Journal of Chromatography, 114 (1975) 63–79

CHROM. 8408

DETERMINATION OF COMPLEX ASSOCIATION CONSTANTS FROM GAS CHROMATOGRAPHIC DATA

III. HYDROGEN BONDING BETWEEN SUBSTITUTED ALCOHOLS AND SOME HEXADECYL DERIVATIVES AND DIOCTYL COMPOUNDS

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(First received January 20th, 1975; revised manuscript received April 29th, 1975)

SUMMARY

The equilibrium constants for hydrogen bonding of a series of β-substituted alcohols with a number of monofunctional hexadecyl derivatives and dioctyl compounds have been measured by gas chromatography. For ethanol, propanol and butanol, the enthalpy and standard entropy of hydrogen bonding have also been determined. An analysis is presented on the precision and the accuracy of the data. The acceptor strengths of the proton acceptors are compared on the basis of the enthalpies and standard entropies of hydrogen bonding, and a comparison is made of the enthalpies of inter- and intra-molecular hydrogen bonding with the same proton-acceptor group. The influence of the substituents in the alcohols on the values of the association constants is investigated; evidence is presented for a mesomeric substituent effect, probably caused by intra-molecular hydrogen bonding in the substituted alcohols. It is shown that the effect of intra-molecular interaction of two substituents on partition equilibria is, formally, fully analogous to the effect of intra-molecular interaction between a substituent and the reaction centre on chemical equilibria. By using the mathematical technique of factor analysis, it is shown that the factors governing substituent effects on both types of equilibria are closely related.

INTRODUCTION

The potentialities of gas chromatography (GC) as a method of determining complex association constants have been surveyed by Purnell[1] in a classical paper.

One of us has described a method for the determination of association constants from GC data, wherein the involved equilibria are represented rigorously in terms of activities, and wherein a reference solute is used[2]. This has the advantages that activity coefficients partially cancel and that only relative retention volumes are required.

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This method has now been applied to the study of hydrogen bonding between a series of β-substituted alcohols and a series of monofunctional hexadecyl derivatives and dioctyl compounds. This study forms part of a research programme aimed at giving more insight into the effect of inter-molecular interactions on chromatographic separations.

THEORY

Comparison of various methods for the determination of complex association constants

Hitherto, the most frequently applied methods for the determination of complex association constants of organic complexes are spectroscopy in the infrared (IR), ultraviolet (UV) and visible regions and nuclear magnetic resonance (NMR) spectroscopy.

As there is close analogy between spectroscopic, GC and electrophoretic methods of investigating complex association, a brief comparison of the principles of these techniques is of interest. (More elaborate comparisons were presented by Eon and Guiochon[3] and by Martire[4], and a critical review on GC studies of complexing reactions has been given by Wellington[5].

The simplest case of complex association can be represented as follows:

$$A + B \rightleftarrows AB$$

The equilibrium condition is:

$$K\frac{f_A f_B}{f_{AB}} \equiv K' = \frac{x_{AB}}{x_A x_B} \qquad (1)$$

where K is the association constant, f is the activity coefficient and x is the mole fraction.

To find K, some property (R) of the solution of A, B and AB in the solvent S must be measured, *e.g.*, its absorbance. Usually, this property is additively composed of contributions of A, B and AB, but, by choosing appropriate experimental conditions, *e.g.*, the wavelength of the incident light, the contribution of one of the components (B, say) can be made to vanish. Customarily, this component is used in excess so that its concentration is not appreciably changed by complex association and hence is known. It then holds that:

$$R = R_A\frac{x_A}{x_A+x_{AB}} + R_{AB}\frac{x_{AB}}{x_A+x_{AB}} = R_A\frac{1}{1+K'x_B} + R_{AB}\frac{K'x_B}{1+K'x_B} \qquad (2)$$

The first problem is the calculation of K' from the observed value of R; for this, R_A and R_{AB} must be known.

In NMR[6,7], R is the chemical shift, R_A being the value of R for a solution of A alone. If A shows strong self-association, as in the case of alcohols in apolar solvents, measurements must be performed on very dilute solutions of A; in view of the limited sensitivity of the technique, this can present serious difficulties. The value of R_{AB} is obtained from measurements at high concentration of B. In making these measurements, the composition of the solvent is changed, and this may cause secondary effects. Thus this method has several disadvantages.

