussion...50
Summary.....82

Section 3. - Historical.....94
Results.....97
Discussion.....106
Summary and Appendix.....111

Section 4. - Historical.....122
Results and Discussion...125
Summary.....142

Section 5. - Historical.....153
Results.....157
Discussion.....162
Summary.....171
Appendix.....173

Experimental - 180

Introduction.

During the three years 1958-1961, the author has been a member of the staff of the Clinical Chemotherapy Research Unit of the Medical Research Council, at the Western Infirmary, Glasgow. For a considerable period of time one of the principal interests of this Unit has been to explore further and, if possible, to understand the remarkable chemotherapeutic properties of salicylates. The work discussed in this thesis is part of a programme to utilise infrared spectroscopy to throw light on the detailed structure and nature of the interactions of salicylate. It has been attempted, during the course of this work, to establish spectroscopic methods which would be of general use in the investigation of similar important biological systems.

Infrared spectroscopy has been widely used in the service of medicine. Principally the applications have been analytical. A survey of many of the diverse applications of infrared spectroscopy in biology, up to 1957, has been published[1]. The subjects include characterisation of amino-acids, polypeptides, proteins and nucleic acids in various environments; the characterisation of Microbacterial

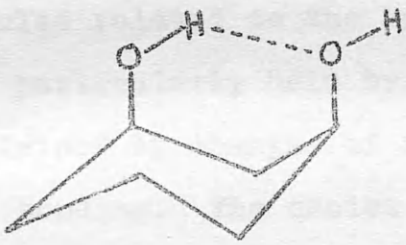
strains, serum and tissue lipids; many other biological applications. This publication[1] also reviews the fractionation procedures (apart from the more recently perfected gas-liquid chromatography) which are convenient to use in conjunction with infrared spectroscopy. With the enormous increase in the use of infrared spectroscopy its applications to biology have been advancing on a wider front; examples range from relatively crude analytical uses (e.g. the classification of gallstones by Chihara et al[2], obtained by examination of nujol mull spectra) to the more refined studies relating biological activity to molecular structure, which have recently been reviewed by Sadler[3].

Few analytical tools are as powerful and accessible as infrared spectroscopy for the study of conformational and configurational details, since the absorptions of similar groups differing only slightly in environment can often be distinguished easily by precision spectrometers. Some examples are the different frequencies due to axial and equatorial hydroxyl[4] and halogen[5] stretching vibrations, the differences of carbonyl groups in 4, 5, and 6 membered rings[6], and the differences in carbonyl frequencies due to dipolar[7] interactions. Hydrogen bonding, so important in all biological systems,

is also readily characterised, due to the extreme sensitivity of X-H vibrations to changes in hydrogen bonding

sensitivity of X-H vibrations to changes in hydrogen bonding.

More recently a great number of advances in conformational elucidation have involved the presence, absence, or degree of hydrogen bonding. The classical example of such a system was cyclohexane-1,3-diol. Kuhn[8] considered that this molecule was retained in the diaxial conformation (Ia) by the hydrogen bond. The OH...O distance of (Ib) was

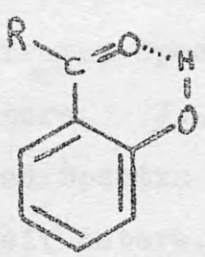


Ia

Ib

too large to permit the hydrogen bonded hydroxyl which was observed in the dilute carbon tetrachloride solution of this compound.

The salicylate system (II) has a chelate ring due to strong hydrogen bonding by the phenolic hydroxyl to the



II R = H, Me, OH, and OMe.

carbonyl group. The stretching vibrations of the carbonyl, the phenolic hydroxyl (and in the acids, the carboxylic OH) groups are all sensitive absorptions which might be expected to respond to minor changes in hydrogen bonding, the deviations from the plane of the ring, or to steric interactions.

Changes of absorption due to minor structural alterations have been studied in some detail for a number of molecules related to the salicylate system. Interest has been particularly held by spectral variations which are best explained by changes of inter- and intramolecular hydrogen bonding. The choice of compounds investigated has been partly determined by their availability. Some compounds of particular structural interest have been synthesised.

The work divides itself into five convenient sections. Sections 1, 2, 3 and 4 have been published in the Journal of the Chemical Society as follows:

Section 1. The Ethynyl-Hydrogen Bond. Association in Ether. J., 1960, 2526-2533.

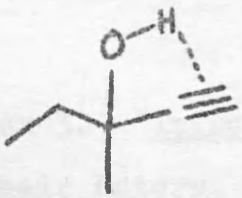
Section 2. The Infrared Spectra of Aryl Carboxylic Acids and Esters. J., 1961, 106-116.

Section 3. Infrared Spectra of Substituted Salicylic Acids and their Esters. J., 1961, 661-667.

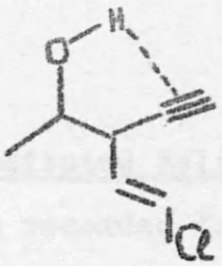
Section 4. Infrared Spectra of Substituted Salicylaldehydes. J., 1961, 3372-3381.

Section 5. "Phenol-Ether Association" has been accepted by the Chemical Society for publication in the Journal of the Chemical Society.

Section 1. The Ethynyl-Hydrogen Bond. Association in Ether Solutions. A number of interesting acetylenic compounds were available for study. These acetylenes offered an excellent opportunity to obtain first hand experience of intermolecular associations where steric interferences, by the proton donating groups involved, were at a minimum. The spectra of these compounds were obtained for liquid or solid state, in hexane, carbon disulphide, and ether solutions, and the effects of self association, and association with ether were evaluated. Although the main interest of this work was to investigate sterically unhindered proton-donating centres in intermolecular hydrogen bonding for comparison with other association systems, it is of interest to note that a number of biologically-active acetylenes exist ranging from 17-ethinyltestosterone and related steroids to the simple compounds III and IV.



Oblivon (sedative)
III



Placidyl (hypnotic)
IV

Volf and Stille[9] have examined the considerable narcotic powers of no fewer than fifty one tertiary acetylenic alcohols. Our studies may be of value in the interpretation of the modes of action of these drugs.

Section 2. Infrared Spectra of Aryl Carboxylic Acids and their Esters. As a necessary preliminary to the understanding of substituted salicylic acid and ester spectra, some substituted benzoic acids and esters were studied. Complex carbonyl absorption in ortho halogeno-benzoic acids and esters, was observed and ascribed to conformational isomerism. This finding initiated a larger scale investigation into the spectra of benzoic acids, benzoic esters, benzaldehydes and acetophenones. The correlations between relative acidity and infrared spectra were considered. The incidence of split carbonyl absorption, due to conformational isomerism and to Fermi resonance, is discussed.

Section 3. Infrared Spectra of Substituted Salicylic Acids and their Esters. Spectra have been recorded for a large number of substituted salicylic acids, among which were those used therapeutically in rheumatic fever treatment, and those which were known to be effective, to differing degrees, in treatment of myxoedema. Marked frequency shifts by 6-alkyl or bulky 3-alkyl groups have been ascribed to steric enhancement of chelation by compression of the phenolic hydroxyl group. The frequency shifts of the 3-alkyl substituted compounds parallel the potency of these acids as metabolic stimulants.

Section 4. Infrared Spectra of Substituted Salicylaldehydes. A number of substituted salicylaldehydes and ortho-hydroxy-acetophenones have been examined. It was hoped to demonstrate the steric enhancement of chelation by bulky alkyl groups, as found in substituted salicylic acids and esters. A parallel trend has been indeed observed. However the subject matter of this section is mostly concerned with the competitive intramolecular hydrogen bonding afforded by a 3-nitro-substituent. The character of hydroxyl, carbonyl and nitro absorptions (in a non polar medium) shows that the phenolic group is bonded principally to the nitro group, but that the chelated o-hydroxy-carbonyl species predominates

in 2-hydroxy-3-nitroacetophenone and methyl 3-nitro-salicylate.

Section 5. Phenol-Ether Association. This work is an investigation into the nature of shielding afforded to phenolic hydroxyl groups and ether oxygen atoms by alkyl groups in the course of intermolecular association between these two active centres. 2-Alkyl- and 2,6-dialkyl-phenols have been examined in dialkyl ether/carbon tetrachloride solutions. It has been found that systematic alkyl substitution in the ortho positions of phenols and the α-positions of the ether molecules, lowers the equilibrium constants for the phenol...ether association. However the strength of the bond as indicated by the hydroxyl frequency shift is affected only in solutions of the extremely hindered 2,6 di-t-butylphenol or in di-t-butyl ether solutions of 2,6-dimethyl,2,6-diethyl-, and 2,6-di-i-propyl-phenols.

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Section I.

The Ethynyl Hydrogen Bond - Association in Ether Solution.

Historical. As early as 1938 the extremely high solubilities of a number of haloforms in donor solvents were accounted for on the basis that complexes were formed through the bonding of the haloform hydrogen to the lone electron pair of an oxygen or nitrogen atom in the solvent[1-3], $X_3C\text{-}H \cdots :S$. Supporting evidence, for such hydrogen bonds, was obtained when infrared spectroscopic studies[4] revealed a CH stretching frequency shift in suitable chloroform-polar solvent mixtures. In 1939 Copley and Holley[5] considered that any strongly electronegative group, attached to a CH radical, would probably lead to similar behaviour by the hydrogen. They measured the solubility of acetylene in a number of donor solvents and found values in excess of those predicted by Raoult's law. They noted that a considerably larger heat of solvation was observed for phenylacetylene in ether solution, than in acetone or methyl acetate. Gordy[6] had previously observed that when CH_3OD was mixed with ethers, esters, and ketones, the largest shift in the OD stretching vibration, ν (OD), was shown with the ethers. Copley and Holley[5] commented that, among the solvents examined,

the best electron donor atom for forming hydrogen bonds with phenylacetylene was the nitrogen atom of N,N-dimethyl-acetamide.

Stanford and Gordy[7] undertook spectroscopic studies to prove that the acetylene-donor solvent complexes did in fact involve a hydrogen bond through the ethynyl C-H, RC≡C-H---:S. Frequency shift data $\Delta\nu$(CH) for three oxygenated and six organic nitrogen compounds were assembled. Unfortunately there were not enough data to allow correlation of C-H frequency shift with the solubility measurements of Copley and Holley[5].

Cook[8] has considered that there is a satisfactory linear relationship between ν(CH) of phenylacetylene in a number of carbonyl compounds, and the ionisation potential of these carbonyl compounds. He has claimed that there is only a slight scatter from the linear relationship between ν(CH) of phenyl-acetylene in carbonyl compound X and ν(HCl) in X.

Drs. J.C.D. Brand and G. Eglinton of Glasgow University, became interested in the quantitative nature of the acetylene-donor solvent association. An account of their initial results, obtained using a rock-salt prism, was given in March, 1958 to a meeting of the Infrared Discussion Group held in Edinburgh. At this point the author was invited to join in these investigations using the newly acquired Unicam S.P.130 prism

grating spectrometer described in the Experimental. The ensuing work has been published in the Journal of the Chemical Society, 1960, 2526.

While our results were being prepared for publication Murahashi, Ryvtani and Matada[9] demonstrated that there is a close relationship between the solubility of acetylene and the donating power of the solvent molecule, as measured by the shifts in the ethynyl C-H stretching ν(CH) and deformation frequencies δ(CH). They examined ν(CH) data of four mono-substituted acetylenes in carbon tetrachloride and ethylene glycol dimethyl ether solutions. They considered that $\Delta\nu$(CH) $\left[\nu CCl_4 - \nu(MeOCH_2)_2\right]$ depends on the electronegativity of the substituents. They noted that the magnitude of the ethynyl CH stretching frequency shifts of the pure mono-substituted acetylenes RC≡CH corresponded to the electron donating character of the substituent R.

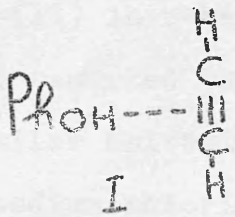
Results and Discussion.

Ethynyl CH stretching region.

Spectra have been recorded for compounds in the liquid (or solid) state and in dilute solution in ether and n-hexane. The hexane values are accepted as reference spectra for unassociated compounds. Experience has shown that $\nu_{(XH)}$ values in hexane are closer to the $\nu_{(XH)}$ vapour values than those observed in any other of the commonly used solvents. The liquid or solid spectra in all examples studied (Table 1) show evidence of self association. In every example the half band width ($\Delta\nu_{\frac{1}{2}}^{a}$) has increased significantly, compared with the hexane value and with two exceptions the increased $\Delta\nu_{\frac{1}{2}}^{a}$ parallel the $\Delta\nu(\nu_{\text{hexane}} - \nu_{\text{liquid}})$ values. The two exceptions are benzoylacetylene (11) and p-nitrophenyacetylene (10), measured in the solid state. Despite large $\Delta\nu$ values, 73 and 66 cm.$^{-1}$, indicative of a strong hydrogen bond, the half band widths are only approximately 26 and 20 cm.$^{-1}$. This may indicate that there is a correlation between band width and mutual orientation of associating molecules, since orientation is expected to be more restricted in the crystal lattice than in the liquid phase. The formation of intermolecular hydrogen bonds, by the ethynyl CH group, has not so far been

substantiated by x-ray crystalographic studies. Compounds (10) and (11) would apparently be good examples for such a study.

The penultimate column of Table 1 lists the presumed nature of the association. The depressed carbonyl frequencies in benzoylacetylene (11) and ethyl propiolate (12) are confirmatory. The relative $\Delta\nu$ values are approximately in accord with the electron donating powers of the basic centres. The weak self association listed for compounds (1) and (15) may involve the π electrons of the triple bond acting as donor to the ethynyl CH of another molecule. In a publication subsequent to ours, West and Kraihanzel[10] have shown by elegant concentration studies with phenol, acetylene, and carbon-tetrachloride mixtures, that the triple bond can act as an electron donor site for the phenolic hydrogen (I).



I

Table 2 summarises measurements near 3300 cm.$^{-1}$ in n-hexane and ether. The general spectral characteristics in this region were the same for all the compounds studied: (a) the hydrogen bond complex in ether (II) gave a broad band displaced 50-90 cm.$^{-1}$ to lower frequency from the free ethynyl absorption.

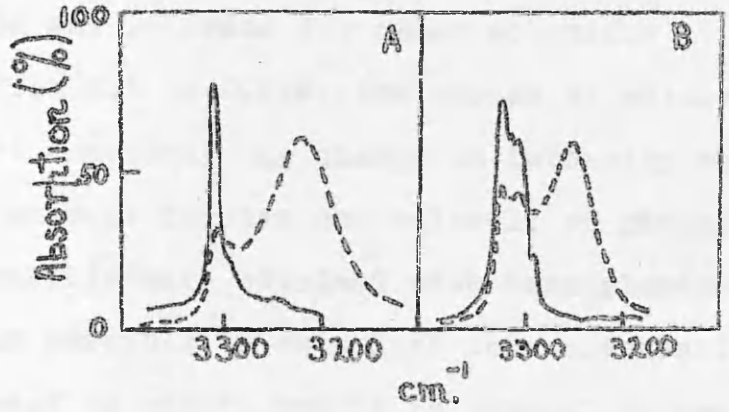
II

(b) the association was incomplete so that ether solutions showed both "free" and "associated" ν(CH) peaks and (c) the free ν(CH) band had a slightly lower frequency and appreciably greater half width in ether than in hexane.

The "free" ν(CH) bands were symmetrical for n-hexane solutions, except for weak absorption (presumed to be a combination tone intensified by Fermi resonance) present on the low-frequency wing in all examples studied. Fermi resonance was strong in the spectra of the aryl-acetylenes (see below). Fig. 1 shows the shape of the ν(CH) band of phenylacetylene(9) and benzoylacetylene (11) in n-hexane and in ether. Previous workers[7,8,9] have not remarked the presence of the "free" ν(CH) peak in ether and similar solvents, though it is visible under the resolution of a sodium chloride monochromator.

Fig. 2 shows the appearance of the 3300 cm.$^{-1}$ region of the spectrum of phenylacetylene under the resolution of A. a NaCl prism monochromator and B. the NaCl prism/grating ganged monochromator used in the present studies.

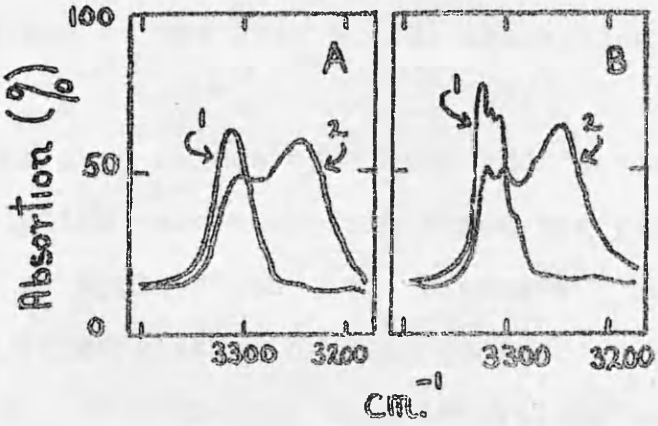
Fig. 1



(A) Ph. CO.C:CH, (1) 0.05M in n-hexane (0.5mm.); (2) 0.1M in ether (0.5mm.).

(B) Ph. C:CH, (1) 0.1M in n-hexane (0.5mm.); (2) 0.1M in ether (0.5mm.).

Fig. 2.



Solutions of phenylacetylene (1)0.1M in hexane, 0.5mm. cell and (2)0.1M in ether, 0.5mm. cell recorded, A using NaCl prism and B using the prism/grating modification.

To confirm the nature of the complex, phenylacetylene absorption was recorded for ether solutions at concentrations ranging from 0.5 to 0.01M, the number of molecules in the path being kept constant; no change in intensity was observed and so the complex must involve one molecule of phenylacetylene only. Similar results were obtained with benzoylacetylene (11). Although it was not possible to establish the molecularity of the complex with respect to ether, yet it is natural to assume that bonding leads to binary (1:1) association. At all events, 2: 1 complexes (e.g., $(Ph.C_2H)_2,OEt_2$) are not produced.

The final column of Table 2 gives for some molecules an estimate of the degree of association in ether, obtained from the ratio of areas of the free ν(CH) absorption in n-hexane and ether.

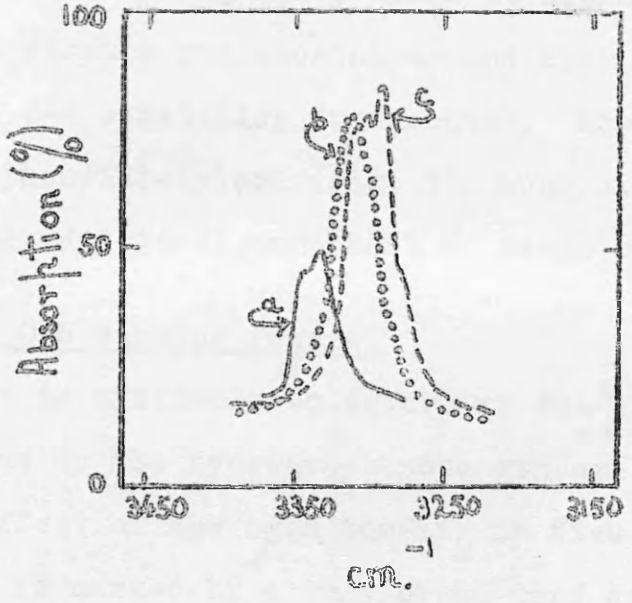
The area values of "free" and "associated" ν(CH) peaks in ether solution were uncertain since the peaks are fused. Direct integration or application of Ramsay's[11] method can only be achieved by extrapolation of band contour or half band width respectively. Nevertheless relative values have significance. For purposes of comparison a reasonable measure of the areas could be obtained by multiplying ε_a by the half band width. Corrections to allow for the finite spectral slit width were neglected since the half band width in almost all cases was not

less than four times the spectral slit width employed ($4\ cm.^{-1}$). Only a few of the half band widths used in these calculations are given in Table 2. The others have been obtained by reflection of the side of the absorption band free from overlap.

Table 3 shows that there is a good correlation between frequency displacement and relative proportions of hydrogen-bonded complex. The anomalous position of compound No. 3 is almost certainly due to the inclusion of some bonded OH absorption within the envelope of the unassociated ethynyl C-H absorption. The arrangement of the compounds in Table 2 (according to $\Delta\nu$) is broadly that expected from the electronic properties of the substituent groups. This arrangement roughly parallels the acidity of the ethynyl groups as judged by their reactivity in chemical processes initiated by the removal of the ethynyl proton (e.g., ethynylation of benzaphenone[12] and oxidative coupling[13]; Grignard exchange does not fall in this class[14]).

Good parallelism between $\Delta\nu$ values and relative intensity was also displayed by three analogous phenols in an ether/chloroform solvent, Table 4 (the acetylenes are included for comparison). As will be shown later (section 4), this correlation of $\Delta\nu$ values and relative intensities of free and associated absorptions depends on the absence of steric

Fig. 3.



Ph. C:CH as (a) vapour, (b) 0.1M - soln. in CCl_4 (0.5mm.), and (c) 0.5M - soln. in CS_2 (0.1mm.).

hindrance to the association.

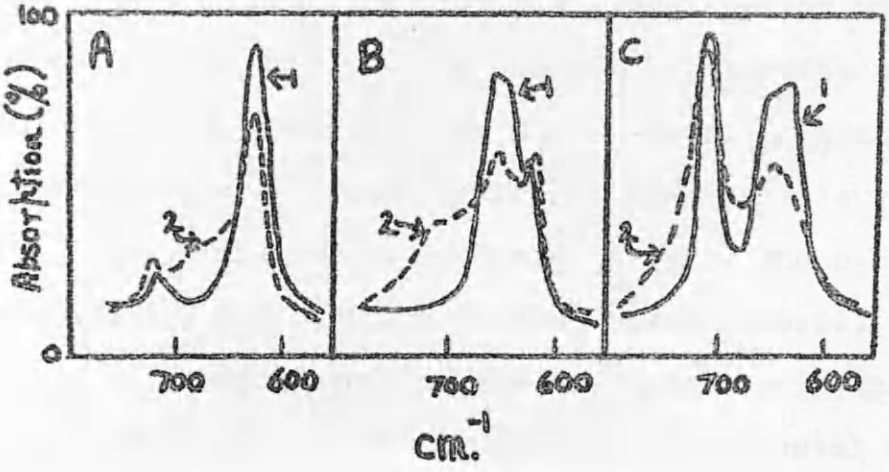
The unassociated ν(CH) of the ethynyl compounds tended to fall with increasing apparent acidity; an exact parallelism was not observed, perhaps because Fermi resonance influences the precise value of ν(CH). Nyquist and Potts[15] have subsequently suggested that a summation of the overtone of the ethynyl C-H bending mode, found at approximately 1250 cm.$^{-1}$, and the C≡C stretch fundamental around 2120 cm.$^{-1}$ resonates with the ethynyl C-H stretching fundamental. However our solvent studies on phenylacetylene (Fig. 3), suggested there might be at least one additional component of Fermi resonance.

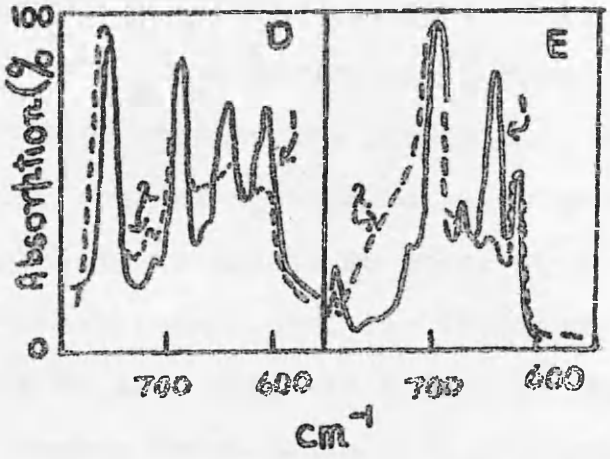
The Ethynyl C-H bending region.

It is difficult to determine the exact bending frequency due to the hydrogen-bonded ethynyl C-H δ(CH). Fig. 4 shows the effect of hydrogen bonding in five selected compounds. The complex is marked by a very broad band displaced to a higher frequency. Murahashi et al[9] were unable to observe any C-H deformation for acetylene in n-hexyl ether but they noted an upward frequency shift of 35 cm.$^{-1}$ for acetylene in ethylene-glycol dimethyl ether. As with the C-H stretching region, they have not mentioned the absorption due to unassociated ethynyl CH.

The integrated absorption intensity of oct-1-yne was evaluated in hexane and ether. There was an increase in

Fig 4





(A) $C_6H_{13}.C{:}CH$, (B) $Br.CH_2.C{:}CH$, (C) $Cl.CH_2.C{:}CH$,

(D) $Ph.C{:}CH$ and (E) $Ph.CO.C{:}CH$ in CS_2 (1) and ether (2)

Solutions ca. 1M in 0.05mm. cell.

intensity from n-hexane ($B = 0.74 \times 10^{4}$) to ether ($B = 1.1 \times 10^{-4}$). Since the degree of association in ether was approximately 30% (Table 2), the complex evidently absorbs with two or three times the intensity of the unassociated oct-1-yne, in this region. In other examples, overlapping absorption precluded a satisfactory evaluation of areas. Spectra in carbon disulphide and n-hexane were essentially the same in the two cases studied.

When several bands were present in the 600-700 cm.$^{-1}$ region the assignment of the δ(CH) fundamental was made as follows. (i) It is well known that the overtone 2 δ(CH) is comparatively strong; in the liquid state this overtone is marked by a characteristically broad band whose identification enabled the fundamental to be picked out. (ii) δ (CH) character could be taken as absent for a band having the same intensity in ether as in an inactive solvent. Phenylacetylene, for instance, absorbed in carbon disulphide at 690, 648, and 611 cm.$^{-1}$ (Table 5). In the overtone region broad bands were observed at 1284 and 1220 cm.$^{-1}$, indicating that the 648 and 611 cm.$^{-1}$ peaks were connected with the C-H deformation: this was supported by the fact that their intensity (ε_a) fell to less than one-half in ether, whereas the intensity at 690 cm.$^{-1}$ was unchanged (Table 5). In this example interaction with other group vibrations appeared to split the δ(CH) fundamental

(doubly degenerate in an axially symmetric molecule) into two components. Ethyl propiolate (12) also yielded a double band (687 and 650 cm.$^{-1}$) though in other instances the degeneracy was unresolved (for propargyl chloride, partly resolved) presumably because the molecules lack a vibration of the right frequency to interact with the C-H deformation.

2100 cm.$^{-1}$ Region. - At the relatively low resolving power available (sodium chloride prism, 1500 lines/in. grating blazed for 900 cm.$^{-1}$) no significant differences were evident when the ν(C:C) fundamentals were examined for n-hexane and then for ether solutions. The compounds (in hexane) had ν(C:C) at 2117, (2) 2117, (3) 2110, (4) 2095, (5) 2103, (6) 2126, (7) 2131, (8) 2109, (9) 2110, (10) 2113, (11) 2097, and (12) 2120 cm.$^{-1}$. Apparent extinction coefficients averaged 10-20 l. mole^{-1}cm.$^{-1}$, except for compounds (11) and (12), which absorbed strongly (ca. 150 units) owing to conjugation of the triple bond with the carbonyl grouping.

Thermodynamic Parameters.

In a system containing an ethynyl compound (C) and diethyl ether (D), there are at least three species

C, D, and CD in mutual equilibrium, and their solutions in an inert solvent S form an ideal mixture. In spectrophotometry, [C] is always small with respect to [D]+ [S], thus $X_D + X_S = 1$ (where X is the stoichiometric mole-fraction). Under these conditions the equilibrium constant in terms of mole fractions can be written

$$K = \frac{M_{CD}}{M_C X_D} \quad \ldots\ldots \quad 1$$

where M_C and M_{CD} are the actual molarities of C and CD and X_D is the stoichiometric mole-fraction of D. In practice C and CD give partially superimposed absorption in the ν ethynyl C-H region. Any results based on determination of the absorption due to each species would be subject to considerable inaccuracies, since the interlinked concentration-dependent nature of the absorptions makes systematic separation of the components very difficult. Moreover CD is formed incompletely even in pure ether so that its absorption intensity is not known. However from Beer's law considerations[16] we have as the equation (2) connecting the integrated absorption intensity B of a mixture containing C and CD with the ether mole-fraction X_D

$$\frac{X_D}{(B-A_C)} = \frac{X_D}{(A_{CD}-A_C)} + \frac{1}{K(A_{CD}-A_C)} \quad \ldots\ldots \quad 2$$

Here A_C and A_{CD} are the true absorption intensities of species C and CD; the former can be measured in the pure inert solvent S. Equation 2 can be used to determine K and A_{CD} from the intercept and slope of line obtained by plotting $\frac{X_D}{(B - A_C)}$ against X_D. Equation 2 can be derived from first principles in the following manner.

$$B = A_{CD}\left(\frac{M_{CD}}{M_C+M_{CD}}\right) + A_C\left(\frac{M_C}{M_C + M_{CD}}\right) = \frac{A_{CD}M_{CD} + A_CM_C}{M_C + M_{CD}}$$

$$\therefore \quad B-A_{CD} = \frac{1}{M_C+M_{CD}} \cdot (A_{CD}.M_{CD} + A_C.M_C - A_{CD}M_C - A_{CD}M_{CD})$$

since $$-\left(\frac{A_{CD}M_C + A_{CD}M_{CD}}{M_C + M_{CD}}\right) = -\frac{A_{CD}(M_C + M_{CD})}{M_C + M_{CD}} = -A_{CD}$$

$$B - A_{CD} = \frac{1}{M_C + M_{CD}} \cdot M_C (A_C - A_{CD}) \quad \ldots\ldots \quad 3$$

Similarly

$$B - A_C = \frac{1}{M_C + M_{CD}} \cdot M_{CD} (A_{CD} - A_C) \quad \ldots\ldots\ldots\ldots \quad 4$$

$3 \div 4 \qquad \frac{M_C}{M_{CD}} = -\left(\frac{B - A_{CD}}{B - A_C}\right) = \frac{A_{CD} - B}{B - A_C}$

Now $K = \frac{M_{CD}}{M_C X_D}$

$$\frac{1}{K} = \frac{M_C X_D}{M_{CD}} = \left(\frac{A_{CD} - B}{B - A_C}\right) \cdot X_D = X_D\left(\frac{A_{CD} - A_C + A_C - B}{B - A_C}\right)$$

$$= X_D\left(\frac{A_{CD} - A_C}{B - A_C}\right) - X_D \qquad \text{since} \quad \frac{A_C - B}{B - A_C} = -1$$

$$\frac{X_D}{B - A_C} = \frac{X_D}{A_{CD} - A_C} + \frac{1}{K(A_{CD} - A_C)} \quad \text{i.e. equation} \quad 2$$

The resultant plot for benzoyacetylene in ether-carbon tetrachloride mixtures is shown in Fig. 5.

