Intramolecular Hydrogen Bonds and the Association and Solubilities of Substituted Benzoic Acids.

By Mansel Davies and D. M. L. Griffiths.

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The influence of intramolecular bonding upon the dimerisation and solubilities of some simple benzoic acid derivatives has been studied, and the results are discussed with particular reference to the energy changes associated with these processes. Infra-red data are presented for one case (*o*-methoxybenzoic acid) where they allowed a direct determination of the intramolecular bond energy.

The influence of what is now known as an intramolecular hydrogen bond upon the properties of *ortho*-substituted phenols and benzoic acid derivatives has long been known (Pfeiffer, *Annalen*, 1913, **398**, 137). The earlier studies such as those of von Auwers on molecular weights in solution, or of Sidgwick and Baker on volatility and solubility effects, have frequently been reviewed (see, *e.g.*, Hunter, *Ann. Reports*, 1946, **43**, 141). Infra-red, dipole-moment, and vapour-pressure studies (*inter al.*, Davies, *ibid.*, p. 6; Martin, *Nature*, 1950, **166**, 474; Lüttke and Mecke, *Z. physikal. Chem.*, 1950, *B*, **196**, 56; Wolf and Weghofer, *ibid.*, 1938, *B*, **39**, 194) have provided relevant information in some cases. Nevertheless, relatively few data are available on the energy of intramolecular hydrogen bonds. The present account describes the assessment of this factor in some substituted benzoic acids where its evaluation has been attempted from heats of solution, heats of association, and spectroscopic measurements.

EXPERIMENTAL

Infra-red Spectra.—The infra-red observations were made with a Grubb–Parsons S.3 spectrometer and a quartz prism. The absorption ascribed to the solute was that determined after allowing for the absorption by the solvent in the same cell at the same temperature. The type of cell and the experimental procedure have been described (Thomas, *J.*, 1951, 3307). To eliminate interference from the association band in carbon tetrachloride it was necessary to work at a concentration below 0·004M in a 10-mm. absorption cell. Concentrations were deduced from the peak optical densities.

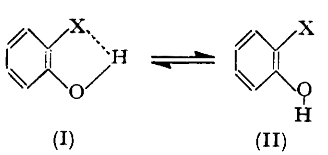
Solubilities.—These were determined as described by us (*Trans. Faraday Soc.*, 1953, **49**, 1405), using Money and Davies's saturator design (*J.*, 1934, 400). Dried " AnalaR " potassium hydrogen phthalate was the ultimate standard.

Distribution Studies.—These were made with the same temperature and analytical control as the solubilities. The frequency and period of shaking to ensure equilibrium was checked in each case, and adequate time was allowed for the complete separation of the layers : in some cases the latter period alone was more than an hour.

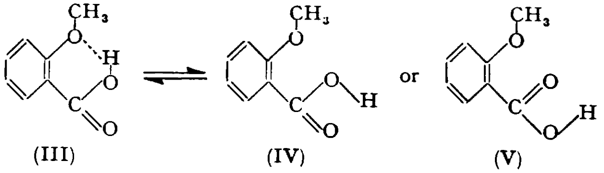
Materials.—" AnalaR " chemicals were used when procurable. The chloroform was freed from alcohol shortly before use, dried, and kept in the dark. The characteristics of some of the other materials after purification are given briefly (all m. p.s are the total corrected temperature ranges of melting) : (*iso*-C_5H_{11})$_2$O, b. p. 172·5—173·8°/760 mm., free from peroxide; Ph·CO_2Et, fractionated, b. p. 81·6°/7·6 mm., neutral; *o*-C_6H_4(OMe)·CO_2H, m. p. 101·5—102·0°, equiv. = 152·15 ± 0·25 (calc. : 152·14); *p*-C_6H_4(OMe)·CO_2H, m. p. 183—185°, equiv. = 152·15 ± 0·05; *p*-C_6H_4(OH)·CO_2H, m. p. 215·5—216·5°, equiv. = 137·8 ± 0·7 (titration indicator, bromothymol-blue; calc. : 138·12).