In electrophoresis, R is the electrophoretic mobility. The method is comparable with NMR, but few authors have used it[8–12].

Optical spectroscopy[7,13] usually presents a more favourable case. The frequency shifts that appear in the IR spectrum on hydrogen bonding, or in the electronic spectrum on charge transfer, are often so large that a wavelength can be selected at which the complex AB does not absorb. This eliminates the need for measurements at high concentration of B, *i.e.*, at a changed solvent composition.

In GC it holds[2], to the same level of approximation as used in the foregoing, that:

$$\left(\frac{V_A^*}{V_A}\right)_{(S+B)} = \left(\frac{V_A^*}{V_A}\right)_{(S)} \frac{1}{1+K'x_B} \tag{3}$$

where V is the retention volume, corrected for gas hold-up in the apparatus, at the mean column pressure and the column temperature, and A* is a solute that is closely related to A but does not form a complex. A and A* are eluted from columns, the stationary phase of which consists of the solvent S or a mixture of S and the complex-forming compound B.

Comparison of eqns. 2 and 3 shows that, in GC, R and R_A represent a relative retention volume, and that $R_{AB} = 0$. This simple result shows that GC is one of the best methods for determining complex association constants.

Gas chromatographic determination of complex association constants

At a higher level of approximation[2], the left-hand side of eqn. 3 is multiplied by $F = (f_A^*/f_A)_{(S+B)}\,(f_A/f_A^*)_{(S)}$.

Algebraic manipulation then gives:

$$\left\{\left(\frac{V_A}{V_A^*}\right)_{(S+B)} \cdot \left(\frac{V_A^*}{V_A}\right)_{(S)} \cdot F^{-1} - 1\right\} x_B^{-1} = K\left(\frac{f_A f_B}{f_{AB}}\right)_{(S+B)} \tag{4}$$

In the general case, where A, A* and B have a dipole moment, the calculation of F is beyond the reach of theory. However, in the present case, F can be estimated empirically as follows. Littlewood[14] has shown that, for alkanes (alk) and polar solutes (pol) dissolved in hexadecane S or a monofunctional hexadecyl derivative B, the relationship holds that

$$\frac{f_{alk(B)}}{f_{alk(S)}} \cdot \frac{f_{pol(S)}}{f_{pol(B)}} = r_b \approx \exp.\,(a\mu_B\mu^b_{pol}) \tag{5}$$

where r_b is the symbol used by Littlewood, a and b are constants and μ is the dipole moment.

From a statistical analysis of Littlewood's data it follows that $a = 0.029$ and $b = 1.47$.

When eqn. 5 is applied to the polar solutes A and A*, then

$$\frac{f_{A(S)}}{f_{A(B)}} \cdot \frac{f_{A^*(B)}}{f_{A^*(S)}} = F \approx \exp.\,0.029\,\mu_B\,(\mu_A^{1.47} - \mu_{A^*}^{1.47}) \tag{6}$$

It follows from eqn. 5 that, for polar solutes A and A* in hexadecane and polar hexadecyl derivatives, F is governed by the dipole moments of A and A*. As the calculation of the correction factor (F) by eqn. 6 is only an approximation, it is advantageous to choose a reference solute (A*) having about the same dipole moment as A. In the present study, alkyl chlorides were used as reference solutes for the investigated alcohols. The dipole moments of alcohols and alkyl chlorides are about 1.70 and 2.05 D, respectively[15].

We further assumed that eqn. 6 was also applicable to mixtures S+B by multiplying the exponent by x_B, and to bifunctional polar solutes, with $\mu_{\mathrm{pol}}^{1.47} = \mu_1^{1.47} + \mu_2^{1.47}$, where μ_1 and μ_2 are the individual group dipole moments. That is, it was assumed that the two polar groups do not interact mutually.