Solution to find the slope and intercept by the method of least squares yields

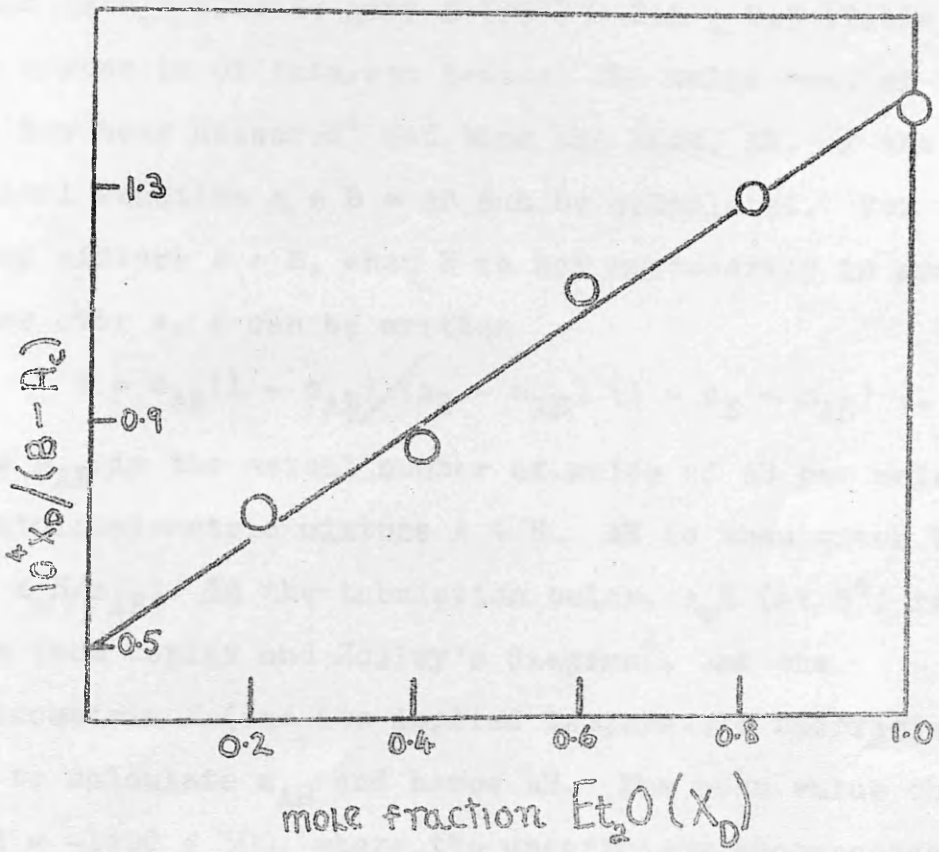
$$K(29^{\circ}) = 2.0 \pm 0.2$$

and $$A_{CD} = 1.7 \times 10^{4} \text{ l. mole}^{-1} \text{ cm.}^{-2}$$

A_C (the integrated absorption intensity of benzoylacetylene in carbon tetrachloride) is 0.72×10^{4} l. mole^{-1} cm.$^{-2}$. Thus the benzoylacetylene-ether complex absorbs with an intensity 2.4 times that of the free molecule. The degree of association $\frac{M_{CD}}{M_C + M_{CD}} = 0.67$. This result agrees fairly well with those values for degree of association obtained by comparing the areas of the free peak in hexane and ether solvents, and given in Table 2.

The values for K and A_{CD} may be in error for two reasons. (1) A_C and A_{CD} are assumed to be constant in ether, carbontetrachloride and their mixtures. (2) Apparent integrated absorption intensities B have been used as a measure of total area due to species C and CD. While this approximation could slightly affect the absorption intensity due to C, it will not affect that due to CD where the breadth of the band assures full resolution. Since the intensity of species CD is 2.4 times that of C, changes in total area will be more dependent on CD than

FIG. 5



Equilibrium in the system Ph.CO.C!CH + Et_2O

C, and any error, due to using apparent intensities, will be minimised.

Similar results for phenylacetylene + ether in carbon tetrachloride gave K (29^{o}) = 1.1 ± 0.3 (Table 4). This system is of interest because the molar heat of mixing, $\Delta_m H$, has been measured[4] and thus the heat, ΔH, of the chemical reaction A + B = AB can be calculated. For the binary mixture A + B, when B is not necessarily in great excess over A, K can be written

$$K = n_{AB}(1 - n_{AB}) / (x_B - n_{AB})(1 - x_B - n_{AB}) \quad .. \quad 5$$

where n_{AB} is the actual number of moles of AB per mole of the stoicheiometric mixture A + B. ΔH is then given by $\Delta H = \Delta_m H / n_{AB}$. In the tabulation below, $\Delta_m H$ (at 3^{o}) is taken from Copley and Holley's diagram[4], and the spectrometric K (and its implied temperature coefficient) is used to calculate n_{AB} and hence ΔH. The mean value obtained is $\Delta H = -1400 \pm 300$, where the uncertainty encompasses that in K as well as in the spread of values resulting from the individual $\Delta_m H$.

Heat of reaction: phenylacetylene + ether.

x_B....	0.720	0.703	0.689	0.511	0.504	0.502	0.438	0.304	0.222
$\Delta_m H$...	182	186	195	270	281	268	266	198	143
ΔH....	1360	1310	1330	1520	1580	1500	1530	1370	1260

An example of a calculation to obtain ΔH is as follows. A first approximation is to assume that K (29°) is not greatly different from K (3°). We can thus get a value for n_{AB} at 3°

$$k\ (3^{\circ}) = \frac{n_{AB}\ (1 - n_{AB})}{(X_B - n_{AB})(1 - X_B - n_{AB})}$$

when $X_B = 0.720$ $\quad K(3^{\circ}) = \dfrac{n_{AB}(1 - n_{AB})}{(.720 - n_{AB})(.280 - n_{AB})} = 1.1$

$$2.1\ n_{AB}^2 - 2.1 n_{AB} + .02217 = 0$$

$$n = 0.117 \text{ or } 0.883$$

The solution $n = 0.883$ is not valid since the molarity of the ether $x_B = .720$ is less than this.

We now have a value of ΔH from

$$\frac{\Delta H_M}{n_{AB}} = \frac{-182}{0.117} = -1556.$$

With this value of ΔH we can calculate an improved K_M (3°) from the formula

$$\log \frac{K_1}{K_2} = - \frac{\Delta H}{2.303R} \left(\frac{1}{t_1} - \frac{1}{t_2} \right)$$

$$\log \frac{K\ (29^{\circ})}{K\ (3^{\circ})} = - \frac{(-1556) \times 26}{2.303 \times 2 \times 302 \times 276}$$

$$= - 0.1047 = \bar{1}.8953$$

$$\frac{1.1}{K\ (3^{\circ})} = 0.786$$

$$K(3^{\circ}) = 1.4 \text{ i.e. first improved K } (3^{\circ}).$$

We can now calculate new values for n_{AB} and ΔH and continue the process until the parameters are constant. We can summarise this in the following Table.

	$K(3^0)$	n_{AB}	ΔH
Original Approximation	1.1	0.117	-1556
1st improved values	1.4	0.136	-1338
2nd improved values	1.355	0.134	-1356
3rd improved values	1.36		

As the halogenoforms are known[17-19,21] to form C-H....O hydrogen bonds it is of interest to establish how, for instance, chloroform and phenylacetylene compare in this respect. Some recent examples are in Table 6. ΔH and ΔS for chloroform + dioxan[20] and chloroform + acetone[21] are from thermodynamic measurements, supported in the second example by spectrometric nuclear magnetic resonance data[19]. The heat evolved in formation of the Cl_3C-H....O bond (chloroform-dioxan) is somewhat greater than for C:C-H....O (phenylacetylene-ether) on the basis of the information available. It is curious that $\Delta\nu/\nu$ for phenylacetylene (Table 1) is much greater than for chloroform[17,18] and even greater, in relation to ΔH, than the corresponding $\Delta\nu/\nu$ for phenol and alcohols[22]. Evidently, $\Delta\nu/\nu$ is a

comparative measure of hydrogen-bond strength only for molecules of the same type. It is also noteworthy that the decrease in entropy in the system phenylacetylene + ether is relatively small. Complexes of phenol[22] with various oxygen bases have values of ΔS in the range -7 to -9 in the units taken in Table 6 (ideal unit mole-fraction). One factor may be that internal rotation about the -C:C-H...O axis (I) is less hindered by surrounding solvent molecules than the corresponding motion of the angular phenol complexes (II).

(I) Ph-C:C-H...O< $_{Ph}$>O-H...O< (II)

Gas-Liquid Chromatography.

The gas-liquid chromatographic retention times of a number of n-C_8 hydrocarbons gave some evidence for hydrogen bonding by ethynyl C-H groups. The retention times of these compounds are much increased when hydrogen bonds can be formed with the stationary phase. Retention times are not known, but the distances on chart paper given below are directly proportional to the retention times. On Apiezon L (non-basic) at 94° oct-1-ene, oct-1-yne, n-octane and oct-4-yne (67, 73, 76 and 83 mm.) are eluted in that order. On "Carbowax 600" at 24° which contains $(-CH_2.CH_2.O-)_x$ chains the order of elution is n-octane,

oct-1-ene, oct-4-yne and oct-1-yne (36, 55, 250, and 359 mms.). The rearrangement of order of elution and the considerably different order of elution times for oct-1-yne must be connected with the ability of this compound to form hydrogen bonds.

The data below, kindly supplied by Dr. M.M. Wirth of British Hydrocarbon Chemicals, Grangemouth, are retention volumes, relative to n-pentane, of three ethynyl compounds on different stationary phases. Stronger retention on the oxygen-containing phases "Carbitol" (diethylene glycol monoethyl ether) and tritolyl phosphate is clearly seen: moreover, the implication that 2-methylbut-1-en-3-yne (5, Table 1) forms stronger bonds than but-1-yne is also in line with evidence from the infrared studies.

	B.p.	n-Hexadecane (non-basic) $20^\circ \pm 2^\circ$	"Carbitol" (basic) 0°	Tritolyl phosphate (basic) $20^\circ \pm 2^\circ$
But-1-yne.....	8.6°	0.424	2.43	1.24
Diacetylene....	10.3	0.173	20	6.6
2-Methylbut-1-en-3-yne.....	35	0.56	10.5	3.68
n-Pentane.....	36.1	1.0	1.0	1.0

Summary.

Ethynyl compounds RC ≡ CH, in dilute solutions in diethyl ether, are incompletely associated. Only sterically hindered phenols, among the hydroxylic compounds, display a similar equilibrium (cf. section 5 and ref. 23). The degree of association is dependent on the acidity of the ethynyl compound. On association with diethyl ether, the ethynyl C-H stretching frequency ν(CH), is lowered and the intensity is 2-3 times that of the unassociated band. The frequency of the ethynyl C-H deformation vibration δ(CH) is raised while the intensity is again 2-3 times that of the unassociated band. The equilibrium constant K, the entholpy ΔH, and the entropy change ΔS have been evaluated for the association between phenylacetylene and diethyl ether.

Appendix.

After our work was submitted for publication a number of French workers[24-26] have published short papers drawing attention to the complex absorption of acetylenes. Both Jacob[24], and Wojkowiak and Romanet[25] have distinguished effects which can be attributed to the dielectric constant of the solvents from those which are due to intermolecular association. Josien, Pham-Van-Huong and Lascombe[26], have shown that intermolecular and self association of some acetylenes is markedly temperature dependent. They have also demonstrated that the intensity of the associated ethynyl C-H is dependent on the basicity of the acceptor. For example, the intensity of the associated peak increases in intensity through the series diethyl ether, di-n-butyl ether and dioxane.

West and Kraihanzel[27] have acknowledged that their conclusions, about the relative acidities of a number of acetylenes as measured by the $\Delta\nu$(C-H) values in N,N-dimethylacetamide, N,N-dimethylformamide, and 1,2-dimethoxyethane, generally confirm ours. By some elegant studies on ternary mixtures (substituted acetylene-phenol-carbon tetrachloride) they have

assessed the basicity of the triple bond to be greater than that for both olefins and benzenes. Electron withdrawing substituents are shown to lower this basicity.

More recently Kreevoy, Charman and Vinard[28] have studied complexes formed by pyridine and substituted acetylenes by infrared and nuclear magnetic resonance spectrometry. They have noted that while acetylene protons may be difficult to pick out from methine and methylene protons, pyridine solution causes them to be detached and easily observable.

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Table 1. Spectral changes in liquid and solid state.

No.	Compound	ν(CH) in hexane cm.$^{-1}$	$\Delta\nu_{\frac{1}{2}}$	ν(CH) in liquid state cm.$^{-1}$	$\Delta\nu_{\frac{1}{2}}$	Association	$\Delta\nu$ cm.$^{-1}$
1	$CH_3.(CH_2)_5.C{:}CH$	3319	6.5	3316	28	Weak self-association	3
13	EtO.C:CH	3339	12	3315	43	:C-H...O	24
14*	Tp.O.CH_2.C:CH	3319	6	3293	60	:C-H...O	26
11	Ph.CO.C:CH	3306	9	3233[a]	26	:CH...OC	73
12	EtO_2C.C:CH	3310	7.5	3277	70	:CH...O:C	33
10	p-NO_2.C_6H_4.C:CH	3319	9	3253[a]	20	:CH...O_2N-	66
15	Et_2N.CHMe.C:CH	3316	6	3311 3222w	30 160	Self-association :CH...N	5 94
		(C:O) in hexane		(C:O) in liquid state			
11	Ph.CO.C:CH	1668	6	1643[a]	22	C:O...H-C:	25
12	EtO_2C.C:CH	1729	9	1719	25	C:O...H-C:	10

[a] Solid state spectrum (Nujol); the main ν(CH) band is accompanied by a weak but broad "tail", on the low-frequency side. w = Weak. * Tp = Tetrahydropyranyl. $\Delta\nu$ = νhexane - νliquid or solid.

Table 2. 3300 cm.$^{-1}$ region ν(CH).

No.	Compound	n-Hexane solution ν	ε_a	$\Delta\nu_{\frac{1}{2}}$ [a]	Ether solution: Free ν	ε_a	Associated ν	ε_a	$\Delta\nu_{\frac{1}{2}}$ [a]	$10^2\Delta\nu_{\frac{1}{2}}$ [b]	Fraction associated in ether
1	$CH_3.CH_2{}_5.C{:}CH$	3319	(180)	6.5	3317	(50)	3267	(35)	36	1.5_0	0.3
2	$HC{:}C.[CH_2]_{10}.C{:}CH$	3319	(200)[a]	6.5	3317	(65)[a]	3267	(45)[a]	e	1.5_1	0.3
3	$C_6H_{10}<^{C:CH}_{OH}$	3315	(230)	7.5	3313	(80)	3257	(60)	e	1.6_9	-
4	Δ^1-$C_6H_9.C{:}CH$	3319	(130)	6.5	3317	(70)	3260	(55)	e	1.7_2	-
5	$CH_2{:}CHMe.C{:}CH$	3313	(125)	18	3314	(50)	3253	(65)	e	1.8_6	0.6
6	$Br.CH_2.C{:}CH$	3316	(175)	11	3315	(45)	3250	(60)	e	1.9_6	0.6
7	$Cl.CH_2.C{:}CH$	3318	(115)	8.5	3317	(46)	3250	(65)	e	2.1_1	0.6
8	p-$MeO.C_6H_4.C{:}CH$	3323	(175)	9.5	3322	(65)	3252	(65)	e	2.1	-
9	$Ph.C{:}CH$	3323	(125)	22	3320	(55)	3250	(75)	e	2.1	0.6(0.5_5[c])
10	p-$NO_2.C_6H_4.C{:}CH$	3319	d	9	3316	(40)	3232	(85)	56	2.5_3	-
11	$Ph.CO.C{:}CH$	3306	(250)	9	3304	(30)	3219	(70)	70	2.5_7	0.7(0.6_7[c])
12	$EtO_2C.C{:}CH$	3310	(160)	7.5	3309	(25)	3220	(75)	69	2.6_8	0.7

Footnotes to Table on next page

Footnotes to Table 2.

[a] $\varepsilon_{a/2}$. [b] $\Delta\nu$ = ν hexane - ν ether.

[c] From eqn. (2). [d] Sparingly soluble.

[e] Width (approx. 40-50 cm.$^{-1}$) cannot be given accurately owing to fusion with "free" ν(CH) peak.

[f] Includes some absorption from bonded-OH.

Table 3. Relative Areas of free and associated peaks in ether solution.

No.	Compound	$(\varepsilon_a \times \Delta\nu_{\frac{1}{2}})$ unassociated	$(\varepsilon_a \times \Delta\nu_{\frac{1}{2}})$ associated	$\frac{\varepsilon_a \times \Delta\nu_{\frac{1}{2}} \text{ associated}}{\varepsilon_a \times \Delta\nu_{\frac{1}{2}} \text{ unassociated}}$	$\Delta\nu$(CH)
3	$C_6H_{10}<^{C:H}_{OH}$	80 x 20	60 x 44	1.65	56
1	$CH_3.CH_2{}_5C:CH$	50 x 14	35 x 36	1.80	50
2	$HC:C.[CH_2]_{10}.C:CH$	65 x 13	45 x 38	2.0	50
4	Δ^1-$C_6H_9.C:CH$	70 x 13	55 x 48	2.92	57
5	$CH_2:CHMe.C:CH$				61
8	p-$MeO.C_6H_4.C:CH$	65 x 14	65 x 44	3.15	70
9	$Ph.C:CH$	55 x 18	75 x 46	3.5	70
6	$Br.CH_2.C:CH$				65
7	$Cl.CH_2.C:CH$	46 x 14	65 x 50	5.05	67
10	p-$NO_2.C_6H_4.C:CH$	40 x 16	85 x 48	6.38	84
11	$Ph.CO.C:H$	30 x 16	70 x 57	8.31	85
12	$EtO_2C.C:CH$	25 x 16	75 x 69	12.9	89

Table 4. Comparison of the association of some analogous phenols[a] and acetylenes[b].

Compound	R = OH		R = C:CH	
	$\Delta\nu$	Area Assoc./Area Unassoc.	$\Delta\nu$	Area Assoc./Area Unassoc.
p-MeO.C_6H_4.R	300	3.09	70	3.15
Ph.R	305	3.21	70	3.5
p-NO_2.C_6H_4.R	389	13.43	84	6.38

[a] in 2% v.v. diethyl ether in chloroform, 2 mm. cells.

[b] in pure diethyl ether, 0.5 mm. cells. $\Delta\nu = \nu$ unassoc. - ν assoc.

Table 5. 550-800 cm.$^{-1}$ region.

No.	Compound	CS_2 solution[a] cm.$^{-1}$	(ε_a)	$\Delta\nu_{\frac{1}{2}}$ [a]	Ether solution[b] cm.$^{-1}$	(ε_a)	Association band	Other assignments*
1	$CH_3 \cdot [CH_2]_5 \cdot C{:}CH$	629	(180)	17	629	(85)	ca. 670	
		724	(10)	12	726	(10)		$p(CH_2)$
5	$Br \cdot CH_2 \cdot C{:}CH$	622	(60)		619	(65)		
		655	(130)	33	652	(60)	ca. 700	ν(C-Br)
6	$Cl \cdot CH_2 \cdot C{:}CH$	642 / 654	(95)	33	653	(40)	650-750	
		712	(200)	10	711	(160)		ν(C-Cl)
9	$Ph \cdot C{:}CH$	611	(115)	17	611	(40)	650-750	
		648	(120)	15	646	(60)		
		690	(160)	5	692	(160)		
		756	(350)	5	758	(350)		ω(CH)arom.
11	$Ph \cdot CO \cdot C{:}CH$	626	(50)	4	626	(35)		
		646	(160)	11	645	(15)	680-800 (max. ca. 725)	
		677	(weak)		678	(weak)		
		701	(350)		703	(350)		ω(CH)arom.
		792	(weak)	4	795	(weak)		
12	$EtO_2C \cdot C{:}CH$	600	(weak)	15	600	(weak)		
		650	(85)	16	650	(20)	700-800	
		687	(60)	20	690	(25)		
		753	(180)	7	756	(160)		

continued overleaf

Table 5 (continued).

Footnotes.

[a,b] 0.5 and 0.05 mm. cells, respectively.

δ(OH) fundamentals are underlined.

* ν = stretching, δ = deformation, ρ = rocking, ω = wagging.

Table 6. Equilibrium constants and thermodynamic parameters.*

System	$Ph.CO.C{:}CH + Et_2O$ Sp	$Ph.C{:}CH + Et_2O$ Sp	$CDCl_3 + Et_2O$ Sp[17]	$CHCl_3$ + dioxan (1:1 complex) Th[20]	$CHCl_3 + Me_2CO$ Sp[19]	$CHCl_3 + Me_2CO$ Th[21]
Temp.	29	29	22	50	28	25
K	2.0	1.1	7.6	1.11	1.8	0.8
ΔH (cal. $mole^{-1}$)		-1400		-2000	-2500	-2700
ΔS (cal. $mole^{-1}$ $deg.^{-1}$).		-4.5		-6.0	-7.1	-9.5

* Sp, spectrometric, Th, thermodynamic measurements.

Section 2.

Infrared Spectra of Aryl Carboxylic Acids and their Esters.

Historical. The significance of minor variations of carbonyl and other group stretching vibration frequencies in series of related compounds has been discussed by a number of workers. Flett[1] found that an almost linear relationship existed between the monomer carbonyl frequencies of a series of meta- and para-substituted benzoic acids and the velocity constants of their esterification reactions, and thereby with the Hammett substituent constants. Similar relationships were found[1] to exist for substituted aryl amines and benzonitriles. The electron attracting or repelling character of the substituents was considered to be affecting the reaction rates and the vibrational force constants, of the carbonyl and other groups, in a similar manner. Goulden[2] considered that the hydroxyl stretching frequency of monomeric carboxylic acids should be related to their pK_a values. This early correlation of ν(OH) and pK_a divided the forty-nine acids which he studied into three distinct classes. (a) The type $C = CR.CO_2H$. This included α,β-unsaturated aliphatic, cinnamic, naphthoic and benzoic acids. (b) The type $CR_1R_2R_3.CO_2H$ mostly acetic acids where R is alkyl, halogen, phenoxy or methoxy.

(c) The type where a double bond is separated from the carbonyl by a methylene chain. Peltier, Josien and their collaborators[3] have presented more refined data for substituted benzoic acids. ν(OH) and ν(CO) have very precise relationships with pK_a for meta- and para-substituted acids.

The effect of an ortho-substituent on a carbonyl or other vibration is complicated, since steric and field considerations are superimposed to some extent on the polar effects transmitted through the molecule. Taft[4] has divided the Hammett constant for ortho-substituents into two parts, a polar factor and a steric factor. The polar factor is essentially equal to the Hammett constant for the same substituent in the para-position. O'Sullivan and Sadler[5] found that the differences in carbonyl frequency afforded by ring substitution, in some benzoic acids, acetanilides and other carbonyl functions, increased, although not linearly, with increasing Taft polar factor, but showed no correlation with the Taft steric factor.

The relationships between absorption intensities and Hammett constants have been studied by Thompson et al[6]. The frequency and intensity of any absorption are dependent on electronic character of the bond, although the factors affecting the two are not necessarily the same. Although

both frequency and intensity of meta- and para-substituted benzonitriles were dependent on Hammett constants, only the frequency of the related carbonyl compound was markedly affected. Krueger and Thompson[7] have found better correlation between intensities and the more refined inductive and resonance parameters derived by Taft[8]. The δ_I (inductive) components were related to intensity of the absorption of meta-substituted benzonitriles and carbonyl compounds, while δ_R (resonance) components were related to the absorption intensity of para-substituted compounds. However only in the benzonitriles have the authors considered that any satisfactory relationship between δ factors and γ or intensity exists for ortho- substituted compounds. They noted that both ethyl benzoates and benzaldehydes, substituted in the ortho-position, had shoulders on the carbonyl absorptions which complicated measurement and interpretation. Krueger and Thompson[7] considered that intramolecular hydrogen bonding gave rise to this complex absorption, but it is difficult to conceive the nature of the hydrogen bonding in some of the compounds mentioned e.g. the ethyl esters of o-bromobenzoic, o-iodobenzoic and o-toluic acids.

As a preliminary to the spectroscopic study of substituted salicylic acids, it was felt necessary to examine spectra of a number of benzoic acids, including examples with

ortho-substituents. The comparatively well resolved complex carbonyl absorption afforded by acids having polar ortho-substituents prompted a survey of the spectra of other substituted aryl carbonyl compounds.

While our results were being prepared for publication Peltier and Pichevin[9] published a further paper principally concerned with the correlation of ν(OH), ν(C=O), and pK_a. The authors have attempted to explain the minor variations of the ν(C=O)/pK_a relationship observed in substituted benzoic and toluic acids. For example, the decreased carbonyl frequency of 3-substituted ortho-toluic acids and the complex absorption of the ortho iodo substituted acids have been ascribed to a slight interaction of an unspecified nature between the carbonyl group and the substituent methyl and iodo groups. Abnormal elevation of the carbonyl frequency of non-chelated 2,6-disubstituted acids has been considered to be due to the inhibition of conjugation by steric factors. They have noted complex absorption for some of the ortho-substituted acids, which are mentioned below in our work, but they have failed to observe the carbonyl splitting of the esters of ortho halogeno-benzoic acids. They have completely discounted the possibility that the complex carbonyl absorption of these acids is caused by chelation to the

ortho halogen atom since the ν(OH) in all cases are normal. They have commented however that the failure to relate ν(C=O) with pK_a, in the 6-substituted orthotoluic acids, may be similar to the case of chloro-acetic acid, where two carbonyl absorptions, corresponding to the rotational isomers, are observed. Peltier and Pichevin[9] have suggested that deviations from the pK_a/ν(C=O) relation could be attributed to using the wrong ν(C=O) or to the fact that the pK_a measured is really the resultant of the two species present.

The split carbonyl absorption for ortho alkyloxy-benzoic or toluic esters, has been noted by the same authors, but they have commented that the explanations forwarded by them to explain the complex absorption of the corresponding acids, will not cover the esters.

The complex nature of the absorption of the ortho-substituted benzoates disclosed in our own work was not revealed by the work of Forbes et al[10], published during our investigations. This is particularly surprising because these workers examined o-fluorobenzoic acid where the complex carbonyl absorption is most clearly resolved.

Results and Discussion.

This section describes infrared spectroscopic studies of a series of monosubstituted benzoic acids and the

corresponding methyl esters. Attention has been given primarily to the regions of absorption due to the stretching vibrations of the hydroxyl and carbonyl groups, which are conveniently studied using dilute solutions in carbon tetrachloride. Other solvents have been used in certain instances in order to favour particular conformations and to examine specific solute-solvent interactions.