RESULTS AND DISCUSSION

Infra-red Study.—The intramolecular equilibrium between *cis-* (or bonded, I) and *trans-* (or free, II) hydroxyl groups in *ortho*-substituted benzenes, whilst frequently observable in the O–H stretching mode absorptions, cannot in many cases be directly evaluated therefrom. Among the reasons for this are the unsatisfactory resolution of the component absorptions for (I) and (II), or the diffuse nature of the absorption of (I), or interference from other absorptions, very frequently the association band arising from dimeric and higher aggregates of both (I) and (II). The uncertainties in this respect, even for the halogenophenols, have recently been emphasised (Lüttke, Mecke, and Rossmy, *J. Chem. Phys.*, 1953, **21**, 1606). However, we have found the conditions for *o*-methoxybenzoic acid in carbon tetrachloride to be favourable. Fox and Martin (*Nature*, 1939, **143**, 199) located the O–H absorption for (III) at 3362 cm.$^{-1}$, for (IV) (and/or V) at 3530 cm.$^{-1}$, whilst the association band is centred near 2950 cm.$^{-1}$. The intensities of the individual absorptions due to (III) and (IV) can thus be separately measured. To evaluate the equilibrium constant K = [Monomeric III]/[Monomeric IV], the relation from Beer's law, $[A] = [1/(\alpha_A d)] \ln (I_0/I)$ was applied to the absorption maxima, where α_A is the molar extinction coefficient of A. In fact, K was not determined but a factor proportional to it, *i.e.*, $\bar{K} = K . \alpha_{IV}/\alpha_{III}$. Individual values of $\bar{K}$ at 23° ± 1° were 8·6, 10·0, 8·8, 9·0, 10·1, *i.e.*, 9·3 ± 0·6; similarly at 48° ± 2°, $\bar{K} = 6{\cdot}3 \pm 0{\cdot}4$; at 72° ± 2°, $\bar{K} = 4{\cdot}2 \pm 0{\cdot}3$. On the assumption that the ratio α_{IV}/α_{III} does not vary with temperature,[*] these figures give for the equilibrium (III) $\rightleftharpoons$ (IV), $\Delta H = 3{\cdot}3$ kcal./mole with a ***maximum*** uncertainty of 0·5 kcal./mole.



(I) (II)



(III) (IV) (V)

As the equilibrium constants are determined from direct observations of both components and the ΔH value is deduced with the minimum of assumptions, it may be accepted as a standard for comparison with other less direct estimates.

Association Studies.—It is well known that the association of hydroxylic compounds is markedly reduced when the hydroxyl group is involved in intramolecular interactions (Hunter, *loc. cit.*). By the comparison of suitable cases it should be possible to estimate the energy involved in this internal process or, at least, to determine the extent to which the association energy is changed. The hydroxy- and methoxy-benzoic acids have been examined in this respect—the former in a number of solvents.

First, an accurate determination of the dimerisation equilibrium constant, K^S_{12} = [Monomer]^2/[Dimer] in the solvent S is required. This may be obtained over a range of temperatures by the distribution of the acid between water and an immiscible solvent (Moelwyn-Hughes, *J.*, 1940, 850). The principal assumptions involved are that the acid forms an ideal monomeric solute in water (correction for slight ionisation is readily made), and that both monomer and dimer are ideal solutes in the immiscible solvent. In these conditions it follows (Gross and Schwarz, *Monatsh.*, 1930, **55**, 287; Moelwyn-Hughes, *loc. cit.*) that:

$$C_S/C_W = K_D = K_{D1} + 2(K^2_{D1}/K^S_{12})C_W$$

Here C_S is the observed total molar concentration in the non-aqueous solvent, C_W the un-ionised acid concentration in water, *i.e.*, $C_W = C_W{}^t(1 - \beta)$, where $C_W{}^t$ is the total aqueous acid molarity and β the degree of ionisation. K_{D1} is the distribution constant for the monomer, *i.e.*, [Monomer in S]/[Monomer in H_2O]. Conformity to the above assumptions leads to a linear plot of K_D against C_W from which K_{D1} and K^S_{12} can be evaluated. Significant deviations from this simple behaviour (usually for $C_W > 1$M) can readily be recognised (Davies and Griffiths, *Z. physikal. Chem.*, in the press). They have been avoided in what follows by considering the data only for those concentration regions, of adequate extent, where the above relation holds. It should be noted that the dimerisation constants (K^S_{12})

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[*] Theory does not suggest that α itself would be temperature-dependent. The most immediately relevant evidence in favour of its constancy is the quantitative agreement of the infra-red values of equilibrium constants and heats of association for a variety of solutes with those determined by osmotic methods (cf., *inter al.*, Mecke, *Discuss. Faraday Soc.*, 1950, **9**, 161, and some half-dozen, as yet unpublished, further examples studied in these Laboratories).