The next step is the choice of a reference state in which the activity coefficients are by definition equal to 1, and the extrapolation of the right hand side of eqn. 4, determined for a range of mixtures S+B, to this reference state. In this way, the thermodynamic association constant in the chosen reference solvent is found. A plausible reference solvent is pure S or pure B, the former being the best choice from the theoretical point of view. Association constants with a range of B reactants can be compared, as they are all related to the same reference state, S. Further, it can easily be shown that an error in the calculation of F (caused, *e.g.*, by statistical errors in the constants of eqn. 6) has less influence on the calculated value of the association constant in pure S than in pure B. However, in practice, the latter reference state has the advantage that one may limit oneself to measurements on the stationary phases S and B instead of making measurements on a range of mixed stationary phases S+B, as, by definition:

$$\left(\frac{f_A f_B}{f_{AB}}\right)_{(B)} = 1 \tag{7}$$

In this work, the latter convention was chosen, except when B was hexadecyl cyanide; association constants with hexadecyl cyanide were determined both in pure hexadecane and in pure hexadecyl cyanide.

EXPERIMENTAL

Chemicals

The alcohols A, the corresponding alkyl chlorides used as the reference solutes A*, the hexadecyl derivatives, dioctyl compounds and 2-pentadecanone (B) and hexadecane and octadecane (S) were obtained from Fluka. 2-Fluoroethyl chloride and 2-methoxyethyl chloride were synthesized from the corresponding alcohols and thionyl chloride.

Porous Teflon 6 (DuPont, Wilmington, Del., U.S.A.) was used as the support for the stationary phase in order to minimize adsorption.

Apparatus

A Becker gas chromatograph equipped with a katharometer detector and stainless-steel columns (2 m × 4 mm I.D.) were used.

Procedure

To minimize adsorption effects, both at the surface of the support and at the surface of the stationary phase, a rather large amount of the latter (10–12 %) was used (indeed, adsorption could hardly be detected).

All manipulations with the Teflon were made at a temperature of 3–4°, at which the Teflon was no longer sticky (probably as the result of a change to another modification at 8°, as judged by the large heat effect in differential thermal analysis) and reasonably efficient columns could be packed, having a plate height of 1.5 mm.

It was verified that the relative retention volumes V_A/V_A^* were independent of the gas flow-rate.

As also observed by Martire and Riedl[16], the retention volumes of most alcohols and some alkyl chlorides showed fairly strong dependence on the sample size. In our work, the slopes of graphs of retention volume *vs.* sample size were rectilinear over the size range 0.05 to at least 0.3 μl, permitting extrapolation to zero sample size. The slopes seem to be correlated with the difference of the solute boiling temperature and the column temperature.

Measurements were made at 62.6° on all alcohols, and on ethanol, propanol and butanol at about 40° and 80° also. From the data on the latter alcohols, the enthalpy and standard entropy of hydrogen bonding were calculated.

RESULTS AND DISCUSSION

The results are given in Tables I–III.

Precision

From the relative retention volumes for the stationary phases hexadecane and octadecane in Table I, as well as from a number of replicate measurements, it follows that the standard deviation of the relative retention volumes is about 1 %. This results in a standard deviation of the association constants that decreases with increasing value of K; for $K = 0.3, 0.5, 1, 2$ and 4, a standard deviation of 5, 3.5, 2.5, 2 and 1.5 %, respectively, is calculated.

These values agree with estimates from linear least-squares analyses of the data on $Kf_A f_B/f_{AB}$ for mixtures of hexadecyl cyanide and hexadecane: the standard deviation of a single determination in pure B is found to be 2.8, 1.7 and 1.7 % for $K = 1$, 2 and 4, respectively.

From the temperature dependence of the K values of ethanol, propanol and butanol, an average standard deviation of a single determination of K of 4.5 % is found.

The association constants for hydrogen bonding with hexadecyl cyanide are based on least-squares analyses of data for mixed stationary phases S+B and for pure B. In the solvent hexadecyl cyanide, they are more precise by a factor of about 1.2 than single determinations. In the solvent hexadecane, they are less precise by a factor of about 1.3 than single determinations in pure B, because of the involved extrapolation.

The standard deviations of the values of the enthalpy and standard entropy of hydrogen bonding in Table III are equal to 0.2 kcal mole^{-1} and 0.6 cal mole^{-1} deg^{-1}, respectively.