It is well known that carbonyl stretching vibrations can be treated as dependent principally on the immediate environment of the group concerned. From Fig. 1, which represents an extension of the ν_{CO}/δ plots due to Fuson, Josien and Shelton[11], and Thompson et al.[6], it is clear that the frequency separations (in carbon tetrachloride) between an aryl methyl ketone (Ar CO.Me) and the corresponding compounds of the types $(ArCO_2H)_2$; $ArCO_2Et$; $ArCO_2Me$; $ArCO_2H$ remain essentially constant at 7, 34, 39 and 52 cm.$^{-1}$, respectively in the group of m- and p-substituted derivatives considered. (Peltier et al.[3] have already pointed out the regularity of the frequency differences between acids (monomers) acids (dimers) and methyl esters in a large number of examples). The same degree of consistency is not observed in the substituted benzaldehydes. In general, the influence of X on the carbonyl frequencies is ascribed to

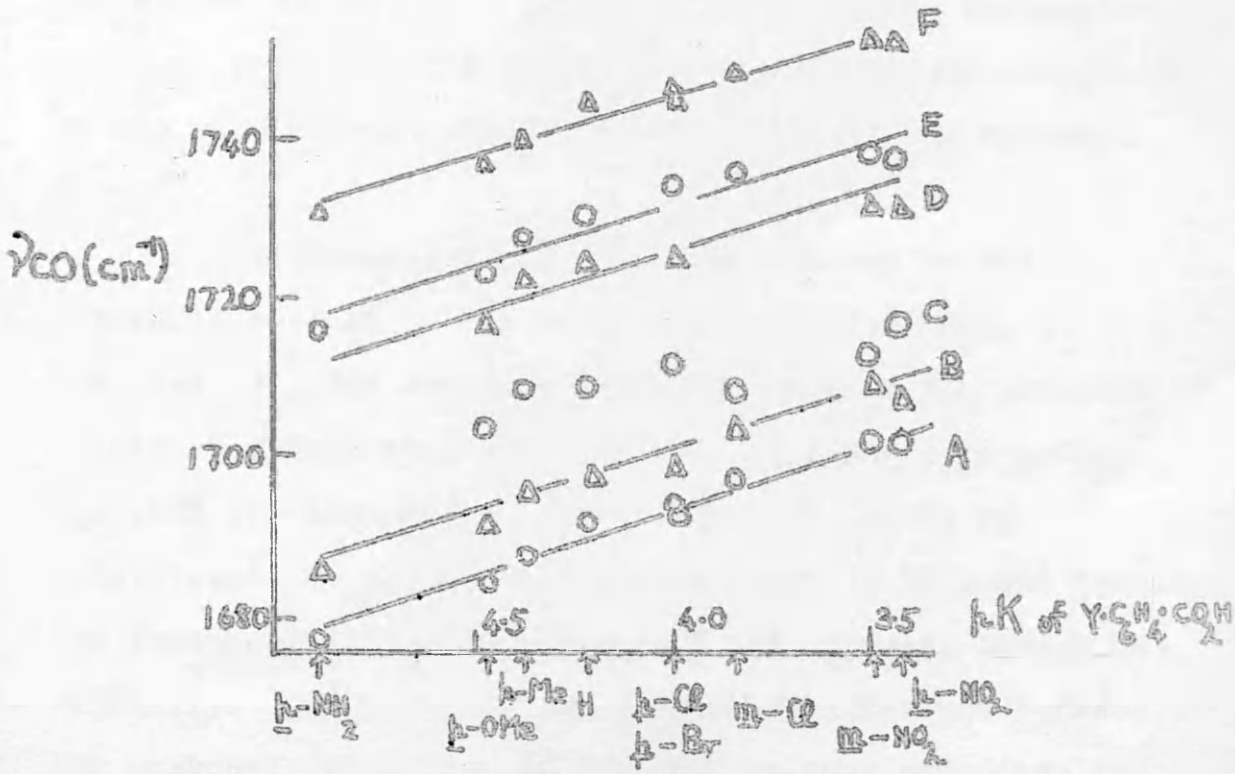


FIG.1. Carbonyl stretching frequencies (CCl_4) of $Y.C_6H_4.COX$ and (abscissa) pKa of $Y.C_6H_4.CO_2H$ (ref.1.). (A) Aryl methyl ketones (X=Me).[a,b] (B) Aryl carboxylic acids (X=OH; dimers).[b] (C) Aryl aldehydes (X=H).[b] (D) Ethyl esters of carboxylic acids (X=OEt).[b] (E) Methyl esters of aryl carboxylic acids (X=OMe).[b] (F) Aryl carboxylic acids (X=OH:monomers).[b]

[a] Jones, Forbes and Meuller, Canad. J. Chem., 1957, 35, 504

[b] Present work

mesomeric and particularly to inductive effects[12,13]: the marked elevation of frequency in monomeric carboxylic acids as compared with the methyl ketones may be attributed to the strong electron-withdrawing power of the hydroxyl group[14].

Although o-substituted derivatives do not generally conform to the equations implied in Fig. 1 (cf. ref. 7), the discrepancies are often in the absolute values of ν(C=O) thus the shifts on changing X in o-CH_3.C_6H_4.COX are similar to those of Fig. 1. Where o-substituents (e.g. OH, NH_2) are involved in hydrogen bonding, the frequency shifts on changing X are altered, though not radically. For example, the frequency difference between the carbonyl absorption of the acid monomer and dimer is 45±2 $cm.^{-1}$ in the group of m- and p-substituted acids of Fig. 1, in agreement with the extensive results of Peltier et al.[9]

The distinctly smaller frequency difference for o-hydroxybenzoic acid, the consistency of which we have been able to confirm in a study of substituted salicylic acids (section 3), is considered to be due to the reduced basicity of the carbonyl group in these compounds. In their later paper[9], Peltier and Pichevin have also remarked on the distinctly lower monomer-dimer frequency differences for

ortho-hydroxy and ortho-amino benzoic acids, 36±2 and 37±1 cm.$^{-1}$ respectively and their explanation of this phenomena is similar to ours.

Methyl Esters:- The results of the measurements in carbon tetrachloride solution are collected in Table 1. The carbonyl frequencies of the m- and p-substituted esters confirm and extend the previous data[3] and parallel the data for the corresponding ethyl esters[6]. No striking trends are observed in $\Delta\nu_{\frac{1}{2}}^{a}$ or ε_a.

The frequency and band intensity values for ν(C=O) of a group of o-substituted ethyl benzoates have been stated[7] not to fall in line with the data for the meta- and para-substituted esters. Single bands, sometimes with shoulders, were reported. With the improved resolution afforded by the prism-grating spectrometer it has now been found that while methyl, o-methyl, o-nitro- and o-acetoxy-benzoate exhibit single sharp peaks, methyl o-halogeno-, o-methoxy- and o-allyloxybenzoate present two carbonyl bands separated to various degrees. The occurrence of these split bands is not due to intermolecular effects, since dilution studies have shown that the relative intensities of the bands are independent of concentration. The band splitting observed in carbon tetrachloride solutions is more clearly defined in hexane solutions (Fig. 2 and Table 2).

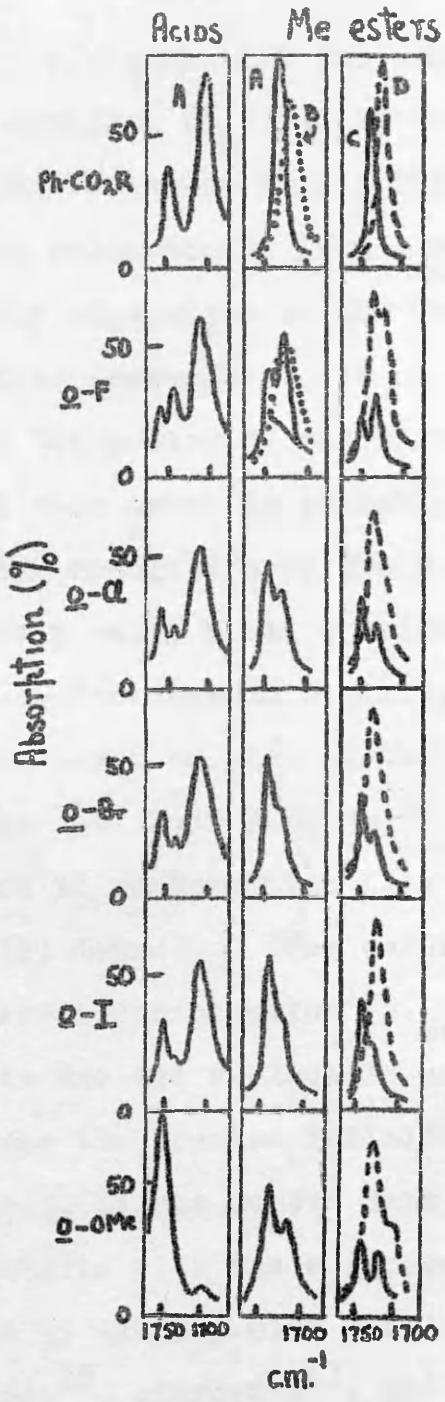


FIG.2. Carbonyl absorptions of benzoic acid, methyl benzoate and ortho substituted derivatives in various solvents.

(A) CCl_4 ; (B) $CHCl_3$;

(C) n-hexane;

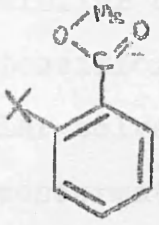
(D) MeCN.

The relevant concentrations and path lengths are as given in Tables 1, 2, and 3 except for B (0.0015M- solution in 5mm. cells).

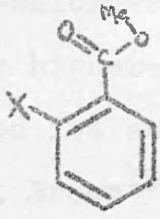
The frequency values are slightly higher, but the same trends are observed in the intensities (ϵ_a) and in the breadth of the bands: the lower-frequency band falls in relative intensity and broadens successively from o-F to o-Cl and to o-Br. The frequency separation of the two bands falls from 18 cm.$^{-1}$ in the o-fluorobenzoate to 10 cm.$^{-1}$ in the o-iodobenzoate: in carbon tetrachloride and carbon disulphide (Table 2) solutions this trend is probably obscured because of the inferior resolution of the bands.

Of the two explanations which merit consideration for this band splitting, viz. conformational equilibria or Fermi resonance, we favour the former in view of the evidence adduced below. Accordingly the band near 1730 cm.$^{-1}$ in the o-halogenobenzoates is assigned to conformation (Ia; X=Hal), and that near 1740 cm.$^{-1}$ to (Ib; X=Hal). (The ester group is depicted in the normally preferred conformation[15]). Coplanarity of the substituents and the nucleus is not implied in these representations the precise definition of which must await further evidence (e.g. dipole moment data). The higher-frequency band is associated with the alignment of carbonyl and C-halogen dipoles by analogy with α-halogeno-carbonyl compounds (e.g. ketones[16], aldehydes[17], and esters[16,18,19]). These assignments parallel those made in the o-halogenoacetophenones by R.N. Jones and his colleagues[20].

The changes in the relative intensity of the two bands through the series o-F to o-I are most simply rationalised (taking the intensities as approximately indicative of concentrations) in terms of the size of the halogen atom, the small fluorine atom permitting a preponderance of (Ia; X=F) in the equilibrium mixture.



(Ia)



(Ib)

The band separation (for n-hexane solution) in methyl o-methoxybenzoate is slightly greater than that found in the o-halogeno-esters. The bands at 1723 and 1745 cm.$^{-1}$ are ascribed to conformations (Ia and Ib; X=OMe) respectively by analogy with the o-halogeno-esters and with the assignments made by T.L. Brown[19] for ethyl ethoxyacetate. In carbon tetrachloride the higher frequency band is complicated by the presence of a shoulder, whereas in n-hexane it is only slightly asymmetric.

Additional support for the conformational assignments made for the o-halogeno- and o-methoxybenzoates was derived from measurements in acetonitrile (Table 2 and Fig. 2). The carbonyl frequencies are generally about

6 cm.$^{-1}$ lower than in carbon tetrachloride. In each example, the intensity of the higher-frequency band is relatively higher in acetonitrile (and the lower-frequency band becomes less and less distinct in the series o-F, o-Cl, o-Br and o-I; Fig. 2). Bellamy and Williams[16] observed a similar effect in α-chloroketones, and pointed out that intensification of the higher-frequency band in the more polar solvent supported its assignment to the more polar conformation. T.L. Brown[19] has reported similar results for ethyl chloro- and dichloro-acetate in chloroform and acetonitrile as compared with carbon tetrachloride.

Methyl-o-nitrobenzoate shows only a single (slightly unsymmetrical) band in the carbonyl region. Possibly in this ester the carbomethoxyl group is so displaced by the preferential coplanarity of the nitro group that there is essentially only one conformation. The elevated carbonyl frequency (1747 cm.$^{-1}$) is compatible with this explanation. On the other hand the split band observed in o-nitroacetophenone is attributed[20] to conformational isomerism. It is of interest to note that while slight asymmetry has been observed in our work for methyl-o-nitrobenzoate, Peltier and Pichevin[9] describe only a single peak,

yet they observe additional monomer carbonyl peaks for o-nitro-benzoic, 2-nitro-metatoluic, 2-nitro-paratoluic, and 6-nitro-orthotoluic acids. Only one monomer carbonyl is observed for o-nitro-benzoic acid by us.

Single symmetrical bands are exhibited by methyl o-toluate (methyl and bromine have approximately the same Van der Waals radii) and o-acetoxybenzoate. Evidently these weakly polar substituents do not induce markedly different ν(C=O) values in the two possible conformations (cf. ref. 20). Two disubstituted esters have been briefly examined. Methyl 2,6-dimethoxybenzoate shows a single symmetrical carbonyl band in n-hexane (1750 cm.$^{-1}$; $\Delta\nu_{\frac{1}{2}}^{a}$ = 8 cm.$^{-1}$) and in carbon tetrachloride (1723 cm.$^{-1}$; $\Delta\nu_{\frac{1}{2}}^{a}$ = 17 cm.$^{-1}$; ε_a = 745). The remarkable solvent effects on the frequency and half-band width are presumably associated with the steric strain in this ester. Methyl 2,3-dimethoxybenzoate shows the expected split carbonyl band in n-hexane (1743 cm.$^{-1}$, $\Delta\nu_{\frac{1}{2}}^{a}$ 11 cm.$^{-1}$, ε_a 440; 1729 cm.$^{-1}$, ε_a ~ 175) and, less clearly resolved, in carbon tetrachloride (1736 cm.$^{-1}$, $\Delta\nu_{\frac{1}{2}}^{a}$ 18 cm.$^{-1}$, ε_a 435; 1721 cm.$^{-1}$, ε_a 130), and in acetonitrile (1730 cm.$^{-1}$, $\Delta\nu_{\frac{1}{2}}^{a}$ 16, ε_a 495; 1719 cm.$^{-1}$, ε_a 95).

With regard to the intensities of carbonyl bands

in substituted methyl benzoates, the apparent half-band widths and extinction coefficients (Tables 1 and 2) show no striking variations. Integrated intensity values computed by Ramsay's method[21] ranged from 2.9×10^4 (No. 9) to 4.1×10^4 l. mole^{-1} cm.$^{-2}$.; (No. 8). The values are based on single determinations and show no regularity. Thompson et al.[6] have demonstrated a linear relation between log A (by area integration) and δ for a group of six m- and p-substituted ethyl benzoates. That the o-substituted esters did not conform[7] is not surprising in view of the complex absorption now disclosed. The values of $A\nu_{\frac{1}{2}}^{a}$ for the methyl esters show the same general trend as those for the ethyl esters (notably the marked broadening in the p-methoxy esters).

The region 1650-400 cm.$^{-1}$. The substituted methyl benzoates have also been examined over the region 2000 - 400 cm.$^{-1}$ in the pure state (liquid films, melts or mulls) and as solutions in carbon disulphide. These spectra will appear in the D.M.S. Index (Butterworths) as spectral cards numbers 6227 onwards. The liquid film and solution spectra are almost identical for a given ester, though a few bands in certain of the o-substituted benzoates show small intensity changes (see later discussion on conformation). Frequency data and probable assignments[22] for the four methyl

o-halogenobenzoates are assembled below. Several interesting frequency trends (e.g. for ν_{C-C} modes) through the series F→I can be discerned. The spectrum of the o-fluoro-ester resembles that of methyl-o-methoxybenzoate more closely than those of the other o-halogeno-esters.

The data are listed as groups of comparable bands in the four o-halogenobenzoates, in the sequence, fluoro-, chloro-, bromo- and iodo-, separated by commas.

1650-1400 cm.$^{-1}$ region (liquid films). ν_{C-C}: 1613m, 1593m, 1591m, 1583m; 1585w, 1573w, 1568w, 1563w; 1492m, 1475m, 1472m, 1467m; 1460m, -, -, -; 1435m, 1435m, 1435m, 1434m.

1400-1000 cm.$^{-1}$ region (CS_2 solutions). ν_{C-O}: 1304s, 1299s, 1296s, 1293s; β_{C-H}(?): 1277m, 1273m, 1269m, 1268m; ν^{a}: 1262m, -, -, -; ν_{C-O}: 1252m, 1254s, 1253s, 1254s; ν^{a}: 1238m, -, -, -; β_{C-H}(?): 1194w, 1194w, 1193w, 1193w; $\beta_{C-H}{}^{b}$: 1158m, 1164w, 1164w, 1166w; $\nu_{C-O}{}^{c}$: 1130sh, 1138m, 1135m, 1134m; $\beta_{C-H}{}^{b}$: 1126m, 1129m, 1128m, 1127m; β_{C-H}: -, 1119m, 1110m, 1105m; ν: 1095w, -, -, -; $\beta_{C-H}{}^{b}$ 1088m[d], 1056m[d], 1047m, 1046m; $\beta_{C-H}{}^{c}$: 1037w[e], 1042w[e], 1031m, 1019m.

1000-400 cm.$^{-1}$ region (liquid films). γ_{C-H}: 964w, 963w, 963w, 963w; ν: 871w and 851w, -, -, -; γ_{C-H}: 842w, 829w, 826w, 825w; 800w, 791w, 791w, 792w; 756s, 746s, 743m,

742m; ν_{C-Cl}: -, 720m, -, -; γ_{C-H}: 693w, 693w, 698m, 690m; 657m, 650m, 645m, 640m: ν: 561w and 541w and 526w, -, -, -; -, 476w and 448w, 462m, 453m.
([a] may be associated with ν_{C-F}. [b] diminishes from F to I. [c] intensifies from F to I. [d] diminishes in CH_3CN-CCl_4 as compared with CS_2. [e] intensifies in CH_3CN-CCl_4 as compared with CS_2).

Substituted Benzoic Acids. - In nonpolar solvents, e.g. carbon tetrachloride, carboxylic acids exist as an equilibrium mixture of monomeric IIa and dimeric forms IIB.

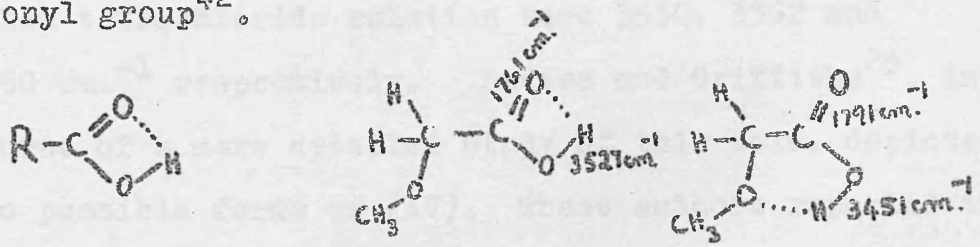
IIA IIB

In the m- and p-substituted benzoic acids each form gives rise to a single, generally symmetrical, carbonyl stretching absorption band. Data for a group of such acids (Table 3) indicate that the monomer band ranges from 1737 to 1752 $cm.^{-1}$ and the dimer band from 1691 to 1709 $cm.^{-1}$. The frequency values observed follow the established trends in relation to the electronic effects of the substituents (cf. Fig. 1 and further discussion below).

Corresponding to the two carbonyl frequencies, stretching absorptions of the hydroxyl group in the monomeric

and dimeric forms are observed, the former as a sharp band (ν max. ranging from 3529 to 3543 cm.$^{-1}$ in the group examined) and the latter as a broad diffuse band (3500 - 2400 cm.$^{-1}$). Whereas the monomer band position is directly dependent on the substituent (and can be related[2] to the pK of the acid - see also below), the dimer band is remarkably constant in appearance throughout the series examined. In view of the similarity and the diffuse nature of the dimer bands these are not discussed further.

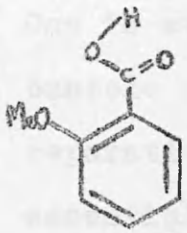
Oki and Hirota[42] have recently postulated that the appearance of a new high frequency carbonyl absorption, which accompanies intramolecular bonding by an acid hydroxyl to an α-oxygen atom, is evidence that the normal carboxylic acid monomer is itself an internally bonded form (IIIA). The equilibrium between the monomeric forms of methoxy acetic acid, with frequency[42] assignments is indicated below (IIIB and IIIC). The higher carbonyl frequency of (IIIC) is considered to be due to the "freeing" of the carbonyl group[42].



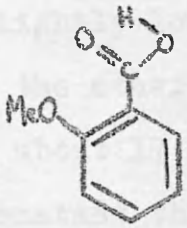
IIIA IIIB IIIC

Data for nine ortho-substituted acids are recorded in Table 3. Of these, o-toluic, o-nitrobenzoic and o-acetoxybenzoic acids exhibit single monomer carbonyl bands. As noted previously, Peltier and Pichevin[9] have presented evidence, conflicting with ours, that o-nitrobenzoic acid has two monomer carbonyl peaks.

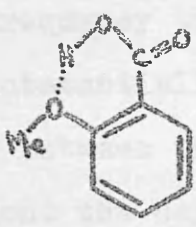
In o-methoxybenzoic acid (the conformation of CO_2H is written as in IV following Mizushima[15]; Davies[23] has depicted it with a hydrogen bond between the carbonyl and hydroxyl groups) the occurrence of the three species (IV) (the two possible forms (IVa)and (IVb) being treated as one), (V) and (VI), was demonstrated spectroscopically



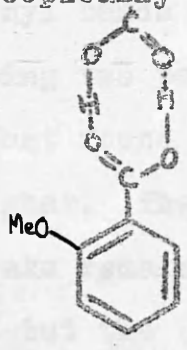
IVa



IVb



V



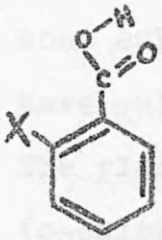
VI

by Fox and Martin[24], who showed that the hydroxyl stretching frequencies due to forms (IV), (V) and (VI) in carbon tetrachloride solution were 3530, 3362 and ca. 2950 $cm.^{-1}$ respectively. Davies and Griffiths[25], in the course of a more detailed study of this acid, depicted the two possible forms of (IV). These authors reported that

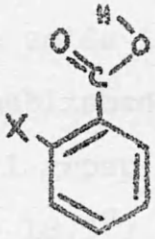
the dimer band was absent at concentrations below 0.004M in carbon tetrachloride: however, we observe low, broad absorption near 2950 cm.$^{-1}$ even at 0.0015M, and the presence of dimer is confirmed by inspection of the carbonyl region. The carbonyl absorption is assigned as follows: (IV), near 1760 cm.$^{-1}$; (V), 1751 cm.$^{-1}$; (VI) (three possible conformations), approx. 1703 cm.$^{-1}$. It seems probable that the principal conformation of the dimer is (VI), as discussed below. Analogous results are found for the o-allyloxy-acid.

The series of o-halogeno-acids presents interesting features. The monomeric carbonyl bands parallel those of the methyl esters in showing two peaks. One is at a slightly lower frequency than that found for benzoic acid, the other is substantially higher. The separation of about 17 cm.$^{-1}$ between the peaks remains essentially constant throughout the series, but the relative intensities (ε_a) change progressively from o-F ($\varepsilon_{1755}/\varepsilon_{1739} = 0.70$) to o-I ($\varepsilon_{1753}/\varepsilon_{1736} \sim 3.3$), as indicated in Fig. 2. The attribution of both peaks to monomeric forms was confirmed in every case by dilution studies. In the hydroxyl absorption region the spectra of the o-halogeno-acids are almost indistinguishable from those of the meta- and para-isomers, except in the exact

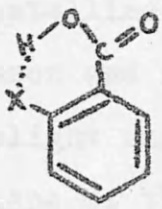
position of the single band near 3530 cm.$^{-1}$ due to the hydroxyl of the monomeric acid. The observed absorption bands near 1738 and 1755 cm.$^{-1}$ are consequently attributed to the conformational isomers (VIIa; X=Hal) and (VIIb; X=Hal) and the absorption near 1700 cm.$^{-1}$ to the three possible dimeric forms derived therefrom. The absorption in the dimer region shows evidence of



(VIIa)
(lower-frequency band)



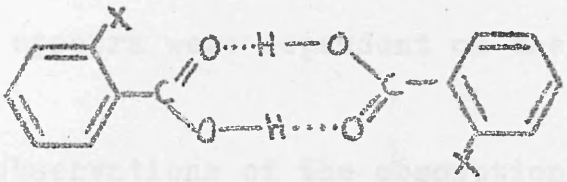
(VIIb)
(higher-frequency band)



(VIIc)

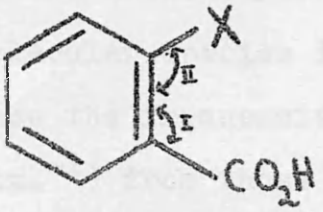
inhomogeneity (slight broadening and lack of symmetry) but no resolution of the bands appears feasible. We believe that the dimers exist principally in the conformation (VIII, X=Hal) for the following reasons: (i) the frequency separations between the carbonyl bands attributed to (VIIb) and the corresponding dimer bands have values close to those (~45 cm.$^{-1}$) found for all the other substituted benzoic acids examined; (ii) in the crystalline state, o-chlorobenzoic and o-bromobenzoic acid exist as depicted in (VIII), as demonstrated by x-ray crystallographic studies (personal communication from Dr. G.A. Sim and

Mr. G. Ferguson, the Chemistry Department, Glasgow University).



(VIII)

Further details of the refined structure of some substituted benzoic acids in the crystalline state have subsequently been published by Ferguson and Sim[43]. The plane of the carboxyl group is at a slight angle (o-chloro 13.7°, o-bromo 18.3°) to the plane of the benzene ring. The valency angles I and II, shown in the diagram, are both more than the normal 120° (o-chloro, I 122.5°,



II 124.7° and o-bromo I 123.4°, II 124.9°). Both the halogen atoms (o-chloro + 0.036Å, o-bromo + 0.064Å) and the exocyclic carbon atoms (o-chloro- 0.058Å, o-bromo - 0.057Å) are displaced from the plane of the ring. Solid state spectra of the acids were not informative: both solidified melts and Nujol mulls gave carbonyl bands of

irregular contour, all at frequencies lower (8-31 $cm.^{-1}$) than for solutions but showing no apparent regularities. The Nujol mull spectra were dependent on the mode of preparation.

The observations of the absorption characteristics of o-methoxy-benzoic acid and of the o-halogenobenzoic acids in carbon tetrachloride were supplemented by measurements on equimolar (0.0015M) solutions in chloroform and in mixtures of ether and carbon tetrachloride. The results are recorded in Tables 4 and 5.

The splitting of the monomer carbonyl absorption is not obvious in chloroform (e.g. Fig. 3), an effect partly attributable to the usual band-broadening induced by this solvent. The molecular species involved are doubtless solvated monomers, since the frequencies are markedly displaced (-7 to -17 $cm.^{-1}$) from those observed in carbon tetrachloride, whereas the dimer absorption frequencies are almost unaltered. The monomer frequency shifts (ν_{CO} in CCl_4 - ν_{CO} in $CHCl_3$ are of the same order as those we have observed for substituted methyl benzoates p-NO_2, - 11; p-Cl, -9; unsubstituted, -10; m-NMe_2, - 10 $cm.^{-1}$. The similarity of the dimer frequencies in chloroform and carbon tetrachloride is regarded as due to the virtual elimination

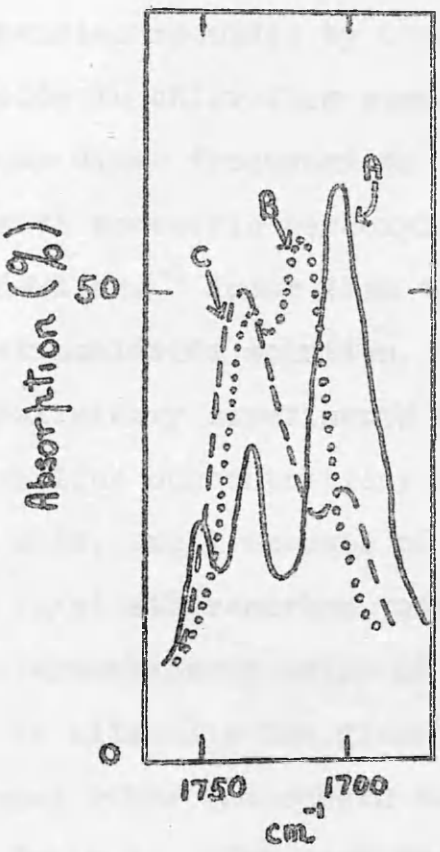


FIG.3. Carbonyl absorption of O - fluorobenzoic acid in (A) CCl_4, (B) 8% (v/v) ether - CCl_4 and (C) $CHCl_3$. Solutions are 0.0015M in 5mm. cells.

of the basicity of the carbonyl group consequent upon dimer formation cf. 26,27). Cole and Michell[28] have proposed an explanation based on steric shielding. The single frequencies recorded by O'Sullivan and Sadler[5] for these acids in chloroform appear to correspond approximately to our dimer frequencies. In the hydroxyl region associated with monomeric carboxyl, single bands are again observed, 16-21 $cm.^{-1}$ lower than the corresponding bands in carbon tetrachloride solution.