are those for the solvent S saturated with water. Whilst there is an increasing number of examples of the type discussed here in which saturation with water has been proved to have little effect on K^{S}_{12} (Davies and Griffiths, *loc. cit.*; unpublished vapour-pressure lowering, spectroscopic, and distribution data in these Laboratories), what is of immediate interest in the present study is the difference between K^{S}_{12} and, more particularly, ΔH^{S}_{12} values in the wet solvent for different benzoic acid derivatives. However, for benzoic acid in benzene we would specifically indicate that the value of K^{S}_{12} from freezing points in the dry solvent at 5·5° (Barton and Kraus, *J. Amer. Chem. Soc.*, 1951, **73**, 4561) is identical with that evaluated from distribution studies at 6° for the wet solvent, *i.e.*, $6\cdot4 \times 10^{-4}$ mole/l. (Wall, *ibid.*, 1942, **64**, 472). The corresponding ΔH^{S}_{12} values are: for the dry solvent, 8·4 ± 0·4 kcal./mole (Wall and Baines, *ibid.*, 1945, **67**, 898); and for wet benzene, 8·7 kcal./mole (Hendrixson, *Z. anorg. Chem.*, 1897, **13**, 73).

From the distribution data the following values of $10^4 \times K^{S}_{12}$ (mole/l.) are found in benzene at 40°: benzoic acid, 32; *p*-methoxybenzoic acid, 47; salicylic acid, 950; *o*-methoxybenzoic acid, 4360. These results measure the great reduction of association in the *ortho*-compounds. The newly determined equilibrium constants are given in Table 1 where, in addition, ΔH_1 and ΔS_1 are the molar heats and entropies for transferring monomer molecules from water to the organic solvent, and ΔH_{12} and ΔS_{12} are the same factors for the dissociation process per mole of dimer. For comparison, some of Hendrixson's data (*loc. cit.*) are inserted in the Table.

In assessing the contribution of the intramolecular interactions in these data, the *ortho*- and *para*-isomers are the most strictly comparable. Unfortunately, attempts to find a suitable solvent for comparison of the hydroxy-acids failed, since, for those solvents in which the solubility of the *p*-hydroxy-acid was adequate (*e.g.*, di*iso*pentyl ether), the association was too small to be measured.

It might be expected that the partial molar heat contents of the *ortho*- and *para*-isomers would be more nearly equal in aqueous than in organic solutions, as the water will *tend* to break down any intramolecular hydrogen-bonding. This effect is seen in the sign and magnitude of the difference (~1 kcal./mole) in the ΔH_1 values for *p*- and *o*-methoxybenzoic acids. The fact that this difference is not equivalent to the intramolecular bond energy could be most readily explained by assuming that the interaction is only partly suspended for the *ortho*-isomer in water (cf. salicylic acid, p. 137).

A much more certain measure of the intramolecular bonding is provided by the difference in the values of ΔH_{12} for the *ortho*- and the *para*-isomers. If we try the reasonable assumption that in forming the dimer the intramolecular interaction within *o*-methoxybenzoic acid is completely eliminated, the difference in the association energies between *para*- and *ortho*-isomers, *i.e.*, (10·0 − 3·4) kcal./mole of dimer, gives the energy of two intramolecular bonds. This value, 3·3 kcal./mole per bond for wet benzene, agrees well with the direct spectroscopic determination in dry carbon tetrachloride.

A comparison of the ΔH_{12} values for salicylic and benzoic acid in benzene would, in the same way, give 1·4 kcal./mole as the energy of the *ortho*-effect in the former, but the very uncertain status of this value is shown by the almost identical ΔH_{12} values for these acids in chloroform. Apart from the fact that salicylic acid should more properly be compared with its *para*-isomer, there is little doubt that the inconsistency here arises largely from the persistence of some interaction of the phenolic hydroxyl with the adjacent carboxylic group even when the latter is involved in dimerisation. In the methoxy-compound this could not occur, as the only active hydrogen there is (apparently) completely inactivated within the dimer. The existence of a residual *ortho*-interaction in salicylic acid dimer is shown by the absence from its solutions of any absorption near that of a " free " hydroxyl group (Martin, *Nature*, 1950, **166**, 474). The energy of this residual interaction varies from benzene to chloroform solutions.

The influence of the solvent upon the association is well illustrated by the values of 10^4K_{12} for benzoic acid at 35°; in benzene 27; chloroform 210; di*iso*pentyl ether 6200; ethyl benzoate 28,600. The ΔH_{12} values, for both benzoic and salicylic acid, show the same influence, and the variation in these cases is not determined by the dielectric properties (cf. Moelwyn-Hughes *et al.*, *J.*, 1951, 1249). In the oxygenated solvents specific interactions with the acid solutes are involved (Flett, *J. Soc. Dyers Col.*, 1952, **68**, 59) and for salicylic acid the varying intramolecular bonding complicates the relations.