Accuracy

In our opinion, the accuracy of the ratio of relative retention volumes in eqn. 4 is about equal to its precision. However, the coefficients in eqn. 6 (and, therefore,

TABLE I

RELATIVE RETENTION VOLUME V_A/V_A^*, WHERE A IS A β-SUBSTITUTED ETHANOL DERIVATIVE AND A* IS THE CORRESPONDINGLY SUBSTITUTED DERIVATIVE OF ETHYL CHLORIDE, AT 62.6°, AND THE CORRECTION FACTOR, *F*, WITH ITS STANDARD DEVIATION

Solvent	*Substituent*												
	$-H$	$-CH_3$	$-C_2H_5$	$-F$	$-Cl$	$-Br$	$-OCH_3$	$=CH_2$	$-C_2H_3$**	$\equiv N$	$-CN$	$-SCH_3$	F^*
Hexadecane	0.65	0.68	0.70	0.66	0.67	0.68	0.61		0.98	1.22	0.90	0.67	
Octadecane	0.65	0.69	0.70	0.67	0.67	0.68	0.60	0.71	0.97	1.27	0.90	0.66	
Hexadecyl fluoride	0.88	0.90	0.92	0.82	0.95	0.99	0.69		1.28	2.23	1.14	0.83	0.92 ± 0.01
Hexadecyl chloride	0.82	0.84	0.87	0.77	0.87	0.89	0.68		1.22	1.64	1.00	0.79	0.91 ± 0.01
Hexadecyl bromide	0.92	0.95	0.97	0.86	0.97	1.00	0.76		1.37	2.87	1.32	0.88	0.92 ± 0.01
Hexadecyl iodide	0.84	0.86	0.89	0.80	0.88	0.90	0.70		1.27	1.94	1.17	0.83	0.92 ± 0.01
Hexadecyl cyanide (10.2%)	0.79	0.82	0.85	0.83	0.92	0.96	0.68	0.92	1.18	4.55	1.57	0.76	0.98 ± 0.00^2
Hexadecyl cyanide (25.6%)	1.02	1.06	1.09	1.06	1.28	1.35	0.77	1.24	1.50	7.05	2.11	0.98	0.95 ± 0.00^5
Hexadecyl cyanide (50.2%)	1.38	1.41	1.45	1.42	1.73	1.87	0.91	1.65	2.01	9.81	2.92	1.29	0.91 ± 0.01
Hexadecyl cyanide (75.5%)	1.75	1.76	1.81	1.70	2.16	2.33	1.07	2.07	2 49	12.1	3.33	1.55	0.87 ± 0.01^5
Hexadecyl cyanide	2.04	2.10	2.15	1.95	2.52	2.79	1.18	2.30	2.96	13.7	3.67	1.78	0.83 ± 0.02
2-Pentadecanone	2.03	2.09	2.16	2.02	2.66	2.98	1.15		2.97		4.12	1.75	0.88 ± 0.01
Dioctyl ether	1.45	1.51	1.57	1.57	1.77	1.85	0.94		2.06	10.3	3.17	1.26	0.95 ± 0.00^5
Dioctyl ketone	1.82	1.87	1.95	1.75	2.36	2.64	1.03		2.65	12.3	3.47	1.58	0.90 ± 0.01
Dioctyl sulphide	1.07	1.13	1.16	1.16	1.31	1.38	0.87		1.62	7.87	2.47	1.02	0.93 ± 0.00^5
Dioctyl disulphide	0.91	0.94	0.96	0.84	0.99	1.03	0.71		1.35	2.49	1.23	0.87	0.92 ± 0.01
Dioctylmethylamine	2.26	2.33	2.37	2.88	3.78	4.22	1.49		3.32		12.9	3.13	0.97 ± 0.00^5

* Dipole moments from ref. 15 or estimated from data on related compounds.

** Reference solute A*: 3-chloro-1-butene.

TABLE II

ASSOCIATION CONSTANTS OF β-SUBSTITUTED ETHANOL DERIVATIVES AT 62.6°.

In the calculations, the mean of the values of V_A/V_A^* for the stationary phases hexadecane and octadecane was taken as $(V_A/V_A^*)_{(s)}$.