Preliminary experiments in carbon tetrachloride containing various concentrations of ether indicated that, for benzoic acid, small amounts of dimer were still present even in 20% (v/v) ether-carbon tetrachloride, whereas for the ortho-halogenobenzoic acids 8% (v/v) ether sufficed practically to eliminate the dimer absorption (e.g. Fig. 3). Twenty per cent ether was chosen for the measurements recorded in Table 4. The results parallel those recorded for carbon tetrachloride solutions in respect of (i) the splitting of the monomer absorption bands (ether-bonded monomer ($ArCO_2H...OEt_2$) in this case), (ii) the frequency separation of about 16 $cm.^{-1}$ between the bands, and (iii) the change in relative intensities through the sequence o-F, o-Cl and o-Br. The actual frequencies observed are all about 18 $cm.^{-1}$ lower than the values found in carbon

tetrachloride solutions. This parallels the marked lowering of the carbonyl frequency of acids in dioxan[29] as compared with carbon tetrachloride[1]. In both cases the effect is due to the mitigation of the electron-withdrawing character of the carboxylic OH group by hydrogen-bonding to the ether oxygen atom: the frequencies of carbonyl groups per se are only slightly affected by ether as compared with carbon tetrachloride (e.g. acetophenone, 1694 (ether) and 1692 (carbon tetrachloride) $cm.^{-1}$)[27]. Cole and Michell[28] have reported for benzoic acid, in dioxan, carbonyl bands at 1723 and 1636 $cm.^{-1}$, which they ascribe respectively to monomer and to a hydrogen-bonded benzoic acid - dioxan complex. We observe no carbonyl band at or near 1636 $cm.^{-1}$ for benzoic acid in ether-carbon tetrachloride. In Table 5 data are recorded for the carbonyl absorption of o-methoxybenzoic acid in ether-carbon tetrachloride (0, 4, 20, 50 and 100% ether by volume). With increasing concentrations of ether the intensity of the band associated with the intramolecularly-bonded conformation (V) is markedly reduced, finally to less than half the value in carbon tetrachloride. Fig. 4 illustrates the latter trend and also shows the emergence of two new carbonyl bands (at approximately 1715 and 1735 $cm.^{-1}$). These are attributed to the ether-bonded forms corresponding

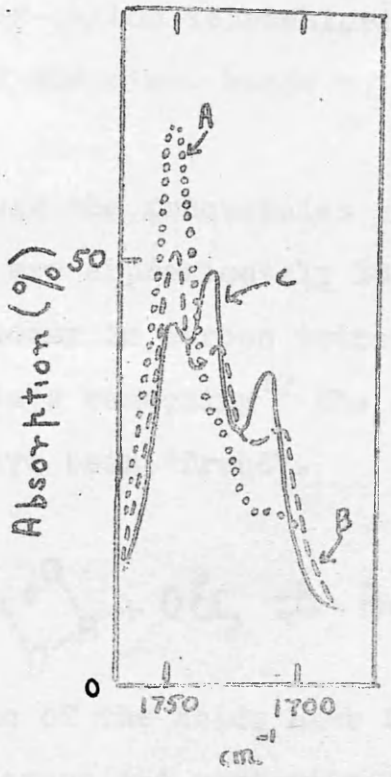
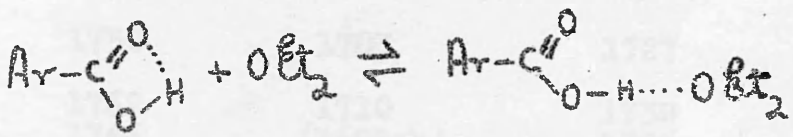


FIG.4. Carbonyl absorption of O-methoxybenzoic acid in ether - CCl_4 mixtures. (A) 0.0015M in 4% (v/v) Et_2O - CCl_4:5mm.cells. (B) 0.015M in 20% (v/v) 0.5mm.cells.(C)0.015M in 100% Et_2O:0.5mm.

to the two conformations (IVa) and (IVb). The possibility that the band near 1715 cm.$^{-1}$ is due to a dimeric form is rejected since it increases in intensity with increasing ether concentration, whereas in the other benzoic acids examined in ether-carbon tetrachloride a small concentration of ether reduces the dimer bands to insignificant proportions.

Although the frequencies attributed to our ether-bonded monomers are approximately 18 cm.$^{-1}$ lower than for the ordinary monomer in carbon tetrachloride, on the basis of Oki and Hirota's reasoning[42] the carbonyls must be considered to have been "freed".



Certain of the acids have been examined as solutions in n-hexane and acetonitrile. At approximately equimolar concentrations the acids appear to be almost wholly dimeric in the non-polar hydrocarbon solvent and monomeric in the highly polar acetonitrile. The intensity ratio of monomer to dimer absorption thus increases through the sequence of solvents, n-hexane, carbon tetrachloride, carbon disulphide, chloroform and acetonitrile. Even at high

concentrations (~1M, 0.05 mm.) in acetonitrile, benzoic acid shows negligible dimer absorption. o-Fluoro-benzoic acid gives two monomer carbonyl bands in n-hexane and in acetonitrile: in the latter solvent they are of equal intensity. The carbonyl absorption of o-methoxy-benzoic acid is relatively unaffected by the solvent: this is explicable in terms of the stability of form (VI). Typical data are assembled below.

Substituent	Solvent		
	n-hexane		acetonitrile
	νCO (monomer) cm.$^{-1}$	νCO (dimer) cm.$^{-1}$	νCO (monomer)[a] cm.$^{-1}$
None	1750	1703	1727
o-F	1762 1746	1710 (1698sh)	1738 1726
o-I	*	*	1736
o-OMe	1759 (1763sh)	(1707)	1739

[a] Half-band widths ($\Delta\nu_{\frac{1}{2}}$) 20 ± 2 cm.$^{-1}$.

Values in parentheses are approximate.

* Not measured. sh = shoulder.

The results described above suggest that the occurrence of two monomer carbonyl bands in the spectra of these acids is not connected with hydrogen bonding between

the carboxyl and halogen groups[10,30,31]. The single monomer hydroxyl bands observed require discussion: our assignments imply that forms (VIIa and VIIb; X=Hal) absorb at approximately the same frequency (the slight broadening as compared with the m- and p-halogeno-acids may be significant). It is also conceivable that internally-bonded forms (VIIc) might absorb at the same frequencies as the corresponding forms (VIIa) and (VIIb). However the closely similar monomer hydroxyl frequencies (3527-3530 $cm.^{-1}$ in carbon tetrachloride) observed for the four o-halogeno-acids appear incompatible with this proposal. (In the o-halogenophenols (hydrogen bond in 5-membered ring) ν_{OH} ranges[32] from 3584 (o-F) to 3500 (o-I) $cm.^{-1}$). Possibly hydrogen bonding is inhibited in the o-halogeno-acids by steric displacement of the carboxyl group due to repulsion between the halogen and hydroxylic oxygen atoms. In support of this we note that in 6-chlorosalicylic acid, in which proximity and coplanarity of the halogen and hydroxylic oxygen atoms are both enforced by the powerful chelation of the remaining groups, two bands, at 3508 $cm.^{-1}$ (free) and 3430 $cm.^{-1}$ (bonded) are observed.

Evidence relating to conformational assignments. - We now turn to a more detailed examination of the basis for the interpretations of the band splitting in ortho-substituted

derivatives presented above. In recent papers[33,34] R.N. Jones and his colleagues have pointed out that solvent- and temperature-dependent modifications of carbonyl frequencies have been commonly attributed to conformational equilibria wherever plausible structures could be written. They, and other workers[35], have emphasised that Fermi resonance and other vibrational interactions can produce very similar spectral behaviour, and have accounted in this way for the well-defined doublets observed in inter alia cyclopentanone, benzoyl chloride and certain butenolides.

Our principal evidence in support of the conformational interpretation is as follows:-

(a) The retention of similar absorption patterns (Figs. 2 and 4 and Tables 2, 3 and 4) by the methyl o-halogeno-benzoates in n-hexane and carbon tetrachloride, and by the corresponding carboxylic acid monomers in carbon tetrachloride and ether-carbon tetrachloride, offers strong circumstantial support for the conformational explanation as it seems unlikely that Fermi resonance would operate with such regularity.

(b) The regularly increasing preponderance of the higher frequency band though the series of ortho-substituents H, F, Cl, Br, I parallels the trend already

described in conformational terms for the o-halogeno-acetophenones[20] and may be readily rationalised in steric terms (see earlier). If Fermi resonance is invoked decreased coupling would have to occur for a smaller frequency separation between the bands - the inverse of normal experience. Furthermore, there are no obvious frequencies (400 $cm.^{-1}$ upwards) which might be consistently employed to provide overtone or combination bands close to 1730 $cm.^{-1}$ either in the acids or their methyl esters.

(c) The effects of solvents on the frequencies and intensities of the split carbonyl bands are significant. Relevant data are collected in Table 6. It will be noted that the solvent shifts of the split carbonyl bands in methyl o-fluoro, o-chloro- and o-methoxybenzoates, and in o-fluorobenzoic acid, are not much different from the values observed for the unsubstituted compounds. On the other hand, in the examples (coumarin[34] and cyclopentanone[33,35]) ascribed to Fermi resonance, the solvent shifts are irregular, since neither of the observed fundamental bands represents the simple carbonyl group frequency[36]. The ratio ($\varepsilon_1/\varepsilon_2$) of the intensities of the two bands (higher ν_1/lower ν_2) observed in Fermi resonance decreases markedly as the solvent polarity is increased. In the substituted benzoic acids and esters the reverse trend is clearly shown, in

accordance with the increasing preponderance of the more polar conformation in the more polar solvent. Preliminary observations of the temperature dependence of the absorption of methyl o-fluoro-benzoate in carbon tetrachloride indicate that over the range 30-70°, the higher frequency band (attributed to (VIIb; X=F)) becomes relatively more intense as the temperature rises: at 70° the ratio of intensities was 7% above that found at 30°. A frequency shift of 1 cm.$^{-1}$ to 1727 and 1742 cm.$^{-1}$ was also observed. These small but definite effects are consonant with our assignments but do not in themselves exclude Fermi resonance[34]. A study of deuterated compounds would be desirable.

(d) Where detectable conformational isomers are not expected, the carbonyl bands are not split, e.g., the m- and p-substituted benzoic acids and esters and methyl 2,6-dimethoxybenzoate. The weakly polar substituents ortho-methyl and ortho-acetoxy produce single carbonyl frequencies.

(e) Careful comparison of the spectra of the methyl halogenobenzoates as liquid films, and as solutions in carbon disulphide and acetonitrile reveals that intensity changes paralleling those in the carbonyl region occur in at least two pairs of bands (near 1040 cm.$^{-1}$ and near

1260 cm.$^{-1}$) in the region 400-1600 cm.$^{-1}$. This behaviour, which is entirely consistent with the presence of two isomers, is exemplified in the data given below (in the ortho-fluoro ester it is difficult to distinguish the intensity changes owing to superposition of bands).

		CS_2		CH_3CN	
		cm.$^{-1}$	$\varepsilon_1/\varepsilon_2$	cm.$^{-1}$	$\varepsilon_1/\varepsilon_2$
Methyl-o-chloro-benzoate	(1)	1055	3.15	1055	2.3
	(2)	1042		1041	
Methyl-o-iodo-benzoate	(1)	1046	0.39	1045	0.38
	(2)	1019		1018	

The m- and p-halogenobenzoates do not show these marked effects.

Correlation of frequencies with acid strengths. - As described earlier, correlations have been established by previous investigators between carbonyl and hydroxyl frequencies and various parameters denoting the electronic effects of substituents. The very complete data of Peltier et al.[3,9] relating carbonyl frequencies (of monomeric acids and of methyl esters) to pK render further examples of this type unnecessary. However, Davis and Hetzer[30] have suggested that frequency data determined in relatively non-polar

solvents might display improved correlations with comparative acid strengths determined in similar solvents. We have therefore plotted (in Fig. 5) carbonyl frequencies of monomeric acids and of methyl esters in carbon tetrachloride against these authors' values of log K" for the neutralisation of the acids by diphenylguanidine in benzene[1]. Those substituted acids and esters which give rise to split carbonyl bands afford no obvious correlation and are omitted. The two series of values fall on approximately parallel straight lines.

With regard to the hydroxyl stretching absorption of the monomeric acids, Goulden[2] established a linear relationship between ν_{OH} and pK (in water) for a number of m- and p-substituted benzoic acids. Davis and Hetzer have re-plotted Goulden's values against log K", and our data, in which ν_{OH} values for o-substituted acids are included, are similarly presented in Fig. 5: the m- and p-substituted acids are well accommodated, but the values for o-substituted acids are displaced, mostly to lower frequencies. We conclude that while the use of non-aqueous acid strengths might appear desirable it does not in this instance greatly improve the consistency already shown by the pK or δ values. The possible correlation of ν_{OH} in o-substituted benzoic acids with Taft's[4] polar substituent constants δ^{*} was

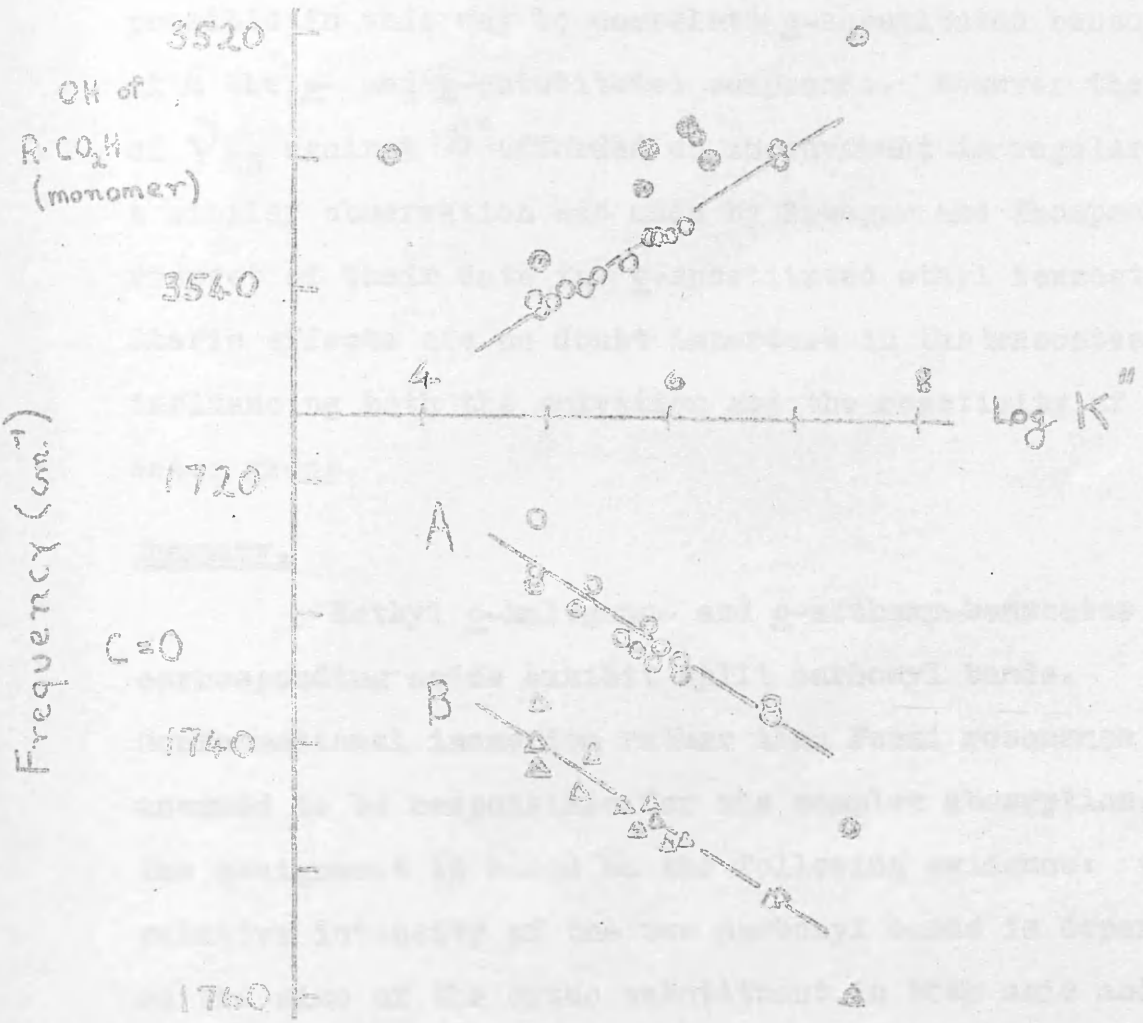


FIG.5. Carbonyl and hydroxyl stretching frequencies (CCl_4) of aryl carboxylic acids and methyl esters, and (abscissa) log K" for the neutralisation of acids by diphenylguanidine in benzene (ref 1.).

● ▲ ortho - Substituted derivatives.

A, $R.CO_2Me$; B, $R.CO_2H$ (monomer)

briefly examined, since Krueger and Thompson[7] found it possible in this way to correlate o-substituted benzonitriles with the m- and p-substituted compounds. However the plot of ν_{OH} against δ^{*} afforded no improvement in regularity. A similar observation was made by Krueger and Thompson[7] in respect of their data for o-substituted ethyl benzoates. Steric effects are no doubt important in the benzoates, influencing both the solvation and the reactivity of the ester group.

Summary.

Methyl o-halogeno- and o-methoxy-benzoates and the corresponding acids exhibit split carbonyl bands. Conformational isomerism rather than Fermi resonance is assumed to be responsible for the complex absorption. The assignment is based on the following evidence: the relative intensity of the two carbonyl bands is dependent on the size of the ortho substituent in both acid and ester spectra: selected compounds studied in solvents of differing polarities display spectral effects not normally attributed to Fermi resonance, but easily explained in terms of the conformational isomers proposed.

Some regularities in carbonyl stretching frequencies

of the series Ar.COX (where X = Me, OH dimer, H, OEt, OH monomer) have been briefly discussed. Hydroxyl and carbonyl stretching frequency data of *meta*- and *para*-substituted derivatives have been satisfactorily correlated with the relative acidity values reported by Davis and Hetzer[30].

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Table 1.

Methyl esters of monosubstituted benzoic acids (CCl_4)[a].

m- and p-substituents					o-substituents				
No.		ν_{CO}	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a	No.		ν_{CO}	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a
1	m-NMe_2	1727	15	680	13	o-OMe	1745sh[+]	*	*
							1736	*	430
							1718	(25)	265
2	m-OMe	1728	15	660					
3	None	1730	11	900	14	o-O-allyl	1748sh[+]	*	*
							1737	*	450
							1718	(23)	260
4	m-F	1733	11	795	15	o-Me	1728	13	710
5	m-Cl	1735	11	915	16	o-F	1741	(12)	315
							1726	14	510
6	m-Br	1734	11	850					
7	m-NO_2	1738	10	890	17	o-Cl	1744	13	410
							1727	(22)	240[+]
8	p-OMe	1723	16	725	18	o-Br	1744	12	465
							1727sh	*	(195)[+]
9	p-F	1732[+]	11	775					
10	p-Cl	1731	11	920	19	o-I	1740	12	550
							1727sh	*	(160)[+]
11	p-Br	1734[+]	12	820	20	o-NO_2	1747	14	710
12	p-NO_2	1737	12	750	21	o-OAc[b]	1733	12	865

Compounds Nos. 4, 5, 9 and 10 showed $\varepsilon_{max.}$ in carbon disulphide 1-2 $cm.^{-1}$ lower than the values for CCl_4, with $\Delta\nu_{\frac{1}{2}}$[a] 9±1 $cm.^{-1}$. Values in parentheses are approximate.
sh = shoulder. * Not measured. [+] Estimated by band reflection.

Footnotes continued overleaf

Footnotes to Table 1. (continued).

‡ Unsymmetrical band. [a] Measured as approximately 0.0015M solutions in 5 mm. cells. [b] Acetate carbonyl absorption at 1775 cm.$^{-1}$ ($\Delta\nu_{\frac{1}{2}}^{a}$, 16; ε_{a}, 550).

Table 2.

Methyl benzoate, methyl o-methoxybenzoate and methyl o-halogenobenzoates in various solvents.

	No.	Substituent	Absorption bands in carbonyl region					
			ν_{CO}	$\Delta\nu_{\frac{1}{2}}$ [a]	ε_a	ν_{CO}	$\Delta\nu_{\frac{1}{2}}$ [a]	ε_a
n-Hexane[a]	3	None	-	-	-	1735	9	1035
	13	o-OMe	1745	14	395	1723	16	305
	16	o-F	1749	9	260	1731	9	425
	17	o-Cl	1750	8	465	1733	14	285
	18	o-Br	1750	8	550	1735	18	240+
	19	o-I	1746	8	630	1736sh	*	(200)+
Acetonitrile[b]	3	None	-	-	-	1724	11	790
	13	o-OMe	1731	16	505	(1709sh)	*	(105)+
	16	o-F	1733	12	520	1723	13	425+
	17	o-Cl	1736	18	480	(1724sh)	*	(120)+
	18	o-Br	1737	(16)	535	(1729)§	*	(135)+
	19	o-I	1733	(15)	540	(1725)§	*	(85)+
Carbon disulphide[c].	3	None	-	-	-	1723	8	*
	13	o-OMe	1735	(15)	*	1713	24+	*
	16	o-F	1739	(11)	*	1724	12	*
	17	o-Cl	1743	(13)	*	1726	(16)	*
	18	o-Br	1741	11+	*	(1725) §	*	*
	19	o-I	1738	9+	*	(1725) §	*	*

- No band present. § Concealed band. For other symbols see Table 1.

[a] ca. 0.0076M, [b] ca. 0.019M, [c] ca. 0.015M solutions; all in 0.5 mm. cells.

Table 3.

Monosubstituted benzoic acids (CCl_4)[a].

No.	Substituent	Monomer ν_{CO}	Monomer $\Delta\nu_{\frac{1}{2}}$[a]	Monomer ε_a	Dimer Monomer[b,c] ν_{CO}	Dimer Monomer[b,c] $\Delta\nu_{\frac{1}{2}}$[a]	Dimer Monomer[b,c] ε_a	Dimer Monomer[b,c] ν_{OH}	Dimer Monomer[b,c] $\Delta\nu_{\frac{1}{2}}$[a]
22	m-NMe_2	1740	14	245	1693	15	660	3541	29
23	m-OMe	1741	13	215	1698	17	640	3539	30
24	m-Me	1742	13	260	1698	14	805	3540	27
25	None	1744	13	270	1697‡	16	750	3540	27
26	m-F	1748	11	270	1703	13	685	3536	30
27	m-Cl	1748	12	285	1703	16	700	3535	30
28	m-Br	1748	12	275	1702	14	685	3535	31
29	m-NO_2	1752	10	305	1709	18	575	3530	35
30	p-OMe	1737	13	*	1691	12	*	3542	25
31	p-Me	1740	12	265	1697‡	12	995	3541	26
32	p-F	1745	13	255	1699	12	880	3538	30
33	p-Cl	1745	11	*	1698*	10	*	3536	32
34	p-Br	1746	13	*	1698	16	*	3536	32
35	p-NO_2	1752	13	*	1707	15	*	3529	*
36	o-OMe	(1760sh) 1751	* 14	* 670	1702 ¶	*	*	3530 3365	40 80
37	o-O-allyl	1751	15	880	1703	*	*	3529 3354	38 90
38	o-Me	1742‡	16	250	1696‡	18	590	3538	30
39	o-F	1755 1739	12 *	155 220	1707 (1700sh)	23 *	535 *	3529	32
40	o-Cl	1756 1738	12 *	200 (105)+	1706	25	440	3527	38
41	o-Br	1757 1738	12 *	200 (95)+	1711‡	26	420	3528	38
42	o-I	1753 (1736sh)	12 *	230 (90)+	1708‡	22	465	3530	38
43	o-NO_2	1760	16	*	1715	19	*	3520	35
44	o-OAc[d]	1747‡	14	395	1702	18	545	3532	35

Footnotes to Table 3.

¶ Very weak band: νmax. confirmed by measurement at higher concentration. For other symbols see Table 1.

[a] Measured as 0.00150 ± 0.0002M solutions (except for Nos. 36 (0.0018M) and 30, 33, 34, 35 and 43 (saturated solutions)) in 5 mm. cells (ν_{CO}) or 20 mm. cells (ν_{OH}).

[b] In the region 3650 - 2500 cm.$^{-1}$ the following additional assignments were made: No. 22, 2807 cm.$^{-1}$ (ν_{CH},NMe); Nos. 23 and 30, 2835 and 2841 cm.$^{-1}$ respectively (ν_{CH}'OMe). No. 36 showed no sharply defined peak attributable to the latter vibration. Nos. 36 and 37 showed a weak band near 3475 cm.$^{-1}$ presumed to be the first overtone of the intense carbonyl band at 1751 cm.$^{-1}$

[c] ε_a for ν_{OH} was virtually constant at about 50 cm.$^{-1}$ l. mole^{-1} except for Nos. 36 and 37 for which ε_a values were: No. 36, 15 and 100; No. 37, 10 and 105.

[d] Acetate carbonyl at 1776 cm.$^{-1}$ ($\Delta\nu_{\frac{1}{2}}^{a}$ 15, ε_a 505).

[e] Hill and Meakins, J., 1958, 760.

[f] Henbest, Meakins, Nicholls and Wagland, J., 1957, 1462.

Table 4.

Benzoic acid and ortho-substituted benzoic acids[a].

No.	Substituent	Chloroform: Monomer ν_{CO}	Monomer $\Delta\nu_{\frac{1}{2}}^{a}$	Monomer ε_a	Dimer ν_{CO}	Dimer $\Delta\nu_{\frac{1}{2}}^{a}$	Dimer ε_a	Monomer ν_{OH}	Ether-CCl_4 (20:80 v/v): Bonded monomer ν_{CO}	Bonded monomer $\Delta\nu_{\frac{1}{2}}^{a}$	Bonded monomer ε_a
25	None	1734	25	360	1697	20	235	3524	1726	15	720
39	o-F	1738	34	375	1706	(25)	(195)	3514	1737 1721	17 17	355 485
40	o-Cl	1744‡	30	380	1706	(28)	(170)	3512	1738 1720	14 *	465 (190)+
41	o-Br	1743	25	395	1706	(24)	(160)	3512	1737 (1722sh)	13 *	450 (150)+
42	o-I	1746‡	30	355	1709	(38)	(155)	3509	*	*	*
45	o-CH_2OH	1721	*	*	1687	*	*	3515	*	*	*

For symbols see Table 1. [a] Measured as 0.0015M solutions in 5 mm. cells ($CHCl_3$), except No. 45 (saturated solution), and in 2 mm. cells (ether-CCl_4).

Table 5.

Carbonyl bands of monomeric forms of o-methoxybenzoic acid in ether-carbon tetrachloride.

			Monomer (III)		Ether-bonded monomer (IIb)?		(IIa)?	
Molarity	Cell Path (mm.)	Ether % v/v	ν_{CO}	ε_a	ν_{CO}	ε_a	ν_{CO}	ε_a
0.0018	5.0	0	1751	670	-	-	-	-
0.0015	5.0	4	1752	630	(1735sh)	*	(1710)	*
0.015	0.5	20	1751	405	1734	(265)	1712	(205)
0.015	0.5	50	1751	(325)	1735	(345)	1714	(240)
0.015	0.5	100	1752	(315)	1738	(385)	1715	(260)

For symbols see Table 1.

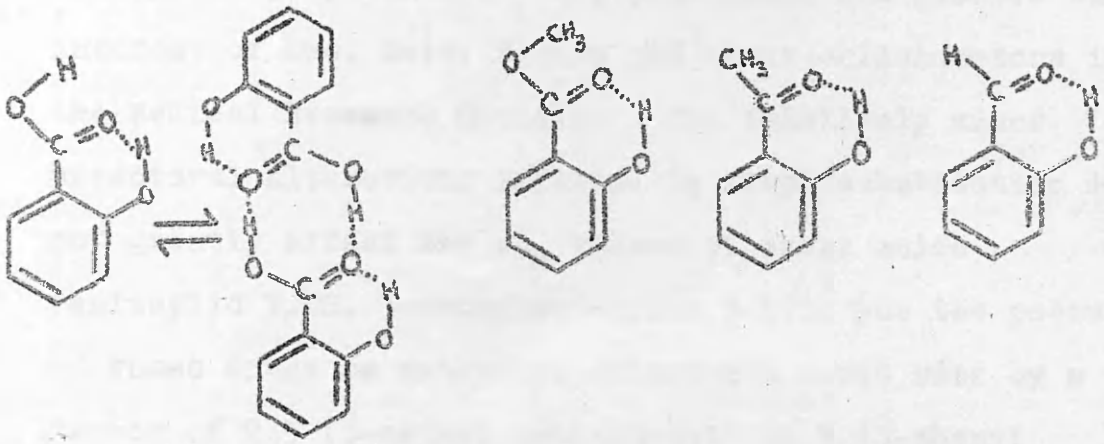
SECTION 3.

Infrared Spectra of Substituted Salicylic Acids and their Esters.

Historical. Well known differences in the properties of ortho compounds compared with their meta and para isomers have long been ascribed to interaction between the substituents. Fox and Martin[1a,b] were among the original authors to demonstrate, by spectroscopic means, that intramolecular hydrogen bonding or chelation could explain these differences in a number of compounds. For example methyl salicylate[1b] in CCl_4 had an intense broad band at 3200 $cm.^{-1}$ while no trace of the normal phenolic hydroxyl at 3611 $cm.^{-1}$ could be found. No change in absorption was found in dilution studies when the number of molecules in the light path was kept constant. This characteristic distinguishes the intramolecular type of bond from that formed between molecules.

In a review of the hydroxyl absorption of chelated compounds Martin[2] demonstrated, by dilution studies, how salicylic acid (I) in CCl_4 displayed intermolecular bonding by the carboxylic hydroxyl in addition to the intramolecular bonding shown by the phenolic hydroxyl as in methyl salicylate (II), o-hydroxyacetophenone (III), and

salicylaldehyde (IV). The intensity of the sharp absorption



I II III IV

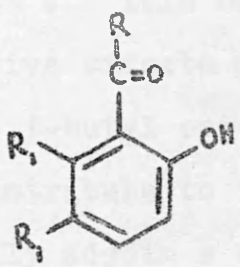
peak at 3534 cm.$^{-1}$ normally attributed to a monomeric carboxylic acid hydroxyl and the broad intense absorption from 3330-2750 cm.$^{-1}$ characteristic of carboxylic acid dimer, were both markedly concentration dependent. The intensity of the hump-shaped absorption around 3200 cm.$^{-1}$, due to the chelated hydroxyl, remained reasonably constant.