Solubilities.—Our determinations of the solubilities of benzoic and salicylic acids in carbon tetrachloride were made at a number of temperatures from 25° to 55°. At 25° the

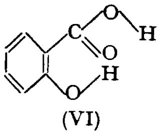
TABLE 1. *Distribution data.*

Solute	Solvent *	Temp. (c)	K_{D1}	10^4K_{12} (mole/l.)	ΔH_1 (kcal./mole)	ΔS_1 (cal./mole °K)	ΔH_{12} (kcal./mole)	ΔS_{12} (cal./mole °K)
$C_6H_5{\cdot}CO_2H$ …………	B	—	—	—	Wall and Baines's data		8·4 ±0·4	15·4 ±1·0
	C	15·00°	3·5$_6$ ±0·1	83±3	1·03 ±0·15	6·1 ±0·7	8·2 ±0·2	18·8 ±0·7
		44·95	4·2$_1$ ±0·1	320±2				
	A	25·00	8·9$_1$ ±0·06	6000 ±140	−2·6 ±0·3	—	0·8 ±0·3	—
		40·00	7·40 ±0·04	6200 ±120				
		55·00	5·96 ±0·04	6700 ±120				
	D	35·05	31·4 ±0·2	28,600 ±500	Only very slight association			
o-$C_6H_4(OH){\cdot}CO_2H$ …	B	10 and 40	—	—	Hendrixson's data		5·6	—
	C	10	2·3	340	Hendrixson's data		7·7	—
		40	2·6	950	0·6 ±0·1	5·8 ±0·5	7·8$_3$ ±0·2	20·6 ±0·7
		15·05	4·21 ±0·06	387				
		35·03	4·50 ±0·05	938				
	E	40·00	0·498 ±0·005	47·7 ±0·9	2·0$_8$ ±0·1	5·2 ±0·3	12·2 ±0·4	28·$_3$ ±1·2
		55·00	0·584 ±0·005	110 ±2				
		70·00	0·671 ±0·005	263 ±4				
	D	35·05	79·3 ±0·8	—	—	No detectable association		
p-$C_6H_4(OH){\cdot}CO_2H$ …	A	25·00	0·409 ±0·003	—	−4·8$_5$ ±0·1	No detectable association		
		55·00	0·194 ±0·001	—				
	D	15·07	5·62 ±0·05	4260 ±300	—	Only very slight association		
o-$C_6H_4(OMe){\cdot}CO_2H$ …	B	40·08	4·40 ±0·05	4360 ±100	−0·45 ±0·1	1·5± ±0·3	3·4$_0$ ±0·2	9·3 ±0·8
		50·00	4·31 ±0·05	4990 ±250				
		60·00	4·23 ±0·05	5770 ±260				
		70·08	4·14 ±0·05	7400 ±400				
p-$C_6H_4(OMe){\cdot}CO_2H$ …	B	40·08	2·90 ±0·05	46·7 ±1·2	0·50 ±0·1	3·7 ±0·3	10·0 ±0·2	21·2 ±0·9
		50·00	2·97 ±0·05	75·5 ±1·5				
		60·00	3·04 ±0·05	117 ±3				
		70·08	3·10 ±0·05	190 ±4				

* A = $(iso\text{-}C_5H_{11})_2O$; B = C_6H_6; C = $CHCl_3$; D = $Ph{\cdot}CO_2Et$; E = CCl_4

values were: for benzoic acid 0·3422 molal (0·0500 mole-fraction unit); and for salicylic acid 0·01910 molal (0·002930 mole-fraction unit). Within the experimental accuracy the temperature variation strictly conformed to $\ln N_S = \Delta S/\boldsymbol{R} - \Delta H/\boldsymbol{R}T$, where N_S is the mole-fraction of solute in the saturated solution and ΔS and ΔH are the molar entropy and enthalpy changes on solution. Accordingly, we have not quoted further individual solubility values but give in Table 2 the ΔS and ΔH values with estimates of the maximum uncertainty in them. For benzene and water good data were already available both for these acids and for the *meta*- and *para*-isomers. These have now been evaluated in the same way: for the aqueous solutions N_S is the mole-fraction of un-ionised solute at saturation. For all the aqueous solutions the apparent heats of solution are markedly temperature-dependent (cf. Davies and Griffiths, *Trans. Faraday Soc.*, 1953, **49**, 1405).

These solubility parameters include variations due to differing extents of association and/or solvation in the saturated solutions, but apart from these variations, the differences between them arise principally from changing interactions in the solid state. It appears that in benzene the heats of solution can be accounted for in simple terms. For the *m*- and *p*-hydroxy-compounds they are 4·0 and 3·3 kcal./mole greater than for benzoic acid. This is clearly an expression of the interaction of the phenolic hydroxyl groups in these cases, *e.g.*, the *p*-hydroxy-acid will be packed in the solid in an array AϕB·BϕA·AϕB·BϕA·, etc., where A is the carboxyl and B the hydroxyl group. Mecke (*Z. Elektrochem.*, 1944, **50**, 57) has determined this hydroxyl–hydroxyl interaction energy (in benzene solutions) as 3·5 kcal./mole for phenol and 4·4 kcal./mole for benzyl alcohol.



(VI)

The heat of solution of salicylic acid in benzene is intermediate between those of benzoic and the *p*-hydroxy-acid. This is qualitatively what would have been expected: the fact that it is not coincident with that of benzoic acid indicates that in such a structure as (VI) the *o*-hydroxy-group, although possibly " bound " in the geometrical sense, can still contribute appreciably to the intermolecular field holding the molecules together in the solid lattice (cf. preceding section). On this basis it would follow that the residual intermolecular contribution of the *o*-hydroxy-group is of the order of (8·6—6·9) = 1·7 kcal./mole in the solid state. Comparison of the values of ΔH(solution) for benzoic and salicylic acid in carbon tetrachloride gives a difference, identical within the possible errors, of 1·4 kcal./mole. Confirmation of this interpretation is provided by the fact that the heat of sublimation of salicylic acid is 1·0 kcal./mole greater that that of benzoic acid (Davies and Jones, *Trans. Faraday Soc.*, 1954, **50**, 1042).

TABLE 2. *Molar heats and entropies of solution.*

Solute	Solvent	Temp., °c	ΔH, kcal./mole	ΔS, cal./mole °K	Ref.*
$C_6H_5{\cdot}CO_2H$	C_6H_6	25—80	6·9 ± 0·1	18·0 ± 0·3	*a*
	CCl_4	25—55	8·05 ± 0·15	21·0 ± 0·5	*b*
	H_2O	5·0	$4{\cdot}5_4$	—	*c*
		22·5	$6{\cdot}2_6$	—	,,
		45·0	$7{\cdot}7_2$	—	,,
		65·0	$9{\cdot}0_5$	—	,,
o-$C_6H_4(OH){\cdot}CO_2H$	C_6H_6	20—65	$8{\cdot}6_2$ ± 0·15	18·1 ± 0·15	*c, d, e*
	CCl_4	25—55	$9{\cdot}4_8$ ± 0·25	20·2 ± 0·8	*b*
	H_2O	5·0	$5{\cdot}9_8$	—	*c*
		22·5	$7{\cdot}2_0$	—	,,
		45·0	$7{\cdot}8_2$	—	,,
m-$C_6H_4(OH){\cdot}CO_2H$	C_6H_5	45—65	10·9	16·4	*e*
	H_2O	5·0	$7{\cdot}7_7$	—	*c*
		22·5	$7{\cdot}3_8$	—	,,
		45·0	$7{\cdot}4_0$	—	,,
		65·0	$9{\cdot}6_2$	—	,,
p-$C_6H_4(OH){\cdot}CO_2H$	C_6H_6	10—80	10·2 ± 0·15	13·3 ± 2·0	*e*
	H_2O	5·0	$7{\cdot}4_8$	—	*c*
		22·5	$8{\cdot}6_7$	—	,,
		35·0	$9{\cdot}4_2$	—	,,
		55·0	$13{\cdot}5_0$	—	,,

* (*a*) Chipman, *J. Amer. Chem. Soc.*, 1924, **46**, 2445. (*b*) Present work. (*c*) Seidell, " Solubilities of Organic Compounds," 3rd edn., Van Nostrand Co., New York, 1940. (*d*) Sidgwick and Ewbank, *J.*, 1921, **119**, 979; Desai and Patel, *J. Indian Chem. Soc.*, 1935, **12**, 131. (*e*) Walker and Wood, *J.*, 1898, **73**, 620.

The markedly varying heats of solution for these acids in water is probably due to the large and temperature-dependent rôle of solvation in that medium. Thus *p*-hydroxybenzoic acid forms a definite hydrate (Sidgwick and Ewbank, *loc. cit.*). The approximate equality and smaller temperature-dependence of the aqueous heats of solution for the *o*-

and *m*-hydroxy-acids suggest that hydration may be less important (or more temperature-independent) in these cases.

The solvent water, even if it does not succeed completely, will certainly tend to break down the intramolecular bonding in salicylic acid. The solubility data, however, give no clear evidence of this.

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THE EDWARD DAVIES CHEMICAL LABORATORIES,
UNIVERSITY COLLEGE OF WALES, ABERYSTWYTH.

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