Flett[3] pointed out that of nine acids, examined by him, where the carbonyl absorption was below 1680 cm.$^{-1}$, seven were capable of intramolecular hydrogen bonding between the carbonyl group and an adjacent phenolic OH or an NH group. Since then many workers have shown that a lowering of both hydroxyl and carbonyl frequencies accompanies hydrogen bond formation between these groups. Carbonyl bands are however not greatly intensified by hydrogen bonding.

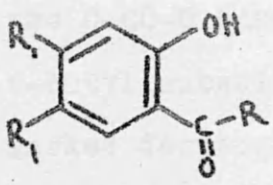
The effect of alkyl substitution on certain

biological properties of salicylic acids had aroused the the interest of Drs. Reid, Brooks and their collaborators in the Medical Research Council. The relatively minor structural alterations afforded by alkyl substitution did not greatly affect the pK_a values of these acids (salicylic 3.08, 3-methylsalicylic 3.17), yet the potency of these drugs as metabolic stimulants could rise by a factor of 2.5 (3-methyl substituent) to 7 (3-phenyl substituent) relative to salicylic acid. It was hoped that an accurate study of the infrared absorption might throw light on the structural basis of these effects.

In 1958, just before the commencement of our experimental work on this subject, Hunsberger et al[5] advanced the theory that, in suitable circumstances, steric overcrowding could enhance the strength of an intramolecular hydrogen bond. They considered that lower ν(C=O) in compounds of type V compared with type VI were readily explained by assuming that R_1 displaces the



V



VI

where R = H_2CH_3, or OCH_3
and R_1 = methylene or methyl

carbonyl oxygen of type V, so that it is closer to the hydroxyl group than in type VI. The alternative explanation, that the decreased ν(C=O) might be due to partial fixation of ring double bonds in type VI, was considered to be less satisfactory.

A preliminary report of our results was read to the Infrared Discussion Group, London, December, 1959. Our data, particularly that for 6-substituted salicylic acids, where the lower ν(C=O) are paralleled by very low ν(OH), appear to support Hunsberger's theory.

Results.

Esters.- As a prelude to the main investigations, the effects of substitution in the methyl group of methyl benzoate, methyl salicylate and methyl 2,6-dihydroxybenzoate were examined (Table 1). The carbonyl frequency falls as the O-alkyl group is changed in the sequence Me: Et, Pr^n: Pr^i: Bu^t. This order would appear to correspond to the inductive effects normally ascribed to these groups[6], though in the t-butyl esters, deformation of the C-CO-O bond angle may contribute to the shift. (Where t-butyl substituents actually adjoin a carbonyl function a marked decrease in frequency is noted[7]). The centres of the broad hydroxyl bands due to the chelated phenolic groups of the salicylates

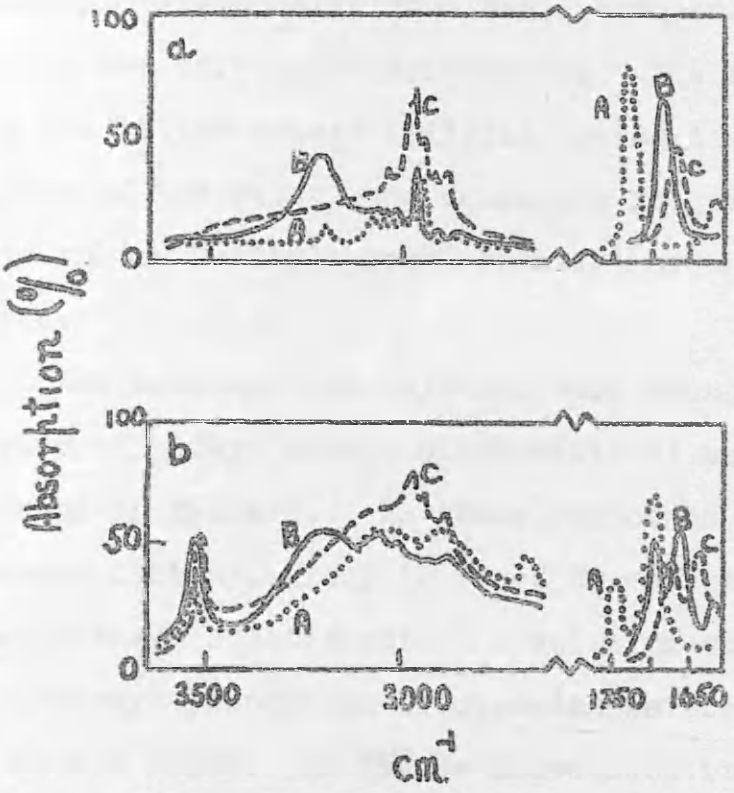


FIG. a. Methyl esters (0.00135M in CCl_4). 2 cm. cells (3650-2600 cm.-1). 0.5 cm. cells (1760-1600 cm.-1). A, benzoate; B, salicylate; C, 6-isopropyl-3-methylsalicylate.

FIG. b. Acids (0.0015M in CCl_4). 2 cm. cells (3650-2600 cm.-1). 0.5 cm. cells (1760-1600 cm.-1). A, benzoic; B, salicylic. C, 6-isopropyl-3-methylsalicylic.

and 2,6-dihydroxybenzoates show small frequency shifts paralleling the carbonyl displacements. The second phenolic group in the latter esters (VII) is bonded to the alkyl oxygen atom of the ester, and again the frequency is dependent on the O-alkyl group, rotation of which is restricted.

The hydroxyl and carbonyl stretching frequencies of a series of methyl esters of substituted salicylic acids are recorded in Table 2. In these compounds the conformation of the ester carbonyl group is fixed by chelation with the phenolic hydroxyl substituent. Precise measurement of chelate hydroxyl absorption frequencies is precluded by the breadth of the bands. In the 3- and 6-substituted esters it is apparent from careful superposition of spectra that the band moves to lower frequencies, eventually merging into the C-H absorption region (Fig. 1a and Table 2). Even where the band maximum is markedly displaced, the region of absorption begins near 3500 cm.$^{-1}$: no such residual "wing" is apparent in the carbonyl absorptions, and the origin of this absorption is obscure: the minor occurrence of carbonyl overtone bands (near 3350 cm.$^{-1}$) could not account for it. The relatively weak chelation in methyl 3-hydroxy-2-naphthoate (No. 21) is reflected in the hydroxyl band at

3266 cm.$^{-1}$ (cf.[8]).

Methyl salicylate shows carbonyl absorption at 1684 cm.$^{-1}$ as compared with 1730 cm.$^{-1}$ for methyl benzoate and 1658 cm.$^{-1}$ for the enol form of ethyl 2-oxocyclohexane-carboxylate. Nuclear alkyl substituents not adjoining the functional groups have only minor effects on the carbonyl frequency. Substitution in the 3- and particularly in the 6-position, however, leads invariably to absorption at lower frequencies (e.g. Fig. 1a), the displacement depending on the bulk of the substituent: the bands remain symmetrical in most instances and undergo little broadening. This "ortho-effect" is conveniently exemplified in the isomers Nos. 2, 3, 5 and 13 and in the benzo-analogues 19 and 20. The data observed for esters 19, 20 and 21 is in good agreement with that of Hunsberger *et al.*[9(a)]. A similar steric effect is apparent in methyl 10-hydroxyphenanthrene-9-carboxylates, in which the carbonyl frequency (1649 cm.$^{-1}$)[9(b)] is much lower than would be expected if only the double-bond character of the C9-C10 linkage were considered[10]. The data for esters and acids Nos. 1, 2, 3, 5 and 13 are in reasonable agreement with that published by Peltier and Pichevin[11] after the completion of our work and report to the Infrared Discussion Group.

We have not observed the subsidiary carbonyl

absorption at 1735 cm.$^{-1}$ recorded by these authors for the methyl ester of acid No. 13. They considered this may have corresponded to a species where chelation had been inhibited by the restrictions on the rotation of the carbomethoxyl group by the ortho methyl. These authors have commented that the considerably lower carbonyl frequencies of 6-methylsalicylic acid and ester (No. 13) are the result of stronger chelation, caused by the buffering of the carboxyl group by the ortho methyl.

Frequencies, half-band widths and intensities (ε_a) of carbonyl absorptions have been determined for some esters in several solvents. The frequency data, summarised in Table 3, show that the solvent shifts for the salicylates are only about half those observed for methyl benzoate, in accordance with the lower carbonyl basicity (Section 2) in the chelated esters. The abnormally small shift for t-butylsalicylate in chloroform is ascribed to steric inhibition of association with the solvent and indeed a part of the more general solvent insensitivity of the salicylates may be attributed to this cause. The approach to the carbonyl, which is rigidly held in the plane of the ring by chelation, may be partially blocked by ring substituents, principally the hydroxyl, but also the alkyl groups of the substituted salicylates. The half-band widths show some regularities:

methyl 3-i-propyl-6-methylsalicylate has the broadest, methyl 3-t-butylsalicylate the narrowest, band (e.g. $\Delta\nu_{\frac{1}{2}}^{a}$ in hexane 16 and 7 cm.$^{-1}$ respectively). Through the sequence of solvents n-hexane, CCl_4, CH_3CN, $CHCl_3$ the half-band widths show a general increase, e.g. methyl 3- and 6-methylsalicylates both have $\Delta\nu_{\frac{1}{2}}^{a}$ 10 cm.$^{-1}$ in hexane, 23 cm.$^{-1}$ in chloroform. At the same time the intensities (εa) generally decrease. For carbon tetrachloride the intensities (εa) range from 785 (compound No. 2) to 370 (No. 18) l. mole^{-1} cm.$^{-1}$. The trend towards lower values with 3,6 disubstitution is accompanied by band broadening leading to approximate constancy of integrated intensities ($10^4\beta \sim 3$ l. mole^{-1} cm.$^{-2}$).

Other Correlations.- In the group of methyl esters examined two intense C-H bands of the ester methyl group occur near 2950 and 2850 cm.$^{-1}$, and are most clearly seen in compounds 19-21 which lack other alkyl groups.

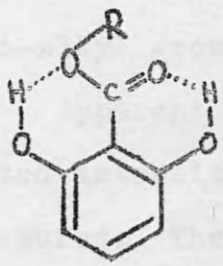
Spectra of methyl esters as liquid films or Nujol mulls will appear in the D.M.S. Index (Butterworths) as spectral cards Nos. 6521 onwards. The general absorption patterns are little dependent on the bulk of the substituents; thus the 3,6-dimethyl and 3-t-butyl-6-methyl derivatives exhibit similar spectra with the principal γ C-H at 804 and 806 cm.$^{-1}$ respectively (c.f. 1,2,3,4-tetramethylbenzene, 804 cm.$^{-1}$)[12].

In the 3-methyl-6-i-propyl derivative this band is shifted to 820 cm.$^{-1}$. Methyl 6-methylsalicylate simulates the 1,2,3,4-tetrasubstituted compounds in having strong γ CH absorption at 808 cm.$^{-1}$, whereas the 3-alkyl and 3-alkenyl esters show the expected bands near 760 cm.$^{-1}$.

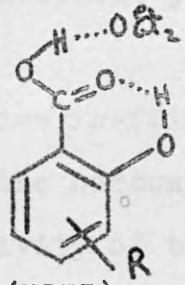
Acids.- Data recorded in Table 2 refer, with a few exceptions, to 0.0015M-solutions: at this concentration the monomeric and dimeric species give rise to carbonyl bands of approximately equal intensity in the acids examined. The generally lower proportions of dimeric forms (1:1 in the salicylic acids, 2-4:1 in unchelated acids (Section 2) (cf. Fig. 1b)) may be ascribed principally to the reduced carbonyl group basicity. The monomer carbonyl bands are displaced from those of the methyl esters by 13 cm.$^{-1}$ (S.D. 1.2), in close concordance with other substituted benzoic acids[11,13] (cf. Section 2). The frequency separation between the monomer and dimer bands (35 cm.$^{-1}$; S.D. 2), however, is significantly lower than that (45 cm.$^{-1}$ S.D. 1.6) observed for unchelated acids. The relatively smaller shift accompanying dimer formation also reflects the lower basicity of the salicylic acid carbonyl group. Peltier and Richevin[11] have noted similar differences in monomer and dimer carbonyl frequencies (unchelated benzoic acids 45 $\pm$ 3 cm.$^{-1}$, chelated

36 ± 2 cm.$^{-1}$). They ascribed the lower value for chelated acids to the effect of the coexisting intramolecular bonding in these compounds.

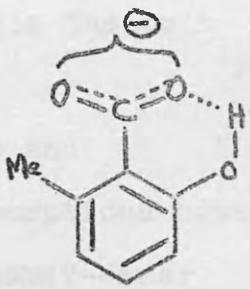
In the groups of acids examined in solutions containing ether, the frequency displacements (-18 cm.$^{-1}$: S.D. 2.5) accompanying formation of the ether-bonded monomers (VIII) correspond to the value observed for benzoic acid (cf. section 2). The concentrations of ether required to eliminate dimer absorption are generally lower than for the benzoic acids, as already noted by Forbes and Knight for ultraviolet absorption[14]. In pure ether (0.5 mm. cells) salicylic acid showed only the band attributed to form (VIII; R=H): there was no indication of any opening of the chelate ring. The effects of nuclear substitution on the acid carbonyl frequencies are closely parallel to those described for the methyl ester bands.



(VII)



(VIII)



(IX)

The broad band near 3200 cm.$^{-1}$ due to the

chelated phenolic hydroxyl group[2], and somewhat obscured by the absorption of the acid dimer, is detectable in salicylic acid. It becomes less well-defined in the alkyl-substituted acids and is not discernible in No. 17, where it has presumably moved into the C-H absorption region. Apart from this detail, all the 6-alkyl acids show similar band outlines between 3600 and 2600 cm.$^{-1}$. The hydroxyl group of the monomeric acid exhibits a sharp band at a position (3530 $\pm$ 3 cm.$^{-1}$) virtually independent of alkyl substitution at the 3-, 4- and 5-positions but occurring at a lower frequency (3513-3519 cm.$^{-1}$) in all the 6-alkyl acids examined, and in the naphthoic analogue (No. 19). This feature may have diagnostic value, not merely to locate a 6-substituent, but also to distinguish its type, since within the small group studied the frequency displacement parallels the bulk of the 6-alkyl group.

Apparent extinction coefficients and integrated intensities of the carbonyl absorptions have been measured. The sensitivity of the monomer-dimer equilibrium to minor changes in concentration precludes correlations[15] with pK's within the narrow range of

acid strengths represented here. It is sufficient to note that for the acids Nos. 1-12, without 6-substituents, the mean value of εmonomer/εdimer is 1.0 (S.D. 0.1) while for the 6-alkylsalicylic acids (Nos. 13-18) known or expected to have slightly higher pKs, e.g. No. 13, 3.32[16]; No. 14, ca. 3.7[17] the ratio is 0.86 (S.D. 0.04). The more marked effect of a greater change in pK is exemplified by 6-chloro-salicylic acid (pK 2.63)[16] for which the ratio in 0.0015M solution is 2.0. The ratios of integrated intensities are less reliable, particularly for the 6-substituted acids, in which the displaced dimer bands are close to the region of aromatic C=C stretching absorption (near 1610 cm.$^{-1}$) and may be affected by Fermi resonance. Moreover, the dividing line between the monomer and dimer bands is difficult to assign with precision. The intensities (εa ranging from 575 to 370) observed for the bonded monomeric acids in ether-carbon tetrachloride show a trend similar to, but less well-defined than that observed for the methyl esters in carbon tetrachloride.

Discussion.

The principal feature of the data is the effect

of 3- and 6-alkyl substitution already remarked upon. The uniformity of the frequency shifts in the three regions of absorption associated with ester, acid monomer and acid dimer suggests that the bands are not seriously perturbed by vibrational interaction. The lower frequencies found for 3-alkylsalicylates (Nos. 5-7 cf. also Nos. 8-11) may be partly due to inductive effects (cf. Section 2, the shifts of 2 $cm.^{-1}$ on m-methylation of benzoic acid and ref. 13) although it should be noted that an opposite effect would ensue from the expected[18a] increase in electron density at the phenolic oxygen atom. The more marked shifts caused by the bulkier 3-alkyl groups are ascribed to the steric enhancement of chelation[5] by compression of the phenolic hydroxyl group, probably with reduction in the O-H....O distance. (Similarly, bulky 6-, but not 4-, alkyl substituents strengthen the intramolecular hydrogen bond in substituted 2-bromophenols[19]). The more striking displacements seen in 6-alkylsalicylates presumably arise from the larger steric requirement of the carboxyl group.

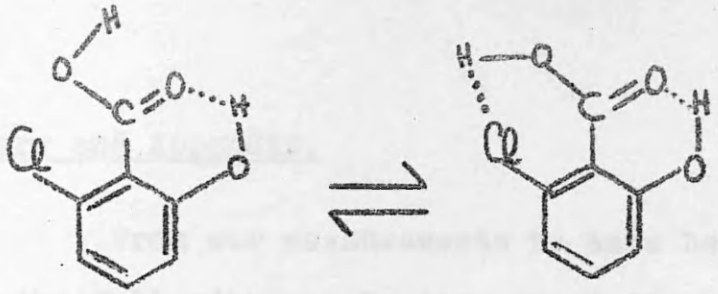
It is difficult to assess from the present data the extent to which the coplanarity of the carboxyl and

phenol groups with the nucleus is disturbed by the 3- and 6-substituents. From models it would appear that some distortion would occur in all the 6-alkyl derivatives, but there is considerable uncertainty regarding the effective "interference radii" (cf. the apparent coplanarity of the substituents in 1,4-dibromo-2,5-di-t-butylbenzene[18b]). Ultraviolet absorption dataare not very informative. Thus, as pointed out by Burawoy[20], the formation of an intramolecular hydrogen bond has little influence on the absorption: salicylic acid and m-hydroxybenzoic acid exhibit closely similar spectra in ethanol[21]. Moreover the introduction of a 6-methyl group causes only a small displacement of the band near 240 mμ, with no appreciable reduction in intensity. Similar small effects are found in the 3,6-dialkylsalicylates: only o-carvacrotic acid (No. 18) among those examined, shows an indication of possible steric inhibition of conjugation in the reduced intensities of both the 246 mμ and the 316 mμ absorption[22]. Comparison of carbonyl frequencies for this compound and the 3,6-dimethyl analogue (No. 15) suggests that the limit of steric enhancement of intramolecular hydrogen bonding by 6-alkylation has been reached: it would be desirable to examine a 6-t-butyl-substituted acid. More direct

evidence as to coplanarity in these compounds (e.g. from X-ray measurements) is required.

Peltier[23] and Dippy and his collaborators[16] have drawn attention to the lower acidity of 6-methyl-salicylic acid (pKa 3.32) as compared with salicylic acid (pKa 3.00); the latter authors have ascribed this to inhibition of intramolecular hydrogen bonding. This view does not necessarily conflict with the infrared data, which refer to the undissociated acid; in the (solvated) resonance-stabilised anion (IX) small deviations from coplanarity could lead to relative destabilisation with consequent weakening of the acid.

The essentially steric basis of the effects of o-substitution in benzoic acids is well established (e.g. [24,25]): the pKs of o-chloro- and o-nitro-benzoic acid are respectively 0.9 and 1.3 units lower than those of their m-isomers. That steric effects predominate in 6-substituted salicylic acids is supported by the weakness of 6-chloro- and 6-nitrosalicylic acid which approximate in strength to their 5-isomers[16]. Moreover, the carbonyl frequency in 6-chlorosalicylic acid is at 1686 $cm.^{-1}$ (monomer), close to that of the 6-methyl analogue despite the different polar character of the substituents.



X XI

Two hydroxyl bands are observed for 6-chloro-salicylic acid; the first (3508 cm.$^{-1}$) is ascribed to the monomer carboxylic free hydroxyl (X) and the second, weaker absorption (3431 cm.$^{-1}$) to a hydrogen-bonded species (XI). Such bonding is not observed in o-halogenobenzoic acids and is attributed to the conformational rigidity imposed by the salicylate chelation (cf. Section 2). The steric compression of species (X) is not expected to be present in species (XI), indeed the competitive intramolecular hydrogen bonding may weaken the salicylate chelation. A strong shoulder at approximately 1695 cm.$^{-1}$ is probably due to the carbonyl of (XI).

Summary and Appendix.

From our measurements we have been able to draw the following conclusions about the structure of salicylic acids.

1. With the exception of carvacrotic acid (No. 18), ultraviolet absorption data suggests that there is no serious deviation by the carboxyl group from the plane of the benzene ring. X-ray evidence on this point would be desirable.

2. 3- and more particularly 6-alkyl substituents enhance the strength of the chelate hydrogen bond, presumably by forcing the carbonyl and phenolic hydroxyl closer. $\Delta\nu$CO and $\Delta\nu$OH are measures of the enhancement.

3. Carbonyl frequencies of both acids and methyl esters suggest that the limit of steric enhancement of chelation has been attained in 3,6-dimethylsalicylic acid. Any further steric compression by bulkier alkyl groups is probably offset by a small amount of deviation from the coplanarity of the benzene ring by the carboxyl or phenolic hydroxyl groups (cf. the U.V. of g-carvacrotic acid).

Subsequent studies of the biological effects of 3-*i*-propyl- and 3-*t*-butyl-salicylic acids have revealed that their relative potency as metabolic stimulants parallels the degree of enhancement of chelation as indicated by the infrared measurements. It is notable the 6-methylsalicylic acid, which has stronger chelation than any of the 3-substituted salicylic acids appears to display no metabolic stimulation properties. However the greater toxicity of this acid renders assessment of the effect somewhat difficult. In view of the complexity of the process of metabolism it may seem surprising that any correlation whatever is obtained between metabolic stimulation and a single physical property of the drug. In connection with the state of the drug in the blood, experiments have been in progress[26] at the Clinical Chemotherapy Research Unit, Western Infirmary, Glasgow, to determine the protein binding powers of the substituted salicylic acids.

It has been found that under similar conditions (pH 7.4) the proportion of salicylate bound to albumin increases in the order salicylate: 3-*i*-propyl salicylate: 3-*t*-butyl salicylate.

Christensen[27] has proposed that salicylates can displace the equilibrium

Protein bound hormone* ⇌ protein + free hormone

(* e.g. : thyroxine),

in favour of the free hormone. This mode of action has been favoured by Christensen to explain salicylate therapy in the treatment of thyroid diseases. It is however not yet possible to assess the significance of the effect of substituents on the ratio of bound to unbound salicylate, in relation to gross biological effects and to the hydrogen bonding already discussed. It is clear that no generalised explanation of the diverse applications of salicylate therapy can be regarded as established until the role of salicylates has been defined in as many biological processes as possible where study is feasible.

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Table 1.

Carbonyl and hydroxyl stretching absorptions of esters of benzoic, salicylic and 2,6-dihydroxybenzoic acids (CCl_4 solutions)[a].

Alkyl group of ester	Benzoates ν_{CO}	$\Delta\nu_{\frac{1}{2}}$ [a]	ε_a	Salicylates ν_{CO}	$\Delta\nu_{\frac{1}{2}}$ [a]	ε_a	ν_{OH}
Me	1730	11	900	1684	14	665	3210‡
Et	1724	14	690	1681	15	655	3200‡
Pr^n	1724	13	750	1681‡	16	625	3200‡
Pr^i	1720	11	855	1678‡	20	515	3190‡
Bu^t	1717	14	675	1674[b]	13	645	3180‡

2,6-Dihydroxybenzoates

Alkyl group of ester	ν_{CO}	$\Delta\nu_{\frac{1}{2}}$ [a]	ε_a	ν_{OH} (chelated)	ν_{OH} (bonded)	$\Delta\nu_{\frac{1}{2}}$ [a]	ε_a
Me	1686	14	730	(3205)[c]	3470‡	32	265
Et	1681	17	715	(3195)[c]	3461‡	40	275
Pr^n	1680	15	780	(3195)[c]	3456‡	30	290

‡ Unsymmetrical band. Values in parentheses are approximate.

[a] Approximately 0.0015M solutions in 0.5 cm. cells (carbonyl region) or 2.0 cm. cells (hydroxyl region).

[b] Determined with the Mark II Unicam S.P.100 (spectral slit width 4 $cm.^{-1}$ at 1650 $cm.^{-1}$).

[c] Subsidiary absorption near 3160 $cm.^{-1}$

Table 2.

Carbonyl and hydroxyl stretching frequencies ($cm.^{-1}$) (CCl_4)[a] in substituted salicylic acids and methyl esters.

Cpd. No.	Substituents	Ester		Acid			
		$\nu_{C=O}$	ν_{O-H} (chelate)[b]	$\nu_{C=O}$ monomer	$\nu_{C=O}$ dimer	ν_{O-H} of CO_2H (monomer)	$\nu_{C=O}$ in presence of ether (4% v/v)
1	H	1684	3210	1698	1663	3530	1679
2	4-Me	1681	3200	1697	1662‡	3532	1679
3	5-Me	1684	3225	1698	1664		1681
4	5-Pr^i	1684	3230	1698‡	1665	3531	1681
5	3-Me	1681	3195	1695	1660	3531	1677
6	3-Pr^i	1679	3180	1693	1659	3531	1678
7	3-Bu^t	1676	(3110)	1691	1657	3530	1670
8	3-Allyl	1681	3185	1695	1660	3530	*
9	3-Propenyl	1682	3170	1693	1660	3529	*
10	3-β-Methyl-allyl	1680	3185	1696‡	1659	3530	*
11	3-Phenyl	1682‡	3155	1695	1660	3528	1675

Table 2 continued overleaf

Table 2. (continued).

Cpd. No.	Substituents	Ester $\nu_{C=O}$	Ester ν_{O-H} (chelate)[b]	Acid $\nu_{C=O}$ monomer	Acid $\nu_{C=O}$ dimer	Acid ν_{O-H} of CO_2H (monomer)	$\nu_{C=O}$ in presence of ether (4% v/v)
12	3,5-di-Pr^i	1677	3185	1691	1657	3531	1675
13	6-Me	1671‡	(3120)	1686	1650	3517	1667 (1660sh)
14	6-Et	1670	(3080)	1683	1649	3515	1665
15	3,6-diMe	1668‡	(3100)	1679‡	1641	3518	1658‡
16	3-Pr^i,6-Me	1663	(3040)	1676‖	1643‖	3518	1660
17	3-Bu^t,6-Me	1662	(3000)	1671	1639	3519	1658
18	3-Me,6-Pr^i	1666	(3020)	1677	1640	3514	1657‖
19	5-6-Benzo-	1656	(3030)	1668	1641	3513	*
20	3,4-Benzo-	1671	(3065)	1683	1650)[b] 1635)	3530	*
21	4,5-Benzo-	1692	3265	1703	1670	3527	*

Footnotes to Table 2 overleaf

Footnotes to Table 2.

* Not measured. ‡ Unsymmetrical band. ‖Irregular contour. sh = shoulder. Values in parentheses are approximate.

[a]Esters were examined as approx. 0.0015M solutions. The molarity of acids in carbon tetrachloride was 0.0015M (±0.00002M) except for Nos. 4 (0.00127M), 18 and 20 (saturated solutions). The solutions in ether-carbon tetrachloride were 0.0015M (±0.00003M) with the exceptions of Nos. 15 (0.00073M) and 17 (0.0016M). Measurements were made in 0.5 cm. cells (carbonyl region) and 2.0 cm. cells (hydroxyl region).

[b] The frequency values quoted are for the band maxima reasonably attributable to this vibration mode: sharp peaks, sometimes more intense than the bands cited, in the 3000 $cm.^{-1}$ region (C-H stretching absorptions) are ignored. In Nos. 7 and 13-20 the appreciable overlap of OH and CH absorptions renders the values approximate, as indicated. Apparent half-band widths ($\Delta\nu_{\frac{1}{2}}^{a}$) were observed as follows. Ester carbonyl bands, 15 ± 2 $cm.^{-1}$ (except No. 7, 11 $cm.^{-1}$ and Nos. 15, 16 and 18, 21 ± 2 $cm.^{-1}$). Ester hydroxyl bands, approx. 120 to 570 $cm.^{-1}$ increasing generally through the series with decreasing values of ν_{OH} and ν_{CO}. Acid monomer carbonyl bands, 12 $cm.^{-1}$ (salicylic acid) to 27 $cm.^{-1}$ (No. 16) with a general trend upwards on increasing substitution. Acid dimer carbonyl bands, 15 to 27 $cm.^{-1}$

footnotes to Table 2 continued overleaf

Footnotes to Table 2 (continued).

with no apparent regularity. Acid carbonyl bands in ether-carbon tetrachloride, 19 to 29 cm.$^{-1}$. Acid monomer hydroxyl bands, 35 ± 2 cm.$^{-1}$ except No. 21 (29 cm.$^{-1}$).

Table 3.

Shifts of ester carbonyl frequencies in different solvents.

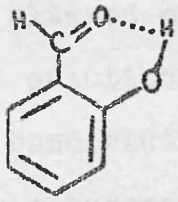
$\Delta\nu = \nu_{CO}(\text{hexane}) - \nu_{CO}(\text{solvent})$

Ester	ν_{CO}(hexane)	CCl_4	CH_3CN	$CHCl_3$
Methyl benzoate	1735	5	11	15
Methyl salicylate	1686	2	5	7
Methyl 3-methyl-salicylate	1682	1	4	6
Methyl 3-t-butyl-salicylate	1678	2	5	7
Methyl 6-methyl-salicylate	1672	1	5	6
Methyl 3-i-propyl-6-methyl salicylate	1666	3	7	8
t-Butyl salicylate	1676	2	5	3

Section 4. Infrared Spectra of Substituted Salicylaldehydes.

Historical.

The characterisation of the infrared spectrum of salicylaldehyde (I) progressed in a manner similar to that described for the other salicylates (Section 3). Errera and Mollet[1] noted that no hydroxyl overtone was observed for this compound. Subsequent investigations in the hydroxyl fundamental region by Errera and Sack[2] revealed that in carbon tetrachloride solution the hydroxyl absorption frequency was displaced from the normal phenolic value at 3620 $cm.^{-1}$ and that complex absorption occurred at 3130-3180 $cm.^{-1}$ and at 3080 $cm.^{-1}$. Even these early investigators



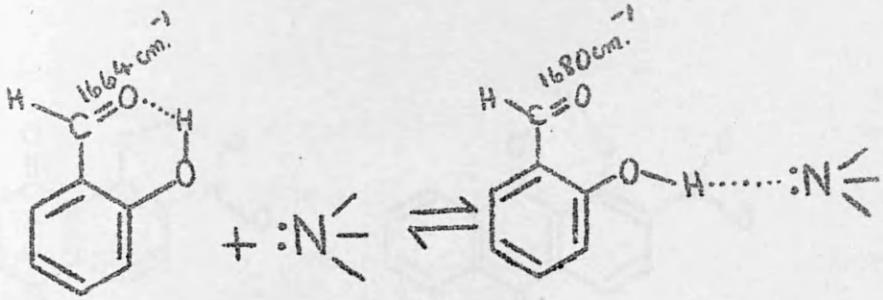
(I)

disclosed that the chelation responsible for the low frequency OH could be disturbed by another basic centre. Errera and Sack[2] observed that for salicylaldehyde in dioxan solution the broad hydroxyl absorption was at a higher

frequency than in CCl_4, viz. near 3250 cm.$^{-1}$. They considered that the "chelated character was loosened" by the dioxan.

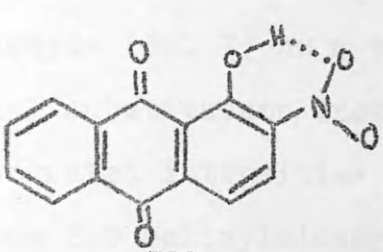
By 1950 the corresponding carbonyl frequency depressions were well characterised. Hunsberger[3] utilised minor differences in hydrogen bond strength of chelated hydroxy naphthaldehydes, as measured by $\Delta\nu$(CO), to support the 9,10 partial double bond fixation in naphthalenes. The stability of the chelate hydrogen bond renders the carbonyl absorption rather insensitive to physical state: for salicylaldehyde the carbonyl frequency has been reported as virtually the same in chloroform, acetonitrile, and n-butanol solutions[4]. The frequencies of the carbonyl absorptions of non chelated benzaldehydes were little altered on changing from carbon tetrachloride to n-butanol solutions. There was however a dramatic increase in half band width (benzaldehyde $\Delta\nu_{\frac{1}{2}}$ - 8.4 in CCl_4, 15.4 in n-butanol[4]). With salicylaldehyde the half-band width was unaltered[4].

The suggestion that the salicylaldehyde chelation could be broken by another basic centre[2] was more convincingly substantiated by Chiorboli and Mircne[5] who made a detailed study of the carbonyl region in pyridine and triethylamine solution. A new band at 1680 cm.$^{-1}$ in pyridine solution was regarded as a "free" carbonyl (II).

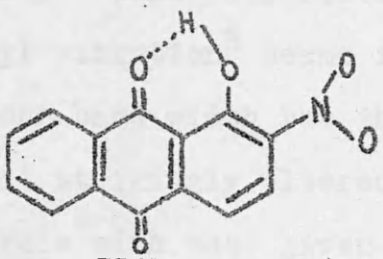


(II)

At the beginning of the present work our two main objectives were to ascertain (a) if competitive hydrogen bonding of the type postulated by Hoyer (see below) existed in a series of nitro-salicylaldehydes (b) if the steric enhancement of chelation, found for substituted salicylic acids and esters, also existed in the corresponding substituted salicylaldehydes. Our early studies indicated that alternative hydrogen bonding is found in 3-nitro-salicylaldehyde and its derivatives and particular attention has been paid to these compounds, and in addition to some corresponding salicylate esters and hydroxy acetophenones. Hoyer[6] has postulated the possibility of competitive intramolecular hydrogen bonding of this type. For example, in a series of nitro substituted hydroxy anthroquinones the infrared spectra indicated that where the hydroxyl could bond to both nitro (IIIa) or carbonyl (IIIb) groups the carbonyl was preferred. Baker and



IIIa



IIIb

and Kaeding[7] have more recently provided a spectroscopic demonstration of coexisting alternative hydrogen bonded forms of 2,6 unsymmetrically-disubstituted phenols. Since the completion of our experiments, Hoyer and Hensel[8] have presented evidence similar to ours, for this type of rotational isomerism in 3,5-dinitro salicylaldehyde.

Results and Discussion.

1600-3650 cm.$^{-1}$ Region.- Data for the hydroxyl, aldehyde C-H and carbonyl absorptions of a group of substituted salicylaldehydes and some related compounds are recorded in Table 1. The carbonyl bands are close to the region of "aromatic" absorption and the possibility of vibrational resonance with combination bands has been invoked[5] to account for the strong band near 1650 cm.$^{-1}$ in salicylaldehyde (cf. Fig. 1). However, the most intense bands in the 1600-1700 cm.$^{-1}$ region are regarded as carbonyl group vibrations since they occur at the expected frequencies and undergo normal solvent shifts (cf. Section 2).

The designation of the 1634 cm.$^{-1}$ band of β-resorcylaldehyde (No. 7) as a carbonyl vibration[9] seems in error. Alkyl substituents increase the band width but the integrated intensities are not strikingly altered; the value for salicylaldehyde agrees with that given by Yamada[4] (A = 2.6 x 10^4 in carbon tetrachloride or chloroform; cf. also Krueger and Thompson)[10]. The marked lowering of the carbonyl frequency in 6-methyl-3-t-butylsalicylaldehyde (No. 5) and in 4,6-dimethyl-2-hydroxyacetophenone (No. 22) parallels the effects attributed to steric compression in the salicylic acid series (Section 3).

The 5-nitroaldehydes (Nos. 8, 9 and 11) show carbonyl bands similar to those of their parent compounds (Nos. 1, 3 and 5), but the spectra of the 3-nitro-derivatives are strikingly different (Fig. 1); in every example the principal band in the carbonyl region occurs near 1700 cm.$^{-1}$ with minor variations depending on the substituent at the 5-position. A second, smaller band is noted near 1670 cm.$^{-1}$. The relative optical density is unaltered by dilution from 0.06M to 0.0017M in carbon tetrachloride but is affected by the solvent (see below). The major band frequency is indicative of an aromatic aldehyde group not involved in a hydrogen bond, and the minor band is at a typical salicylaldehyde frequency.

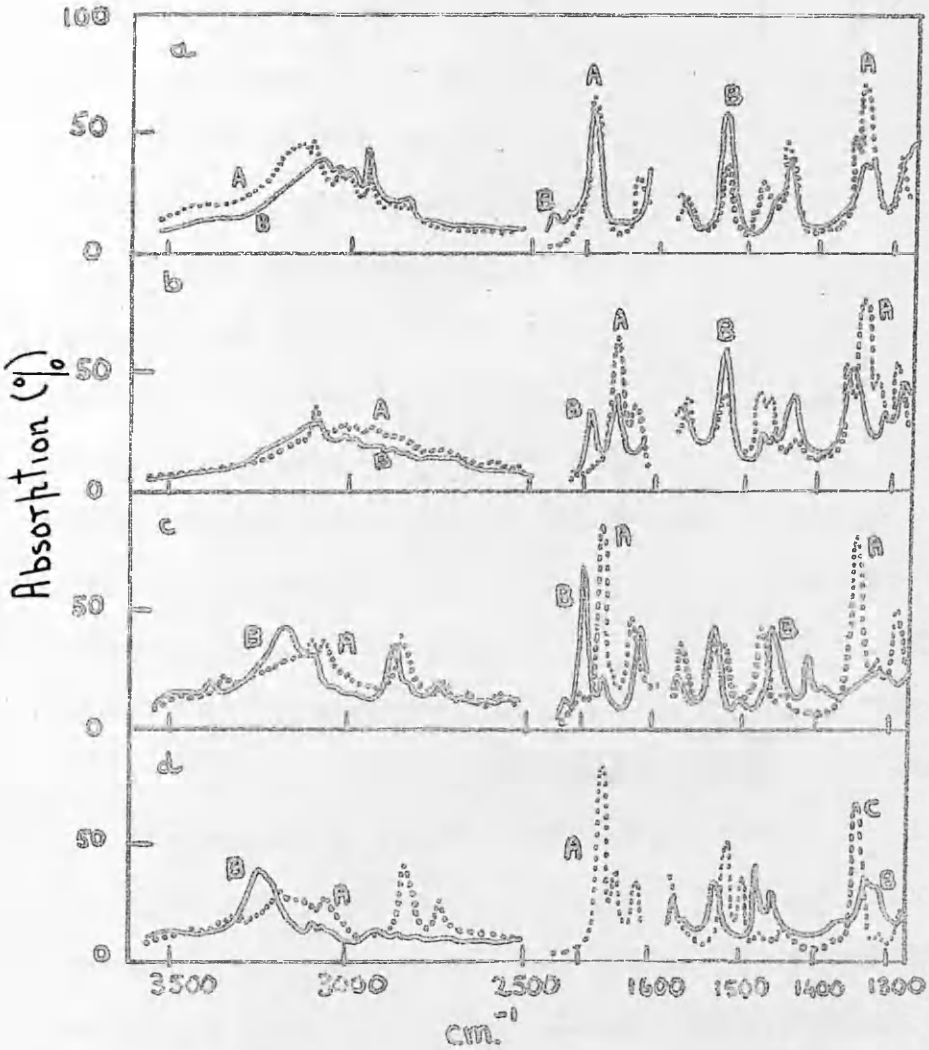


FIG.1a A, Methyl 5-nitrosalicylate; B, methyl 3-nitrosalicylate.

FIG.1b A, 2-Hydroxy-5-nitroacetophenone; B, 2-hydroxy-3-nitroacetophenone

FIG.1c A, 5-Nitrosalicylaldehyde; B, 3-nitrosalicylaldehyde

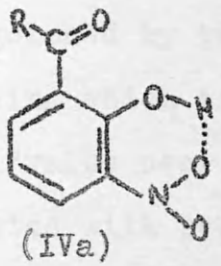
FIG.1d A, Salicylaldehyde; B, o-nitrophenol; C, p-nitrophenol

Concentrations as noted in Tables 1 and 2: CCl_4 solutions, 20mm cells ($3650-2500 cm^{-1}$), 5mm. cells ($1750-1600 cm^{-1}$). $CHCl_3$ solutions, 0.11mm. cells ($1600-1250 cm^{-1}$).

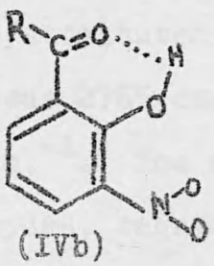
These absorptions are ascribed to the species (IVa; R=H) and (IVb; R=H) respectively (cf. ref. 8): this assignment is further discussed below. The first overtones of the principal carbonyl bands in 3- and 5-nitrosalicylaldehydes are unusually prominent (Fig. 1) and their positions support the assignments made. The effects of nitro substituents on the carbonyl absorptions of 2-hydroxyacetophenone and methyl salicylate (Fig. 1) are in harmony with these views. The 5-nitro-derivatives both show single bands. In the spectrum of 2-hydroxy-3-nitroacetophenone two bands are observed, at the frequencies expected for (IVa; R=Me) and (IVb; R=Me), with the latter predominating, especially in chloroform solution. Methyl 3-nitrosalicylate exhibits only low absorption in the region expected for (IVa; R=OMe): (the bands at 1722 and 1746 cm.$^{-1}$ in carbon tetrachloride solution probably correspond to two conformations of the methoxy-carbonyl group in (IVa; R=OMe) (cf. Section 2) the principal band closely resembles that of the 5-nitro-isomer. Entirely analogous behaviour is shown by methyl 3,5-dinitrosalicylate.

Comment is necessary on two features of the data for substituted benzaldehydes (Table 1, Nos. 28-35). The carbonyl frequency is lowered by ortho-substitution

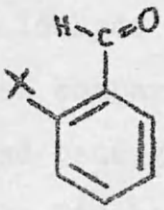
even by the strongly electron-attracting nitro-group. This is assumed to result from dipolar interaction in the favoured conformation (Va) since the frequency shifts are similar to those ascribed to the corresponding species in ortho-substituted methyl benzoates (Section 2). The occurrence of two bands in the carbonyl region of the



(IVa)



(IVb)



(Va)

spectra of o- and m-methoxybenzaldehyde, m-nitrobenzaldehyde, and 3,4-dimethoxybenzaldehyde is also notable. In the first three cases the relatively unperturbed carbonyl band is identifiable by its intensity and position, and by typical solvent shifts: the minor band frequency is solvent-insensitive, but the band intensity falls with increasing separation between this absorption and the carbonyl band. It thus appears probable that these subsidiary bands are combination modes strengthened by resonance with the carbonyl vibrations. The absorption of 3,4-dimethoxybenzaldehyde is regarded as a more extreme

example of this effect in which the carbonyl vibration mode contributes to both the observed bands.

In the hydroxyl region, 3-nitrosalicylaldehyde and its derivatives show a single broad band near 3200 cm.$^{-1}$, similar to that of o-nitrophenol and distinct from the weaker, diffuse bands near 3150 cm.$^{-1}$ typical of salicylaldehyde (cf. Fig. 1).

The 3-nitrosalicylaldehyde structure is further distinguished by the band attributed to aldehyde C-H stretching which occurs near 2765 cm.$^{-1}$ as compared with the "normal"value near 2740 cm.$^{-1}$. The second band generally associated with benzaldehydes, regarded by Pinchas[9] as a combination band of the C_{CHO}-H in-plane bending vibration near 1380 cm.$^{-1}$ with a ring vibration near 1470 cm.$^{-1}$, occurs near 2875 cm.$^{-1}$ in 3-nitrosalicylaldehyde and its nuclear-substituted derivatives: in the remaining compounds it appears to be near 2840 cm.$^{-1}$ but the assignment is uncertain in aldehydes having alkyl C-H bands near 2875 cm.$^{-1}$. Elevation of both "aldehyde" C-H frequencies has been noted[9,11] in 2,3 and 2,6-disubstituted benzaldehydes and attributed to steric effects[11], though in all the examples, except 2,6-dimethylbenzaldehyde[11], the effect could be associated with strong dipole interactions, as proposed by Schneider and Bernstein[12] to account for the

raised C-H frequency in solid aldehydes as compared with solutions. Evidently the normal values for 3-alkylsalicylaldehydes (Nos. 3,4) reflect the stabilisation of the aldehyde C-H environment by the hydrogen bond.

1250-1600 $cm.^{-1}$ Region.- The effects of hydrogen bonding on nitro-group vibrations are not well established. One difficulty lies in the complex nature of these vibrations: another is that the regions of absorption concerned are populated by many other strong bands, particularly in aromatic compounds. Even in the nitro-alcohols Urbanski's[13] report that the symmetric stretching vibration occurs at 1310 $cm.^{-1}$ in the hydrogen-bonded compounds is confused by the absorption at this frequency due to the alcohol group itself. For o-nitrophenol (and o-nitroanisole) the reported[14,15] asymmetric stretching frequency (ca. 1530 $cm.^{-1}$) is little different from that of nitrobenzene. An appreciably lower value (1511 $cm.^{-1}$ in $CHBr_3$) has been recorded for o-nitroaniline[14]. However in view of the conflicting reports on the existence of intramolecular hydrogen bonding in this compound, the significance of this lower value is uncertain. Farmer and Thomson[16] considered that the very small NH frequency shifts in some o-nitrodiazoaminobenzenes, compared to diazoaminobenzene, are

due to the fact that inductive and mesomeric effects of the nitro group compensate for the tendency for the frequency to be lowered by intramolecular hydrogen bonding. Moritz[17] has suggested a similar explanation for the negligible νNH shift in o-nitroaniline, but has not provided adequate proof of the existence of an intramolecular hydrogen bond. Farmer and Thomson[16] considered that the great intensity of the o-nitroaniline peak at 3543 cm.$^{-1}$ in pyridine, in contrast to the weak shoulder observed on the side of the low frequency NH absorption of p-nitroaniline in the same solvent was evidence of an intramolecular hydrogen bond. On the other hand Dyall[18] has more recently applied Bellamy's solvent effect procedure[19] for NH frequencies, to a number of o-nitroanilines. Only 2,6-dinitroaniline shows evidence of intramolecular hydrogen bonding.

In view of the lack of quantitative absorption data for o-nitrophenols, the substituted 3-nitrosalicylaldehydes and other relevant compounds have now been examined. The absorption due to nitro-groups was investigated using 0.11 mm. cells to allow adequate transmission over the range 1250-1750 cm.$^{-1}$. Full data were obtained for chloroform solutions (Table 2): where

solubility permitted, spectra were determined also in carbon tetrachloride, and no major differences were noted. In the 5-nitro-aldehydes the asymmetric and symmetric nitro vibrations give rise to sharp, intense bands near 1540 and 1340 $cm.^{-1}$ respectively: only in the 3-isopropyl derivative (No. 9) is there some ambiguity in the latter assignment, as two equally intense bands occur at 1352 and 1320 $cm.^{-1}$. The 3-nitro-aldehydes also exhibit a band near 1540 $cm.^{-1}$ but in the region of the symmetric vibration they are profoundly different: no notably intense band is present, and apart from a general increase in "background" absorption the spectra in the 1300-1400 $cm.^{-1}$ region resemble those of the aldehydes lacking nitro substituents. This virtual submergence of the symmetric vibration cannot be ascribed purely to hydrogen-bond formation since in 5-nitro-β-resorcylaldehyde (No. 18) and in o-nitrophenol (No. 36) bands attributable to this mode are quite prominent. The effects evidently result from the buttressing inherent in 1,2,3-tri-substitution: thus, from data reported by Dearden and Forbes[15], the symmetric bands shown by ortho-nitrophenols bearing alkyl substituents in the 3- and/or 6-positions are of lower intensity than those of o-nitrophenol and 3,5-dimethyl-2-nitrophenol. (Frequency shifts of the type noted by van Veen, Verkade and Wepster[25]

for 2,3-disubstituted nitrobenzenes are not discernible in our data). It is concluded that the results are consonant with strong hydrogen bonding between the nitro and phenol groups in 3-nitro-salicylaldehyde and its congeners. In 2-hydroxy-3-nitroacetophenone and methyl 3-nitrosalicylate, symmetric nitro bands are observed which are comparable in frequency, intensity and breadth with those of ortho-substituted nitro-compounds lacking hydrogen bonds, e.g. o-nitrobenzaldehyde (No. 30) and o-nitroanisole (No. 39).

Solvent Studies.- In order to confirm that the results so far described could be correctly construed in terms of equilibria between the hydrogen-bonded species (IVa) and (IVb), the effects of (i) a more polar solvent (acetonitrile) and (ii) a basic solvent (pyridine) were explored. Data for acetonitrile solutions are presented in Table 3. The two carbonyl bands observed in the 3-nitro-derivatives undergo solvent shifts comparable respectively with those of typical chelated and unchelated carbonyls. The effect on the relative intensity of the bands is significant (cf. Fig. 2). For 3-nitrosalicylaldehyde the ratios of the intensities (ε_a) of the high- and low-frequency bands in carbon tetrachloride, chloroform and acetonitrile are respectively 5.6, 2.4 and 1.4: for 2-hydroxy-3-nitro-acetophenone, 0.8, 0.3 and ca. 0.15. These

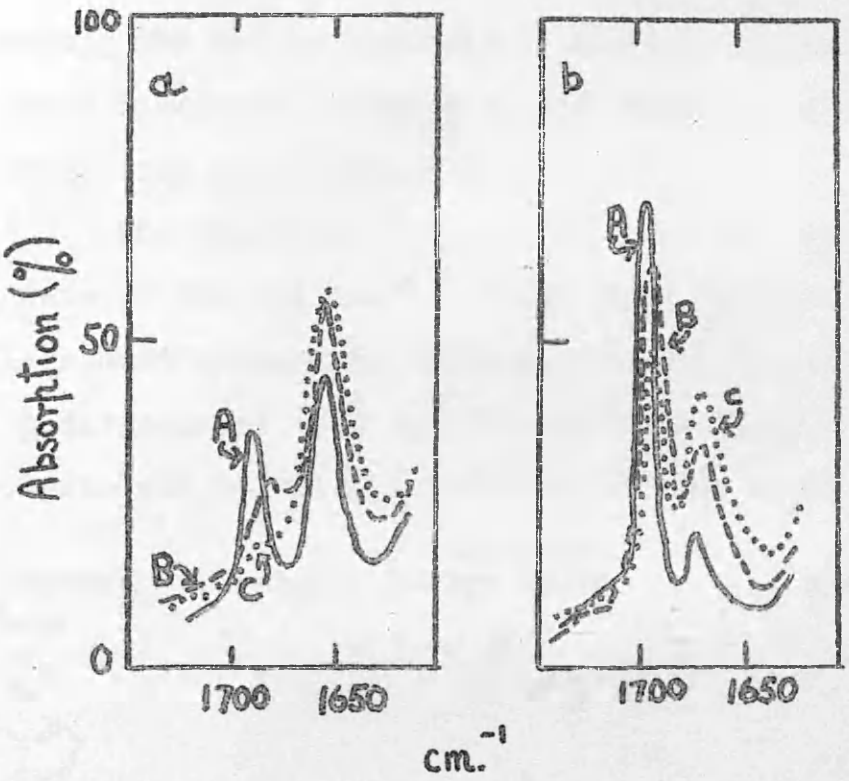


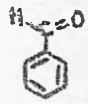
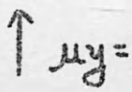
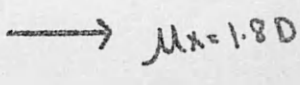
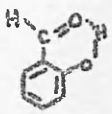
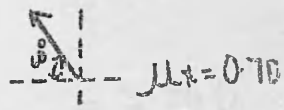
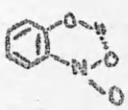
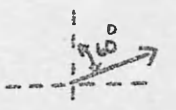
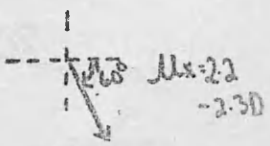
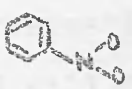
FIG2. (a) 2-Hydroxy-3-nitroacetophenone.

(b) 3-Nitrosalicylaldehyde.

A, 0.0015M in CCl_4 (5mm. cells); B, 0.075M in $CHCl_3$ (0.1mm. cells); C, 0.015M in Me CN (0.5mm. cells).

results support the view that the observed bands correspond to species (IVa) and (IVb) and that the more polar form with the unchelated nitro group is relatively stabilised by increasing the solvent polarity. Similar intensity effects have been discussed (Section 2) for other examples of conformational isomerism.

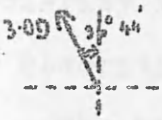
The polarities of IVa and IVb have been calculated from data of Eda and Ito[21]. These authors have recorded dipole moment components of benzaldehyde (V), salicylaldehyde (I), o-nitrophenol (VI) and nitrobenzene (VII). These components can be written relative to each other as below.

Compound	Symbol	y component (Debye Units)	x component
	V		
	I		
	VI		
	VII		

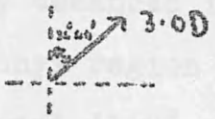
It is reasonable to assume that the dipole moment of species IVa may be approximately obtained by vector addition of the components of V and VI and

similarly that of IVb from I plus VII.

Calculation For IVa - The resultant dipole of species V is

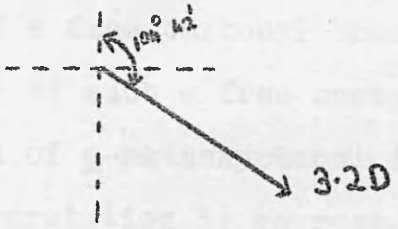


or

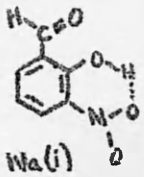


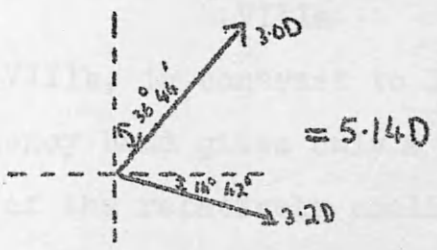
dependent on the conformation of the carbonyl.

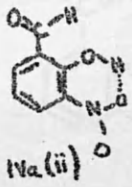
The resultant dipole of species VI is

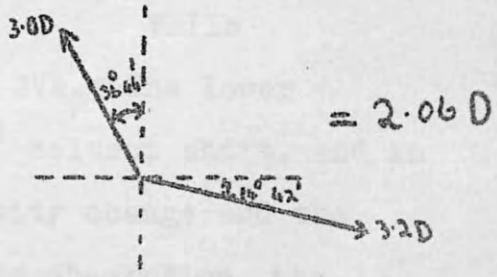


The dipole moment of IVa is therefore the resultant from the vectors below.









Presumably the smaller steric requirements of the aldehyde CH will favour a predominance of IVa(ii). By a similar calculation the dipole moment of IVb is 5.54D. In all events IVb is more polar than IVa and if the above assumption on the steric requirement of the aldehydic CH is correct, then IVb is probably very much more polar than IVa.

An interesting solvent effect is also noted in the case of 3-methoxysalicylaldehyde: the increase of solvent polarity is accompanied by enhanced intensity of two minor absorptions in the carbonyl region (cf. Tables 1 and 3). The higher frequency band (1695 cm.$^{-1}$ in CCl_4) shows a solvent shift ($\nu_{CCl_4} - \nu_{CH_3CN}$) of 6 cm.$^{-1}$, suggestive of a free carbonyl absorption (Sections 2 and 3). The existence of such a free carbonyl is not unlikely since the chelation of o-methoxyphenol is known to be strong[22]. If this interpretation is correct, VIIIa is more polar

VIIIa VIIIb

than VIIIb, in contrast to IVa and IVb. The lower frequency band gives only a 3 cm.$^{-1}$ solvent shift, and in view of the relatively small intensity change and the incompletely resolved nature of this absorption, the possibility of vibrational resonance cannot be ruled out.

The effects of pyridine on the absorption of ortho-hydroxycarbonyl compounds may be expected to derive chiefly from its bonding to the phenolic hydrogen atom. Carbonyl and nitro absorption data are recorded in Table 4.

The nitro absorptions are closely similar to those for chloroform and carbon tetrachloride solutions and require no further comment. The carbonyl region, however, shows several features of interest (cf. also Fig. 3). Pyridine evidently competes with the carbonyl group in forming a hydrogen bond with the phenolic group and giving rise to a new band, at 1682 $cm.^{-1}$ in the case of salicylaldehyde, as already demonstrated by Chiorboli and Mirone[5]: the markedly lower frequency than that found for benzaldehyde in pyridine (1707 $cm.^{-1}$) is attributed to electron donation from pyridine to the phenol group. A similar disruption of the intramolecular bond occurs in 5-t-butylsalicylaldehyde, and is almost complete in the 5-nitro derivative (No. 8): this is regarded as ensuing from the mesomeric effect of the nitro-group on the phenol acidity, since in relatively nonpolar solvents (CCl_4, $CHCl_3$: Table 1) the chelation in 5-nitro-salicylaldehyde appears to be as complete as that in salicylaldehyde. Inhibition of pyridine-phenol hydrogen bonding by steric effects is illustrated by 6-methyl-3-t-butylsalicylaldehyde (No. 5) and its 5-nitro-derivative (No. 11), which exhibit single chelated carbonyl bands, similar in frequency and intensity to those observed in chloroform solution.

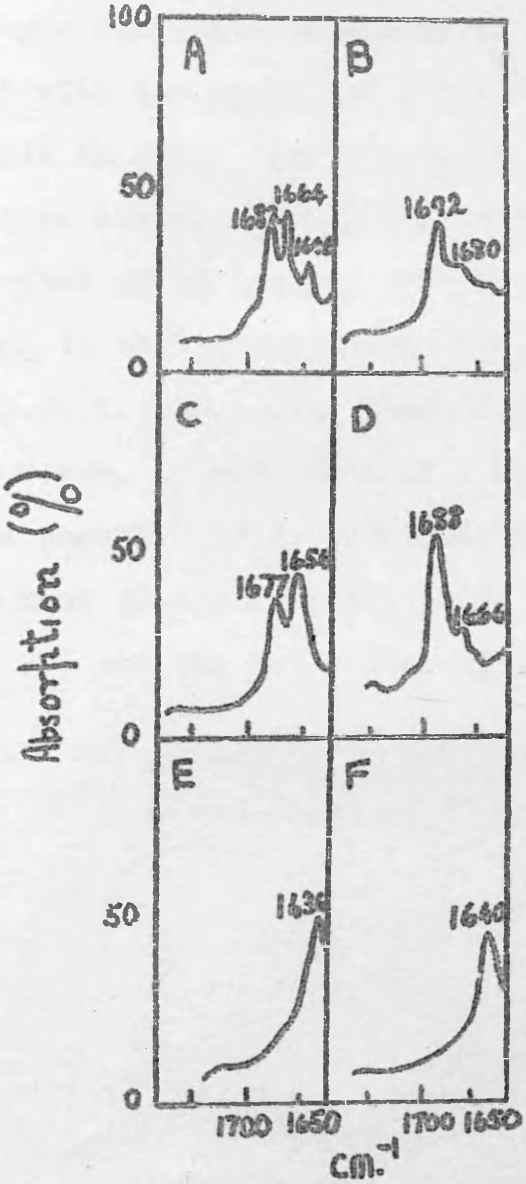


FIG. 3. A, Salicylaldehyde. B,3 - nitrosalicylaldehyde; C, 5-t-butylsalicylaldehyde; D, 5 - nitrosalicylaldehyde; E, 6-methyl - 3-t-butylsalicylaldehyde; 6-methyl-5-nitro-3-t-butylsalicylaldehyde. Pyridine solutions, 0.05M (0.11mm. cells).

Comparison of salicylaldehyde, o-hydroxy-acetophenone and methyl salicylate shows that only the ortho-hydroxyaldehyde chelation is disturbed by pyridine. This is in accord with the stability order of the intramolecular hydrogen bonds in these three types of compound, as implied by the relative extent of competitive bonding by 3-nitro groups described above (and by the frequency displacements corresponding to the introduction of o-OH into the parent compounds Ph.CO.R.:R=H, -40; R=Me, -47; R=OMe, -46 cm.$^{-1}$ (CCl_4). However, introduction of a 5-nitro substituent enhances the phenol acidity sufficiently to permit a partial breaking of the intramolecular bonds in both the ketone (No. 23) and the ester (No. 25).

Summary.

1. The steric enhancement of chelation noted for 3- and 6-alkyl substituted salicylic acids and methyl esters (Section 3), has been found to be operative in 3- and 6-alkyl substituted salicylaldehydes and ortho-hydroxy acetophenones.

2. The character of the hydroxyl carbonyl and nitro-absorptions of 3-nitrosalicylaldehyde (in CCl_4 or $CHCl_3$) indicates that the phenolic group is bonded chiefly to the nitrogroup, whereas in 2-hydroxy-3-nitroacetophenone and methyl-3-nitrosalicylate the chelated o-hydroxy-carbonyl species predominate.

3. A more polar solvent (acetonitrile) will change the equilibrium between the above coexisting alternative hydrogen bonded isomers in favour of the more polar form(in this case the chelated o-hydroxy-carbonyl species).

4. The opening of the salicylaldehyde chelate ring by pyridine is facilitated by increasing the acidity of the phenolic group e.g. by a 5-nitro-substituent. Steric hindrance by alkyl groups can completely prevent rupture of the chelate ring by pyridine e.g. in 3-t-butyl-6-methylsalicylaldehyde and 3-t-butyl-6-methyl-5-nitro-salicylaldehyde.

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Table 1.

Hydroxyl, aldehyde C-H and carbonyl absorptions of substituted salicylaldehydes and related compounds.

No.	Compound Substituents	Carbon tetrachloride ν_{OH}[b]	ν_{CH}		ν_{CO}	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a	Chloroform ν_{CO}	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a
	Salicylaldehydes[j]									
1	None	(3150)	2840	2749	1669	7	1030	1666	9	840
2	5-Bu^t	(3180)	2831	2740	1663	14	830	1656	18	675
3	3-Pr^i	(3130)	2840	2747	1661‡	(25)	460	1653	(33)	465
4	3,5-Bu^t_2	(3100)	2839	2742	1654	14	625	1648	19	655
5	3-Bu^t,6-Me	(3000)	weak	weak	1641	17	550	1635[c]	24	490
6	3-OMe[d]	(3150)	2841[e]	2745	1661	13	665	1659	17	580
					1678sh	*	170	1676	15+	178
					1695	*	53			
7	4-OH[f]	(3060)	2835	2747	1660	10	975	1657	15	745
8	5-NO_2	(3095)	2861	2734	1674	8	1045	1670	13	895
9	3-Pr^i,5-NO_2	(3100)	2851	2737	1668	14	645	1665	16	565
10	3-Ph,5-NO_2	3065	2852	2738	1666	11	665	1663	15	625
11	3-Bu^t,5-NO_2, 6-Me	(2950)	2876	-	1646	15	580	1643	18	550
12	3-NO_2	3170	2876	2770	1701	8	620	1694	13	455
					1676	14	110	1673	17	185

Table continued overleaf

Table 1 (continued).

No.	Compound Substituents	Carbon tetrachloride ν_{OH}[b]	ν_{CH}		ν_{CO}	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a	Chloroform ν_{CO}	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a
Salicylaldehydes[j]										
13	3,5-$(NO_2)_2$	(3140)	2881	2773	1707	7	615	1702	10	440
					1680	11	205	1677	13+	250
								1653	16+	250
14	3-NO_2,5-Bu[t]	3195	2874	2776	1700	6	810	1694	12	495
					1674	13	110	1670	*	215
15	3-NO_2,5-Cl	3200	2878	2766	1702	7	685	1697	11	510
					1678	10	110	1675	12	175
16	3-NO_2,5-OMe	3220	2878[g]	2766	1700	11	525	1694	14	480
					1679	*	55	1676	*	110
17	3-NO_2,5-Ph	3185	2875	2765	1700	8	665	1694	14	455
					1675	12	125	1671	15	220
18	4-OH,5-NO_2	3160	2845	(2730)	1674	(10)	785	1674	11	650
				(2760)	1665	(10)	1035	1663	*	1090
2-Hydroxyacetophenones[k]										
19	None	(3025)	-	-	1646	12	655	1642	17	620
20	3-Me	(3000)	-	-	1641	12	540	1638	16+	445
								(1630sh)	*	*
21	4-Me	(2960)	-	-	1640	(22)	515	1637	21+	590
					(1627sh)	*	290	(1624sh)	*	*
22	4,6-Me_2	(2950)	-	-	1629	*	(450)	1628	17+	540
								(1610sh)	*	*
23	5-NO_2	(3000)	-	-	1657	18	555	1653	21	520
24	3-NO_2	(3100)	-	-	1693	12	250	1684	23+	115
					1658	13	310	1656	17	390

Table contd.overleaf

Table 1 (continued).

No.	Compound Substituents	Carbon tetrachloride ν_{OH}[b]	ν_{CH}		ν_{CO}	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a	Chloroform ν_{CO}	$\Delta\nu_{\frac{1}{2}}$[a]	ε_a
Methyl salicylates[l]										
25	5-NO_2	(3140)	-	-	1690	13	680	1687	18	570
26	3-NO_2	(3100)	-	-	1690	13	575	1688	16	525
					1722	*	60			
					1746	*	60			
27	3,5-$(NO_2)_2$	(3000)[i]	-	-	1695	12	675	1695	14	680
					1727	*	*			
Benzaldehydes[m]					1751	*	50			
28	o-OMe	-	2862	2759	1695	7	735	1688	14	510
					1666[n]	*	60	1665	13+	170
29	o-F	-	2860	2762	1703	7	684	1698	13	*
					(1684sh)	*	70	1683	8+	*
30	o-NO_2	-	2869	2766	1706	10	520	1702	14	450
			2890							
31	m-OMe	-	2834	2726	1709	10	640	1702	15	505
					1686n	11+	105	1684[n]	12	225
32	m-Cl	-	2827	2724	1709	9	730	1703	12	910
33	m-NO_2	-	2833	2730	1713	11	530	1708	12	615
			2809		1727[n]	9	175	1727[n]	10+	105
34	2,3$(OMe)_2$	-	2858	2745	1696	9	620	1690	18	410
35	3,4$(OMe)_2$	-	2839	2754	1701	11+	410	1698	14+	290
			2812	2721	1687	10+	460	1682	16	565

Footnotes to Table 1 overleaf

Footnotes to Table 1.

Values in parentheses are approximate. - No band present. * Not measured. + Estimated by band reflection. ‡ Unsymmetrical band. [b] The approximate band centre is cited. [c] Fused to aromatic band at 1616 cm.$^{-1}$. [d] Bands near 1677 cm.$^{-1}$ are not regarded as carbonyl absorptions. [e] superimposed aldehyde and methoxyl bands. [f] Free OH band at 3593 cm.$^{-1}$. [g] A band at 2839 cm.$^{-1}$ is ascribed to methoxyl[h]. [h] Henbest, Meakins, Nicholls and Wagland, J., 1957, 1462. [i] A strong band at 3095 cm.$^{-1}$ is ascribed to $2\nu_{NO_2}$ (asym.). [j] 0.0017M in CCl_4, ca. 0.02-0.06M in $CHCl_3$. [k] 0.0015M in CCl_4, ca. 0.02-0.06M in $CHCl_3$. [l] 0.00135M in CCl_4, ca. 0.045M in $CHCl_3$. [m] 0.0017M in CCl_4, ca. 0.05-0.08M in $CHCl_3$. [n] Not regarded as carbonyl bands - see text.

Table 2.

Nitro group absorptions of nitrosalicylaldehydes and related compounds (ca. 0.02-0.06M in $CHCl_3$).

Compound No.	Substituents	$\nu_{(asym.)}$	$\Delta\nu_{\frac{1}{2}}^{a}$	ε_a	$\nu_{(sym.)}$	$\Delta\nu_{\frac{1}{2}}^{a}$	ε_a
Salicylaldehydes							
8	5-NO_2	1541 1526	13 13	245 230	1347	9	1120
9	3-Pr^i,5-NO_2	1532	21	385	1352 1320	12 14	675 695
10	3-Ph,5-NO_2	1539	20	310	1346	11	730
11	3-Bu^t,5-NO_2,6-Me	1523	23	335	1342	*	430
12	3-NO_2	1537	16	280	1350 1331	* *	100 100
13	3,5$(NO_2)_2$	(1554)	*	325	1349	12	1045
14	3-NO_2,5-Bu^t	1538	18	415	1369 1325	* *	(200) (200)
15	3-NO_2,5-Cl	1538	19	350	1352 1312	* *	130 185
16	3-NO_2,5-OMe	1541	14	720	1321	18	390
17	3-NO_2,5-Ph	1542	15	470	1332 1312	* *	200 200
18	4-OH,5-NO_2	1538	18	500	1347‡	*	285

Table 2 continued overleaf

Table 2 (continued).

Compound No.	Substituents	$\nu_{(asym.)}$	$\Delta\nu_{\frac{1}{2}}^{a}$	ε_a	$\nu_{(sym.)}$	$\Delta\nu_{\frac{1}{2}}^{a}$	ε_a
2-Hydroxyacetophenones							
23	5-NO_2	1531	18	235	1345	10	985
24	3-NO_2	1532	17	465	1362	21	360
Methyl salicylates							
25	5-NO_2	1530	16	365	1344 1357	10 12+	1130 485
26	3-NO_2	1533	12	700	1347 1334	* *	360 360
Miscellaneous compounds							
36	o-Nitrophenol	1540	14	300	1334 1321	12+ *	330 265
37	m-Nitrophenol	1532	11	1090	1357	9	705
38	p-Nitrophenol	1522	12	595	1346	13	1080
39	o-Nitroanisole	1527	14	695	1356	19	300
30	o-Nitrobenzaldehyde	1532	12	685	1349	10	440
33	m-Nitrobenzaldehyde	1539	9	615	1345	7	700

For symbols see Table 1.

Table 3.

Carbonyl absorptions (CH_3CN solutions, ca. 0.015M).

	Compound	ν_{CO}	$\Delta\nu_{\frac{1}{2}}^{a}$	ε_a
1	Salicylaldehyde	1666	9	780
		1646[b]	13	315
33	m-Nitrobenzaldehyde	1707	8	765
		1727	*	85
8	5-Nitrosalicylaldehyde	1669	14	715
		1691	*	65
		1706	*	65
12	3-Nitrosalicylaldehyde	1696	9	390
		1672	22	295
19	o-Hydroxyacetophenone	1645	16	570
23	2-Hydroxy-5-nitroacetophenone	1654	20	555
24	2-Hydroxy-3-nitroacetophenone	1657	20	445
		(1685)	*	70
28	o-Methoxybenzaldehyde	1690	10	690
		1666[b]	*	125
30	o-Nitrobenzaldehyde	1703	13	465
31	m-Methoxybenzaldehyde	1704	10	660
		1685[b]	12+	175
6	3-Methoxysalicylaldehyde	1658‡	20	495
		1675[b]	*	180
		1689	11+	135

For symbols see Table 1.

[b] Not regarded as a carbonyl band.

Table 4.

Carbonyl and nitro absorptions (pyridine solutions)[b].

No.	Compound Substituents	ν_{CO}	$\Delta\nu_{\frac{1}{2}}^{a}$	ε_a	ν_{NO_2} (ass	$\Delta\nu_{\frac{1}{2}}^{a}$	ε_a	ν_{NO_2} (sym)	$\Delta\nu_{\frac{1}{2}}^{a}$	ε_a
Salicylaldehydes										
1	None	1682	13+	345	-	-	-	-	-	-
		1664	*	400						
		1646[c]	*	195						
2	5-Bu^t	1677	13+	325	-	-	-	-	-	-
		1654	20+	395						
5	3-Bu^t,6-Me	1634	30‡	480	-	-	-	-	-	-
8	5-NO_2	1688	14	560	1527	*	135	1343	11	1035
		1666	*	165						
11	3-Bu^t,5-NO_2,6-Me	1640	24	320	1521	20	340	1337	*	380
12	3-NO_2	1692	14	375	1532	24	325	1351	*	240
		1670	*	(200)						
2-Hydroxyacetophenones										
19	None	1642	17	515	-	-	-	-	-	-
23	5-NO_2	1650	23	345	1528	17	255	1344	12	825
		1677	*	150						
24	3-NO_2	1654	21	350	1530	17	525	1361	23	345
		1683	*	110						

Table 4 continued overleaf

Table 4 (continued).

No.	Compound Substituents	ν_{CO}	$\Delta\nu_{\frac{1}{2}}^{a}$	ε_a	ν_{NO_2} (Asym)	$\Delta\nu_{\frac{1}{2}}^{a}$	ε_a	ν_{NO_2} (Sym)	$\Delta\nu_{\frac{1}{2}}^{a}$	ε_a
Methyl salicylates										
40	None	1678	17	465	-	-	-	-	-	-
25	5-NO_2	1684	20	470	1528	19	365	1343	11	995
		1735	*	120				1356	14+	390
26	3-NO_2	1685	16	415	1532	16	610	1347	*	280
								1335	*	280

Footnotes.

[b] Approx. 0.05M in 0.11 mm. cells.

[c] Not regarded as a carbonyl band.

For symbols see Table 1.

Section 5.

Spectroscopic Studies on the Association of ortho-substituted Phenols with Ethers.

Historical. A number of spectroscopic studies have been carried out with ortho alkyl substituted phenols[1-3]. In early studies $\Delta\nu$ (νfree OH - νself associated OH) was used to characterise the phenols as (a) unhindered - no ortho substituents or one small ortho alkyl substituent, (b) partially hindered - one large ortho substituent or two small ortho substituents, and (c) hindered - two large ortho alkyl groups. Comparison with the $\Delta\nu$(OH) values of the corresponding m- and p-alkylphenols, all of which were classified as unhindered, was taken as evidence that the simple inductive effects of the alkyl groups had little to contribute to these strikingly different frequency shifts within the ortho compounds. However inductive effects have some well defined influences on the absorptions of hydroxyl group involved in intermolecular hydrogen bonding. Barrow[4] has demonstrated that the introduction of alkyl groups had the expected effect of decreasing the acidity of normal carbinols. $\Delta\nu$ and integrated absorption of the associated hydroxyl peaks of a series of carbinols in carbon tetrachloride (self association), diethyl ether (association

with the ether oxygen) and triethylamine (association with the nitrogen atom), decreased from Me → Bu^{t}. Many properties peculiar to ortho alkyl phenols suggest the occurrence of steric effects: these include for example the differing rates of thermal decomposition of ortho-t-butyl- and ortho-i-butylphenols compared with their meta and para isomers[5], the abnormal chromatographic[6], and absorption[7] behaviour, the diminished alkali solubility[8], and the reactivity towards benzoyl peroxide[9]. It has however been difficult to obtain a quantitative evaluation of steric effects alone, since properties could in many cases be ascribed to the inductive effects of the ortho alkyl groups.

More recently, Bellamy and Williams[10] have adduced evidence indicating that steric effects have little importance in solvent association by ortho alkyl phenols. By plotting $\Delta\nu/\nu$ vapour ($\Delta\nu = \nu$vapour $- \nu$solvent associated hydroxyl) of a selection of ortho substituted phenols against $\Delta\nu/\nu$ phenol, they have found no evidence that the strength of the solvent association is weakened by steric effects except in the extreme example of 2,6-di-t-butyl phenol. Indeed any frequency differences within the phenol series have been ascribed to the lower acidity of the alkyl

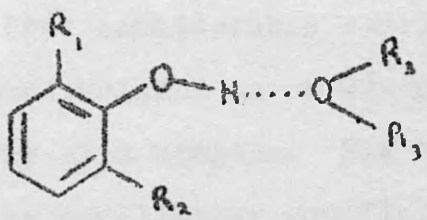
substituted compounds[10]. Obviously an explanation, other than simple direct weakening of hydrogen bonding by steric effects, is necessary to account for the classification of the ortho substituted phenols according to their self association frequency shifts.

The factors affecting the "basicity" of electron donor centres in association with acids have been studied by a number of techniques. Both Gordy *et al.*[11], who measured the shifts of the νOD band of CH_3OD dissolved in ethers, nitro compounds, aldehydes, esters and amines, and Earp and Glasstone[12] who carried out electric polarisation measurements on ether-haloform complexes, considered that their results were best explained by the influence of inductive effects on the electron density at the basic centre. A number of methods, e.g. infrared absorption[11b,13], ultraviolet absorption[14], solubility in water[15], solubility of HCl[16], have established that cyclic ethers are more basic than open chain ethers as regards association with protons and this has been ascribed to ring strain.

Some steric factors affecting the basicity of electron donor centres have been noted. West[17] has measured $\Delta\nu$(OH) for the interactions of phenol and of various alcohols with a series of substituted olefins in carbon

tetrachloride solution and claimed that the "basicity" of the olefin is chiefly influenced by the inductive effects of the substituents. However he noted that his results contrasted with those of Winstein and Lucas[18], who found that the "basicity" of olefins as measured by their equilibrium constants for silver ion complex formation, decreased with increasing alkyl substitution. This decrease was ascribed to steric hindrance to the approach of the large silver ion to the π electrons. Further, Brown and Adams[19] have found that the stability of BF_3-ether complexes decreased in the order tetrahydrofuran $>$ Me_2O $>$ Et_2O $>$ $^iPr_2O$, contrary to that expected from inductive effects. More recently Halleux[26] has convincingly demonstrated that bulky 2- and 2,6-alkyl substituents on the pyridine nucleus effectively lower the association constants for pyridine-phenol complex formation (see discussion).

Our own infrared studies concerning phenol-ether association (I) had already revealed much interesting

I. 

data when we were first made aware of Dr. Bellamy's work

in this field, at that time unpublished. An active collaboration has been ensued during which Dr. Eglinton carried out some survey measurements at E.R.D.E., Waltham Abbey as a Summer Consultant to the Ministry of Supply (Summer 1959). In their own preliminary studies Bellamy and Williams[10] have shown that $\Delta\nu$ (OH) measurements gave no real indication of any steric inhibition to the association of phenols with solvents, with the exception of the acutely hindered 2,6-di-t-butyl phenols. However they did suggest that the relative intensities of free and associated hydroxyl bands indicated large entropy effects dependent on substituent size and pattern. The present author has since investigated the assodation on a quantitative basis and this work is reported herein.

Results. The association of a range of substituted ortho alkyl phenols with ethers, which themselves carry alkyl groups of various sizes, has been studied. Bistrimethylsilyl oxide, with an Si-O-Si angle of 130° [20], has been included as being somewhat similar in shape to di-t-butyl ether and as being likely to produce considerable steric effects. Tetrahydrofuran has been included as an exa ple where steric effects are likely to be at a minimum. The hydroxyl frequency shifts and the equilibrium coefficients for the association of phenols with ethers have been evaluated. The

results are summarised in Tables 1-3 and illustrated in the Figure. Table 1 gives the values of ν(OH) of the various phenols in pure ether solutions and various physical states and Table 2 gives similar data for dilute solutions of the phenols in binary mixtures of ethers and carbon tetrachloride. Table 3 lists the $\Delta\nu$(OH) values and the equilibrium coefficients for many of these systems, under conditions of arbitrary fixed concentrations and temperature (0.1M phenols in 0.5M ether-CCl_4 solvents).

The Figure shows typical phenol spectra in 0.5 molar ether-CCl_4 solvents. In the corresponding pure ether solvents the intensities of the associated peaks are greatly increased while those of the free hydroxyls are decreased. Most of the phenols, in pure ether solvents, display a hump on the high frequency side of the main association peak. This absorption is most prominent in phenol and in the mono ortho substituted phenols. It is not present in the spectra of phenols in the ether-carbon tetrachloride solvents. This rules out a possible explanation, that the absorption is due to species involving more than one phenol molecule with one molecule of ether, for example Ph-O-H...$\overset{Ph}{O}$-H...OEt_2 or Ph-O-H.....  -O-H...OEt_2. Simple self association of the remaining free phenol molecules is not a likely explanation. Phenol, 0.03M in CCl_4 (a concentration greater than that of most unassociated phenols in pure ether

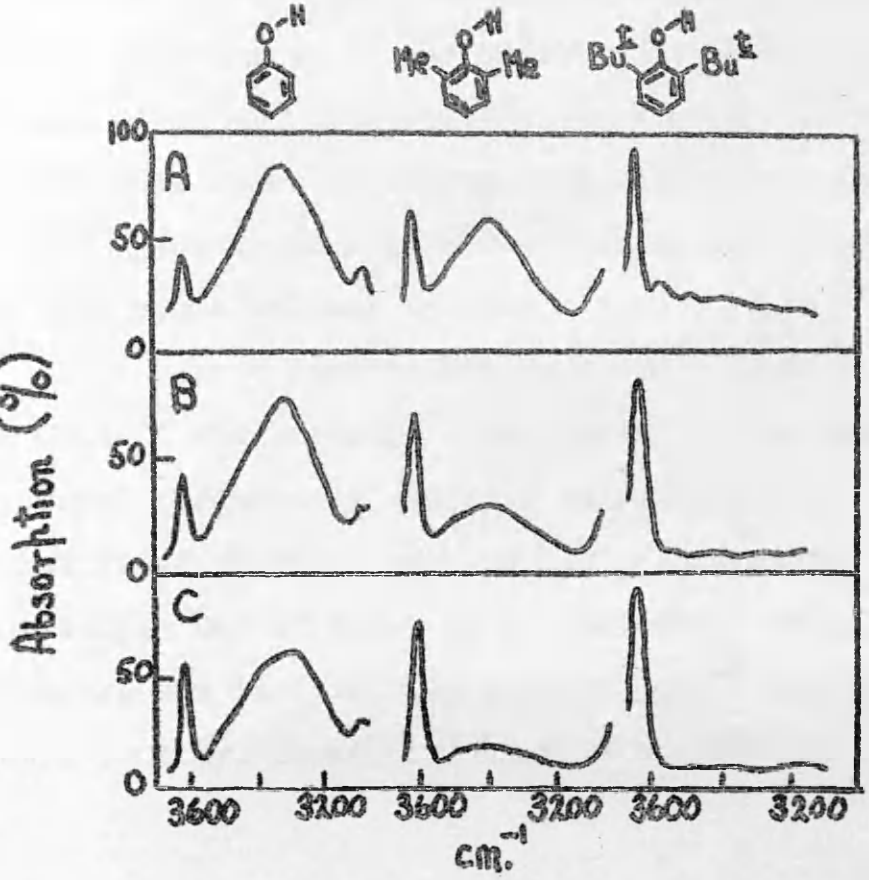
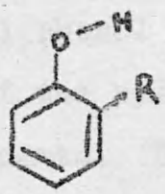


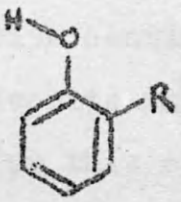
FIG. Phenol, 2,6-dimethyl-phenol, and 2,6-di-t--butyl-phenol in A, 0.5M T.H.F. - CCl_4, B, 0.5M di-i-propyl ether - CCl_4, and C, 0.5M. di-t-butyl ether - CCl_4 (0.5mm. cells).

solutions) shows only free hydroxyl absorption. A more likely explanation of the additional absorption is that traces of water inadvertently included in the initial phenol-pure ether solutions, has been eliminated by the more careful phenol and ether purification and solution preparation for the mixed solvent spectra.

The values in Tables 1 and 2 confirm the findings of Goddu[21] and Puttnam[22] that there are two monomeric hydroxyl frequencies ascribed to IIa and IIb in some ortho substituted phenols, even where intramolecular bonding is unlikely. One of these is at the normal value for alkyl phenols, and the other is about 40 cm.$^{-1}$ higher. 2-t-butyl 5-methyl phenol for example shows bands at 3608 cm.$^{-1}$



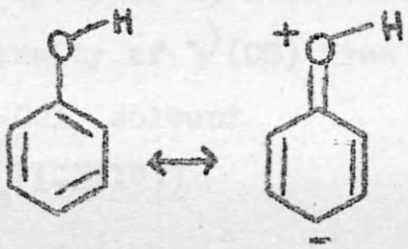
IIa



IIb

(strong (IIb)) and 3647 cm.$^{-1}$ (weak (IIa)) and 2-t-butyl phenol itself behaves similarly. Only the higher frequency absorption is shown by 2,6-di-t-butyl phenol. Puttnam[22] has claimed that all phenols exist with the hydroxyl coplanar

with the ring and in cis- and trans-orientations with respect to an ortho substituent. However the arguments he has forwarded do not necessarily cover the additional high frequency absorption (11a) of the ortho Bu^t, substituted phenols. Bellamy and Williams[10] have suggested that the considerably more intense (ca 3 fold) absorption of phenol compared to methanol, is due to the mesomeric electron delocalisation which is possible when the ring is coplanar (III).



III

They considered that the equally high intensity of 2,6-di-t-butyl phenol was consistent with continued coplanarity of the hydroxyl and ring despite the size of the alkyl substituents. The high ν(OH) for this compound and of the additional peak in o-t-butyl phenol are suggestive of some steric interaction between the hydroxyl and the alkyl substituents while the high intensity (the normal inductive effect of a Bu^t group is to reduce the intensity slightly) may be due to a small opening of the C-O-H angle,

whereby the coplanarity of the ring is retained.

The equilibrium coefficients K (l. $mole^{-1}$) were determined as follows. For acid (a) and base (b) association

$$a + b \rightleftharpoons a.....b$$

the equilibrium constant $K = \frac{(a...b)}{(a)\ (b)}$

where C_a = total concentration of acid ($mole^{-1}$)

C_b = total concentration of base ($mole^{-1}$)

A^o = integrated intensity of ν(OH) in CCl_4 (all "free" i.e. equivalent to A values at Zero ether concentration))

A = integrated intensity of ν(OH) free (unassociated) in the mixed ether-CCl_4 solvent

then $K = \frac{1 - A/A^o}{A/A^o(C_b - C_a(1-A/A^o))}$

Discussion.

The proton donor and acceptor properties in an acid/base system will determine an effective O-H...O distance for the hydrogen bond. This may then be modified by any steric effects operating from either side. The values of $\Delta\nu$(OH) are directly related to the final O...O distance[23], and therefore provide a guide to the resultant of these effects. With unhindered phenols, it is known that the OH stretching frequencies vary systematically with the basicity of the solvent in such a way that the $\Delta\nu/\nu$ values of any

one donor in a series of solvents can be plotted directly against the corresponding values of any other in the same solvents, to give a straight line[10]. In any instance in which steric effects lead to a larger O...O distance than would be expected from the acid/base properties, a deviation from this straight line will occur, and in principle it should be possible to derive the change in O...O distance which has resulted. It has already been shown in this way that 2,6-di-t-butyl phenol is subject to considerable steric hindrance to solvent association, and that other 2,6-dialkyl phenols are not[10]. The application of this technique to the new data now available should give a clear indication of the presence or absence of steric effects with the variously hindered ethers. The $\Delta\nu$ themselves are also informative in providing a direct measure of the hydrogen bond strength. For any one phenol they should therefore change systematically with the basicity of the ether, unless steric effects intervene. Finally, the equilibrium coefficients measured in carbon tetrachloride will be determined by the strengths of the hydrogen bonds, and the entropy effects which are related to the ease with which the bond can reform once it has been broken.

$\Delta\nu/\nu$ Plots. - The data for the solvent shifts of ν(OH) for

many of the phenols now studied are already available[10]. The inclusion of the new data in Tables 1 and 2 on the original plots (fig. 1 of ref. 10), shows that in the great majority of cases the points fall on the lines within the limits of experimental error. 2,6-di-t-butyl phenol, of course, shows marked steric effects with all the ethers studied, and none of the 2,6-dialkyl phenols associates to any appreciable extent with bistrimethylsilyl oxide, although the mono alkyl phenols associate normally. However, only in the case of di-t-butyl ether does there appear to be any other steric hindrance effect, and even this is small. The point for o-i-propyl phenol in this solvent is very slightly displaced from the standard line, in a direction indicating an increased O...O distance, and the effect increases with the degree of phenol substitution. However the effect is not large and even in the more hindered phenols the displacement is only slightly greater than the experimental error of the method. Clearly the steric effects are too uncommon in this series and too small to be capable of interpretation in terms of the alterations they produce in the O...O distances.

$\Delta\nu$ Values. - For unhindered phenols the $\Delta\nu$ values vary

systematically with the basicity of the ethers and follow the same order as phenol itself, i.e. $Bu^t_2O > Pr^i_2O >$ T.H.F. $> Bu^n_2O > Et_2O > (Me_3Si)_2O$. Table 3 shows that this order is effectively maintained for all the phenols up to the 2,6-di-t-butyl derivative, the only exception being with di-t-butyl ether. This last moves down the list as an effective acceptor as the sizes of the substituents of the phenol are increased. This is in line with the findings given above and supports the absence of steric effects in the other cases.

The slopes of the $\Delta\nu/\nu$ curves for 2,6-dialkyl phenols show them to be less acidic than either phenol or its mono alkyl derivatives. This is reflected in the $\Delta\nu$ values in ether, which are smaller by some 60-70 $cm.^{-1}$. This change is too great to be attributed wholly to the inductive effects of the alkyl groups, and in the absence of positive steric hindrance it must arise from some dipolar interaction between the OH and alkyl groups which reduces the acidity of the hydroxyl.

The $\Delta\nu$ values for the liquid phenols are also of interest (Table 1). Mono alkyl phenols (with the exception of a t-butyl phenol) show values typical of the usual polymeric self-association, but as earlier workers have found, 2,6-dialkyl phenols show only small shifts

(circa. 45 cm.$^{-1}$) away from the monomeric value. If it is accepted that 2,6-di-i-propyl phenol is able to associate freely with say di-i-propyl ether, it is difficult to see why the dialkyl phenols should not self associate freely. Indeed, it would seem that they do (with the exception of 2,6-di-t-butyl phenol), at least as far as the dimer stage, as the $\Delta\nu$ values are normal for dimeric association when account is taken of their reduced acidity. According to Puttnam[22] the $\Delta\nu$ value for liquid dimeric phenol is 107 cm.$^{-1}$ and that of the 2,6-dialkyl dimers is about 65 cm.$^{-1}$. The ratio is that which would be predicted from the $\Delta\nu/\nu$ plots[10] based on associations with solvents with which no steric hindrance occurs, and in which the differences in $\Delta\nu$ values arise solely from acidity effects. Further the $\Delta\nu$ values of 2,6-dimethyl, diethyl, and di-i-propyl phenols are all essentially the same and do not show the regular changes which might be expected from a change in the steric hindrance. The problem is therefore not one of whether these materials are able to self associate, but why, having done so they are unable to continue the process by the addition of further units. This problem is intimately connected with the reasons for the strengthening of the hydrogen bonds in polymeric as against

dimeric alcohols. Weltner and Pitzer[24], and Pauling[25] suggested many years ago that polymeric alcohols and phenols took a cyclic structure and that the bonds were stronger than those of the dimer for this reason. More recently Kuhn and Bowman[30] have compared the absorption of some simple alcohols with that of some suitable intramolecularly bonded polyhydric alcohols. They have deduced from these measurements that in more concentrated carbon tetrachloride solutions the simple alcohols exist as acyclic dimers and cyclic polymers. The present findings appear to support these views. In the association of say, 2,6-di-i-propyl phenol, any steric hindrance present would be limited to the interaction between one of the i-propyl groups of each unit. No greater interaction could arise to prevent the addition of a third unit to form a trimer, unless this unit were seeking to make up a cyclic system. In this last case, steric interactions would be operating on the i-propyl groups on both sides of the third unit and could well prevent further association. We would therefore conclude that dimeric association occurs normally in these phenols and that the differences between them and normal phenols arises from their inability to take up cyclic polymeric forms.

Equilibrium Coefficients. - In the present studies the concentrations of the phenol and other components in carbon tetrachloride have been maintained at arbitrary chosen values, as has the temperature at which measurements were made. The observed equilibrium coefficients will depend upon (a) the strength of the hydrogen bonds which determine how readily the bonds will be broken and (b) the entropy effects which are related to the readiness with which a broken bond will reform. Under the conditions chosen the number of collisions between phenol and ether molecules, at any one moment will be more or less the same in all cases. The variations in entropy will arise from the fact that the shapes of the donor and acceptor molecules will play a large part in determining what proportion of these collisions is effective in leading to hydrogen bond formation. Large differences due to this effect have already been demonstrated qualitatively, in this series[10].

The experimental values of K, for the chosen conditions are given in Table 3, and it will be seen that they follow a consistent pattern of behaviour throughout. For any one phenol the K values do not follow in any way the basicity of the ethers as do the $\Delta\nu$ values, but

instead arrange themselves in the order of the steric complexity of the ethers. The order of effectiveness in maintaining the hydrogen bond is therefore T.H.F. > Et_2O, Pr^i_2O > Bu^n_2O > Bu^t_2O > $(Me_3Si)_2O$. This is not surprising, as, apart from bistrimethylsilyl oxide there are only small differences (13-27 $cm.^{-1}$) shown in the $\Delta\nu$ values for any one phenol with the various ethers, showing that the hydrogen bonds are of closely similar strengths. On the other hand there are substantial changes in the shapes of the acceptor molecules which must play a decisive part in determining the number of effective collisions which lead to association. Some part of the low K values found for the bistrimethylsilyl oxide is of course due to the weaker hydrogen bond, but even here entropy effects may be dominant.

A very similar effect is found on passing down the table. The nature of the ether is now held constant and the complexity of the phenol is increased. In any single ether, the $\Delta\nu$ values show that phenol, and its mono alkyl derivatives form hydrogen bonds of very similar strengths. Despite this the K values change dramatically as alkyl groups are introduced. Some part of the lowering of the K values found for the 2,6-dialkyl phenols must be attributed to their lower acidity, but

the changes observed are too great to be due to this alone and entropy changes must play a major part.

As is to be expected, the incidence of entropy effects amongst the various phenols becomes more and more apparent as the complexity of the ethers is also increased. Thus the K values of phenol changes by a factor of 2.7 on passing from tetrahydrofuran to di-t-butyl ether, but the corresponding value for 2,6-di-i-propyl phenol is a factor of 9. The impact of these effects in terms of the relative heights of the free and associated peaks is very marked and a few typical examples are illustrated in the Figure. The differences are unmistakable and could well form the basis of diagnostic techniques for the identification of substitution patterns in phenols and possibly in more complex molecules such as the sterols and triterpenes.

It is interesting to note that Halleux[26] has recently performed similar experiments with the ternary system phenol - substituted pyridine - CCl_4. He illustrated the importance of steric effects in the pyridines in the following manner. A reasonably good straight line relationship existed between the pK_a values of pyridines substituted in positions other than ortho,

and the pyridine-phenol association constants which he derived spectroscopically. Serious deviation from this linear relationship was observed for 2,6-di-t-butyl pyridine. The deviation was considerable for 2-t-butyl pyridine, but was not observable for 2-picoline. He has not listed or commented on the corresponding $\Delta\nu$(OH) values.

Summary. - The association of a range of ortho substituted alkyl phenols with various ethers, which themselves carry alkyl substituents, has been studied spectroscopically. The equilibrium coefficients (29°C) for the association have been determined. $\Delta\nu$(OH) values, a measure of intermolecular hydrogen bond strength, have been tabulated. The results allow us to forward the following hypotheses.

a. Apart from 2,6-di-t-butyl phenol, steric hindrance to association between ortho substituted phenols and alkyl ethers is comparatively rare, although it does occur to a small extent with di-t-butyl ether.

b. Although changes in substituent size do not greatly affect the strength of the hydrogen bond, as measured by $\Delta\nu$(OH), they do give rise to considerable entropy effects, which are reflected in the equilibrium coefficients.

c. The classification of ortho phenols as unhindered and

partially hindered according to their self association hydroxyl frequency shifts is not due to weakening of hydrogen bond strength (as in the truly hindered di-t-butyl phenols), but is a result of steric inhibition to the formation of the strongly bound cyclic polymers.

Appendix.

Since the completion of our work and preparation for publication, a few publications with relevant material have appeared.

Ingold and Taylor[27] have further investigated the cis-trans equilibrium of ortho tertiary alkyl and other buttressed ortho alkyl phenols. They have demonstrated that the trans isomer is stabilised by more polar solvents and that the cis/trans ratio increases with temperature. Thermodynamic parameters ΔH, ΔG, and ΔS, have been evaluated for the cis trans equilibrium. In addition they have noted the following interesting points. The half band width ($\Delta\nu_{\frac{1}{2}}^{a}$) of the free hydroxyl stretching vibration of phenol increases considerably in more polar solvents. The changes for $\Delta\nu_{\frac{1}{2}}^{a}$(OH) of 2,6-di-t-butyl, 4-methyl phenol are small by comparison. However the partially hindered phenols, which they measured, have intermediate values. They interpret this as evidence for some steric inhibition to the association in the ortho mono alkyl phenols, despite their own and Bellamy and William's[10] evidence ($\Delta\nu_{\frac{1}{2}}$).

Wren and Lenthen[28] have further investigated by infra red spectroscopy the ability of 2,6-di-t-butyl,

4-methyl phenol to associate with bases. They have been able to conclude that even with ether, cineole, and triethylamine there is a measurable tendency to form bonds. Thermodynamic parameters for the association with dioxan have been evaluated.

In a nuclear magnetic resonance study of steric effects on hydrogen bond formation by phenol derivatives, Yamaguchi[29], has come to what must surely be an oversimplified conclusion, that the "ability for hydrogen bond formation" is a linear function of size of ortho substituents.

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Table 1.

Hydroxyl stretching frequencies ($cm.^{-1}$) of alkyl substituted phenols

(Apparent extinction coefficients, ε, in parentheses)

State	Phenol Substituent(s)			
	None	2-Me	2-Pr^i	2-Bu^t
Vapour	3654[a]		3654[a]	
Hexane	3622	3623	3625	(3655 (3616 3600sh.
Liquid	3510sh. 3350br.	3550sh. 3395br.	3533sh. 3460br.	3535 tail
CCl_4	3612(205)	3613(165)	3615	(3647(25) (3606(200)
Tetrahydrofuran	3287[a] v.br.	3304(175)	3303[a]	3299(180)
Diethyl ether	3344[a]	3341(165)	3338[a]	3337(170)
Di-t-propyl ether	3625v.w. 3329(180)	3627v.w. 3332(160)	3620v.w. 3330(160)	- 3324(175)
Di-n-butyl ether	3620v.w. 3336(170)	3620v.w. 3345(140)	3622(5) 3341(145)	3613v.w. 3338(165)
Di-t-butyl ether	3618v.w. 3306(130)	3623(10) 3318(115)	3613v.w. 3310(120)	3650v.w. 3613v.w. 3305(120)
Bistrimethylsilyl oxide	3621(80) 3448(80)	3623(80) 3456(45)	3621(75) 3449(55)	(3655(15) (3615(70) (3442(65)

State	Phenol Substituent(s)					
	2-Bu^t-5-Me	2,6-Me_2	2,6-Et_2	2,6-Pr^i_2	2,6-Bu^t_2	2,6-Bu^t_2-4-Me
Vapour		3654[a]	3652[a]	3650[a]		3671[a]
Hexane	(3655 (3616	3629	3629	3627	3653	3655
	3606	-	3622sh.[a]	3618	3644	3648[a]
	3528	3573	3583[a]	3577	-	-
Liquid	tail	3500sh.		tail	-	-
CCl_4	(3647(15) (3608(170)	3621(155)	3623	3642sh. 3620(145)	3647(240)	3651[a]
Tetrahydrofuran	3307(180)	3503[a] v.w.sh. 3383[a] br.	3405[a] br.	3410[a]	3641(45) 3545(70)	3645[a], 3536[a] 3400[a]
Diethyl ether	3343(170)	3407[a]	3620[a] 3412[a]	3624[a] 3428[a]	3649(115) 3385(25)	3651[a]
Di-t-propyl ether	3335(160)	3629(15) 3398(90)	3629(20) 3400(90)	3629(20) 3410(85)	3650(155) 3404v.w.	3654(145) 3450(10)
Di-n-butyl ether	3615(5) 3342(155)	3628(15) 3407(85)	3627(25) 3421(75)	3625(30) 3435(65)	3650(150) 3383v.w.	3651(145) 3405(10)
Di-t-butyl ether	3613v.w. 3314(55)	3629(40) 3418(60)	3628(45) 3424(60)	3627 3425	3651(200) -	3654(195) 3475(5)
Bistrimethylsilyl oxide	3616(75) 3451(55)	3627(110) 3545(15)	3628(130) -	3627(125) -	3653(160)	3654(215)

Not measured. - No absorption. br. = broad.

v.w. = very weak. sh. = shoulder. tail = absorption diminishing slowly towards lower frequencies.

[a] Values taken from ref. 5.

Table 2.

Integrated absorption intensity data (A) for hydroxyl stretching bands of ortho-alkyl substituted phenols in 0.5M ether-carbon tetrachloride solutions

Dissolved ether		Phenol Substituents: None ν(OH)	None 10^{-4}A	2-Me ν(OH)	2-Me 10^{-4}A	2-Pr^i ν(OH)	2-Pr^i 10^{-4}A	2-Bu^t ν(OH)	2-Bu^t 10^{-4}A	2,6-Me_2 ν(OH)	2,6-Me_2 10^{-4}A	2,6-Pr^i_2 ν(OH)	2,6-Pr^i_2 10^{-4}A	2,6-Bu^t_2 ν(OH)	2,6-Bu^t_2 10^{-4}A
Tetrahydrofuran	free	3611	0.225	3613	0.310	3613	0.280	(3647 (3606	0.075 0.275	3619	0.490	3618	0.520	3647	1.45
	assoc.	3321	9.00	3329	8.85	3329	8.70	3332	8.60	3400	4.30	3426	3.45	3557	0.530
Diethyl ether	free	3611	0.345	3613	0.410	3613	0.400	(3648 (3607	0.095 0.360	3620	0.710	3619	0.740	3647	1.35
	assoc.	3334	7.30	3340	6.65	3340	6.25	3338	6.20	3409	2.35	3436	2.05	-	
Di-i-propyl ether	free	3611	0.300	3613	0.430	3612	0.400	(3647 (3607	0.080 0.335	3620	0.725	3619	0.765	3647	1.25
	assoc.	3314	8.00	3322	7.00	3325	7.00	3325	7.10	3395	2.15	3412	1.65	-	
Di-n-butyl ether	free	3612	0.390	3614	0.510	3613	0.430	(3648 (3607	0.100 0.410	3620	0.720	3619	0.830	3647	1.30
	assoc.	3330	6.65	3335	5.80	3336	5.35	3336	5.95	3401	1.80	3426	1.75	-	
Di-t-butyl ether	free	3610	0.450	3613	0.590	3612	0.575	(3648 (3607	0.105 0.505	3621	0.845	3619	0.845	3648	1.30
	assoc.	3297	7.35	3314	5.90	3325	5.85	3336	5.05	3424	1.35	3430	0.985	-	
Bistrimethylsilyl oxide	free	3611	1.00	3613	1.10	3612	1.10	(3648 (3607	0.170 0.945	3621	0.925	3619	0.895	3648	1.20
	assoc.	3454	1.85	3464	1.45	3462	0.650	3447	0.780	-		-		-	

Apparent half-band width's were as follows: free hydroxyl bands, 18±2 $cm.^{-1}$ except the band near 3650 $cm.^{-1}$ in o-t-butylphenol (approximately 24± 1 $cm.^{-1}$) associated hydroxyl bands varied from 150-270 $cm.^{-1}$ with no apparent regularity. The integrated absorption intensities of the phenols in CCl_4, $10^{-4}A^0$ were phenol 1.20, 2-Me 1.05, 2-Pr^i 1.10, 2-Bu^t 0.95, 2,6-Me_2 0.95, 2,6-Pr^i_2 0.90, and 2,6-Bu^t_2-phenol 1.30.

Table 3.

Equilibrium Constants $(K)^x$ for phenol-ether association at 29 ± 2°C

Hydroxyl frequency shifts, $= \nu_{(OH)}^{hexane} - \nu_{OH}^{ether/CCl_4}$, in parentheses.

Phenol Substituent	Ethers					
	T.H.F.	Et_2O	Pr^i_2O	Bu^n_2O	Bu^t_2O	$(Me_3Si)_2O$
None	10.4 (301)	6.0 (268)	7.2 (308)	4.9 (292)	3.9 (325)	0.4 (168)
2-Me	5.5 (294)	3.4 (283)	3.2 (301)	2.6 (288)	1.7 (309)	0 (159)
2-Pr^i	6.7 (296)	3.9 (285)	3.9 (300)	3.0 (289)	2.0 (300)	0.06(163)
2-Bu^t*	5.7 (284)	3.7 (278)	4.1 (291)	2.9 (280)	2.3 (280)	0 (169)
2,6-Me_2	2.0 (229)	0.67(220)	0.62(234)	0.63(225)	0.22(205)	0.03(-)
2,6-Pr^i_2	1.7 (201)	0.51(191)	0.48(215)	0.23(201)	0.19(197)	0.06(-)

x Mole l^{-1}. * Calculations involve band at 3610 only. K values for 2,6-Bu^t_2 phenol are all approx zero. T.H.F. is tetrahydrofuran. The extremely weak associated hydroxyl absorptions for 2,6-dimethylphenol and 2,6-di-i-propylphenol in 0.5M.

$Me_3Si\ _2O$-CCl_4 could not be accurately located and are not quoted. For the same reason values are not available for 2,6-di-t-butylphenol in any of the 0.5M. ether-CCl_4 solvents.

Experimental.

Materials.

Section 1. The compounds 13-15, 4 and 11, and 12 (see Tables 1, 2 and 5) were kindly supplied by Mr. A. Baker, Dr. M.C. Whiting, and Mr. P.A.I. Finan respectively. Compounds 1, 2, 8 and 10 were prepared by Dr. M. Krishnamurti by the respective procedures in the literature[1-4], while nos. 3, 5, 6, 7 and 9 were purified commercial materials. Physical constants were in accord with those given in the literature.

Section 2. Most of the acids were obtained commercially. 6-Chlorosalicylic acid was kindly supplied by Dr. J.F.J. Dippy. o-Allyloxybenzoic acid, m.p. 58-59°, was prepared according to Nummy and Tarbell[5] and o-hydroxymethylbenzoic acid, m.p. 131-133°, from phthalide. Methyl esters were prepared with diazomethane. All samples were carefully purified, finally by sublimation or short-path distillation at 0.1 mm. (with the exception of o-hydroxymethylbenzoic acid). M.ps. of solids agreed with literature values[6], except that of methyl p-chlorobenzoate (34-35°: lit.[6], 44°). The purity of all liquid samples and of methyl p-chlorobenzoate was checked by gas-liquid chromatography.

Section 3. Many acids were obtained commercially. The following were prepared essentially by published methods: 3-allyl-[7], 3-propenyl-[8], 3- and 5-isopropyl-[9], 5-methyl-[10], and 6-methyl-salicylic acid[11]. 3-2'-Methylallylsalicylic acid M.P. 122°, was obtained by thermal rearrangement of O-2'-methylallylsalicylic acid[12]. 3-Phenylsalicylic acid was isolated from Eastman "Practical" grade of acid by dissolution in saturated aqueous sodium carbonate (ca. 1 equiv.), filtration, precipitation with N-hydrochloric acid (0.8 equiv.), and recrystallisation from ethylene dichloride (charcoal). Sublimation at 0.1 mm. afforded acid of m.p. 186-187.5°: its purity was confirmed by paper chromatography. o-Carvacrotic, 3,6-dimethylsalicylic, and 6-methyl-3-t-butylsalicylic acid were kindly supplied by professor W. Baker, F.R.S., and Dr. W.D. Ollis; 3-t-butylsalicylic acid was generously provided by Dr. O. Fancher (Miles Laboratories Inc.), 6-ethylsalicylic acid by Dr. R.E. Kent (Chas. Pfizer and Co. Inc.) and 3,6-di-isopropylsalicylic acid by Monsanto Ltd. Methyl esters were prepared with diazomethane: methyl 3-t-butylsalicylate, m.p. 47-48° (Found: C, 69.15; H, 7.6. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.75%). Treatment of O-methoxycarbonylsalicyloyl chloride with t-butyl alcohol in pyridine afforded t-butyl O-methoxycarbonylsalicylate(bands at 1760 and 1720 cm.$^{-1}$; no hydroxyl

absorption (liquid film), hydrolysed by 2N-sodium hydroxide to t-butyl salicylate, b.p. ca. 180° (decomp.), n_D^{19} 1.5090 (Found: C, 68.0; H, 7.55. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.25%). Samples were carefully purified, finally by sublimation or short-path distillation at 0.1 mm. Purity of liquid samples was checked by gas-liquid chromatography.

Section 4. Many of the substituted salicylaldehydes were kindly supplied by Professor M. Crawford and Mr. J.W. Rasburn[13]. 3-Nitro-, 5-nitro- and 3,5-dinitrosalicylaldehyde[14], 5-nitro-β-resorcylaldehyde[15], 2-hydroxy-3-nitro-[16], 2-hydroxy-5-nitro[16], 2-hydroxy-4-methyl-[17], and 4,6-dimethyl-2-hydroxyacetophenone[18] were prepared essentially by the methods cited. Methyl esters were prepared with diazomethane. All samples were finally purified by sublimation or short-path distillation at 0.1 mm. Purity of liquid samples was checked by gas-liquid chromatography: a minor impurity was detected in the sample of o-fluorobenzaldehyde.

Section 5. The materials were of commercial origin with the exception of di-t-butyl ether[19], 2,6-diethylphenol[20] and of 2-t-butyl phenol and bistrimethylsilyl oxide

which were kindly supplied by Mr. Ivor Brown and Dr. Vincent Davies of I.C.I. Ltd., respectively. The phenols were purified by short path distillation or sublimation at 0.2 mm. and thereafter stored in sealed ampoules, which were resealed immediately after use to avoid water contamination. The samples were of satisfactory purity as shown by their melting points and by gas-liquid chromatography. Diethyl ether was dried over sodium wire. Di-n-butyl, di-i-propyl, di-t-butyl ethers and tetrahydrofuran were all finally purified by refluxing 5-8 hours over sodium, followed by distillation. Bistrimethylsilyl oxide was distilled from KOH, refluxed over P_2O_5 and distilled. Purity of the ethers was checked by gas-liquid chromatography.

Gas-Liquid Chromatography. The purity of the materials was (where mentioned above) checked by gas-liquid chromatography using a Pye "Argon Chromatograph" with instrument settings as recommended by the manufacturer. The columns used for the methyl esters of Sections 2 and 3 and the aldehydes of Section 4 were of Apiezon L (5%) on Celite 545 (120-150 mesh), temperature 100-175°, flow rate approximately 35 ml./min. and exit pressure 760 mm. For the phenols of Section 5 the columns were of apiezon L (25%) on the same

Celite. Column temperature was approximately 115°; flow rate was 60 ml./min. and exit pressure 760 mm. For the ethers of Section 5 the columns were of Carbowax (20%) on C22 Firebrick (Johns-Manville). Column temperature was 50°, flow rate 30 ml./min., and the exit pressure was 760 mm.

Solvents. n-Hexane (spectroscopic grade), carbon disulphide (AnalaR), and carbon tetrachloride (AnalaR) were used without further purification. Chloroform (AnalaR) was freed from ethanol by two successive passages through blue silica gel immediately before use. Diethyl ether was dried over sodium wire. Acetonitrile was purified by prolonged treatments with potassium hydroxide, calcium chloride, and phosphorus pentoxide, followed by distillation. Pyridine was redistilled twice from potassium hydroxide immediately before use. For Section 1 the ether-carbon tetrachloride solvents were measured out weight for weight. For Section 5 it was more convenient to weigh the ether (about 1.5 gm.) into a 25 ml. graduated flask and top up to the mark with carbon tetrachloride. The mixed solvents were used as soon as possible after preparation.

Measurements. The spectra for Sections 1, 2 and 3 and many for Section 4 were determined with a Unicam S.P.100

double beam spectrophotometer operated under dry air conditions. The remaining spectra were determined with a Mark II version of the same instrument, operated under vacuum. Both instruments were equipped with S.P.130 sodium chloride prism-grating double monochromators (1500 lines per inch (650-2150 cm.$^{-1}$) and 3000 lines per inch (2150-3650 cm.$^{-1}$)). Below 650 cm.$^{-1}$ both instruments were operated as potassium bromide prism monochromators. The cell wells were flushed with air, dried by passage through an activated alumina column. The temperature of the cell wells was 29 $\pm$ 2^{o}. The wave number scales of the instruments were calibrated against the vapours recommended by Downie et al[21] for region concerned (e.g. NH_3 and CH_4 for the regions 3510-3170 and 3170-2880 cm.$^{-1}$ respectively) and the KBr region (below 700 cm.$^{-1}$) against 1,2,4-trichlorobenzene and polystyrene. In our earlier work the overall calibration was checked at lengthy intervals only (e.g. several months). Our routine calibrations before and after each set of uninterrupted measurements were made by checking the variation of a few reliable points e.g. acetone in CCl_4 for the carbonyl region, the water vapour bands at 3566 and 3586 cm.$^{-1}$ for the free hydroxyl region, phenylacetylene in hexane for the ethynyl C-H region, etc., and

comparing these with the overall calibration. In our later work full calibration by the appropriate vapour, was always obtained. Generally, measurements are believed to be accurate to $\pm$ 1 cm., although the true band centres of some of the more diffuse peaks, cannot be accurately picked out. The frequency values given are the mean of at least two determinations. The physical slit widths were those given by normal slit programmes for the instruments. This ensured spectral slit widths of approximately 5.5 $cm.^{-1}$ at 3500 $cm.^{-1}$, 4 $cm.^{-1}$ at 3300 $cm.^{-1}$, 4.5 $cm.^{-1}$ at 1700 $cm.^{-1}$, and 4 $cm.^{-1}$ below 700 $cm.^{-1}$. The electronic amplification and the scanning speed controls were adjusted to given an instantaneously stationary pen on cessation of scanning at any stage. These conditions afforded resolution equivalent to that recorded by Downie et al[21] for comparable monochromators, for example equivalent to the resolution of H_2O vapour in the carbonyl region by a calcium fluoride prism double pass spectrophotometer.

Spectra have been recorded linearly in $cm.^{-1}$ as percentage transmission. The linearity of the percentage transmission scale was checked by the procedure of Shrewsbury[22] and all intensity measurements were made on

bands of at least 10% transmission. Unless specified otherwise peaks were symmetrical: the apparent half-band widths ($\Delta\nu_{\frac{1}{2}}^{a}$) are quoted to the nearest integer; where necessary they were determined by reflection of the undisturbed wings of unsymmetrical bands. Peak intensities are given as apparent extinction coefficients ε_a (l. mole^{-1} cm.$^{-1}$) rounded to the nearest 5 units or as integrated absorption intensities A or B (l. mole^{-1} cm.$^{-2}$). ε and A or B have been measured from a solvent-solvent baseline superimposed on the record of the absorption of the solution (determined with solvent in the reference beam).

Two symbols, A and B, have been used in the text for integrated absorption intensity. B is the apparent integrated absprption intensity. $B = 2.303/Cl. \int \log_e T_o/T_\nu \, . \, d\nu$, where C is the molar concentration, l = cell path length in cm., and $\log T_o/T_\nu$ is the apparent optical density. This is in effect the area under an experimental curve between any two given frequencies, and has been determined by measurement of optical density at 5 cm.$^{-1}$ intervals followed by application of Simpson's rule. This measure of intensity is commonly used when the total absorption due to more than one

vibration is being estimated, e.g. the free and associated ethynyl CH stretch of benzoyl- and phenyl-acetylene (Section 1) for the determination of equilibrium constants. It is also commonly used in series of determinations where the overlap of bands makes area measurement between two fixed frequencies the simplest criterion of intensity, e.g. in the evaluation of the areas of the monomer and dimer carbonyl bands of salicylic acids. For benzoylacetylene (Section 1), the limits of integration were 3130-3350 cm.$^{-1}$. For the salicylic acids the carbonyl bands were considered to extend over the following regions: acid monomer +50 cm.$^{-1}$ from the trough between monomer and dimer: acid dimer, -50 cm.$^{-1}$ from the trough; methyl esters, + and -40 cm.$^{-1}$ from the band maxima. The other area symbol A is essentially a measure of the integrated absorption area to which some correction factors have been applied to allow for the various sources of error inherent in the measurement of B. It is conveniently used when the absorption being considered is reasonably symmetrical and free from overlap. The most commonly applied correction factors are those due to Ramsay. The integrated absorption intensity is calculated from the formula A =

$1/C.l.\ K.\ \log_e (T_o/T)_{max}.\ \Delta\nu_{\frac{1}{2}}^{a}$. The band is here assumed to have a perfectly symmetrical (Lorentz) shape. Corrections incorporated in K allow for the effect of finite slit width and for wing absorption. K values can be found by inspection in Ramsay's[23] tables. The value of K is a function of spectral slit width/$\Delta\nu_{\frac{1}{2}}^{a}$ and $\ln(T_o/T)$. Integrated absorption intensities of the more asymmetric associated phenolic hydroxyl peaks in Section 5 were obtained by averaging areas calculated using $\Delta\nu_{\frac{3}{4}}^{a}$ $\Delta\nu_{\frac{1}{2}}^{a}$, $\Delta\nu_{\frac{1}{4}}^{a}$, according to the improved direct integrated-intensity measurement technique of Cabana and Sandorfy[24].

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