Proton acceptor and solvent	*Substituent*											
	$-H$	$-CH_3$	$-C_2H_5$	$-F$	$-Cl$	$-Br$	$-OCH_3$	$=CH_2$	$-C_2H_3$	$\equiv N$	$-CN$	$-SCH_3$
Hexadecyl fluoride	0.47	0.42	0.44	0.35	0.55	0.60	0.24		0.44	0.95	0.39	0.36
Hexadecyl chloride	0.38	0.34	0.36	0.28	0.43	0.45	0.22		0.38	0.44	0.22	0.30
Hexadecyl bromide	0.55	0.51	0.52	0.43	0.59	0.62	0.37		0.54	1.51	0.61	0.45
Hexadecyl iodide	0.41	0.37	0.38	0.32	0.44	0.45	0.26		0.42	0.69	0.42	0.36
Hexadecyl cyanide	2.82	2.71	2.72	2.55	3.48	3.88	1.33	2.92	2.67	12.2	4.0	2.27
Hexadecyl cyanide*	2.42	2.27	2.36	2.72	3.98	4.36	1.29	3.40	2.33	—**	6.3	2.06
2-Pentadecanone	2.54	2.44	2.50	2.46	3.50	3.99	1.14		2.46		4.20	1.98
Dioctyl ether	1.35	1.31	1.36	1.50	1.78	1.88	0.63		1.23	7.68	2.72	1.00
Dioctyl ketone	2.12	2.00	2.11	1.95	2.93	3.35	0.89		2.04	10.0	3.31	1.65
Dioctyl sulphide	0.77	0.77	0.78	0.88	1.10	1.19	0.54		0.79	5.77	1.96	0.65
Dioctyl disulphide	0.52	0.49	0.50	0.39	0.61	0.66	0.28		0.51	1.17	0.50	0.43
Dioctylmethylamine	2.59	2.51	2.51	3.50	4.84	5.46	1.54		2.54		13.9	3.87

* Solvent: hexadecane.

** Not calculated because of pronounced curvature of the graph of $K(f_A f_B/f_{AB})_{(S+B)}$ *vs.* x_B at low values of the latter.

TABLE III

ENTHALPY AND STANDARD ENTROPY OF HYDROGEN BONDING

Proton acceptor and solvent	*Value of* $-\Delta H^0$ *(kcal mole*$^{-1}$*) when R in* RCH_2CH_2OH *is*			*Value of* $-\Delta S^0$ *(cal mole*$^{-1}$ *deg*$^{-1}$*) when R in* RCH_2CH_2OH *is*		
	$-H$	$-CH_3$	$-C_2H_5$	$-H$	$-CH_3$	$-C_2H_5$
Hexadecyl fluoride	1.7	0.2	2.5	6.6	2.4	9.2
Hexadecyl chloride	1.4	−0.2	2.2	6.2	1.5	8.8
Hexadecyl bromide	1.9	0.8	2.4	6.5	3.5	8.5
Hexadecyl iodide	1.1	0.8	1.9	4.9	4.3	7.8
Hexadecyl cyanide	4.1	2.9	3.4	10.4	6.6	8.3
2-Pentadecanone	3.1	2.7	3.0	7.4	6.0	7.1
Dioctyl ether	3.4	2.1	3.6	9.0	5.3	9.8
Dioctyl ketone	3.0	2.8	3.9	7.3	6.8	10.0
Dioctyl sulphide	2.4	1.6	3.5	7.5	5.1	10.8
Dioctyl disulphide	0.4	−0.2	1.8	2.2	1.0	6.7
Dioctylmethylamine	5.3	5.2	5.8	13.2	12.8	14.7

F) are beset with statistical uncertainty (see the last column of Table I), which manifests itself eventually as a systematic deviation in *K* of the same order of magnitude as its random error. This eventual systematic deviation is relatively unimportant when *K* values for the same proton acceptor are compared.

A serious point concerns the validity of the assumption (made in the calculation of *F* for substituted alcohol–alkyl chloride pairs) that two substituents in the same molecule do not interact mutually: in fact, they do. It is known that a number of β-substituted alcohols form an intra-molecular hydrogen bond when dissolved at low concentration in an apolar solvent[17–21].

Even for unsubstituted alcohols in the *gauche* conformation, where the negatively charged –OH group (an electron-attracting group) is in contact with a positively charged γ-CH_3 or γ-CH_2 group (electron-releasing groups), the enthalpy is lower than in the *trans* conformation. Possibly, a weak hydrogen bond is formed[22,23] (see Fig. 1).

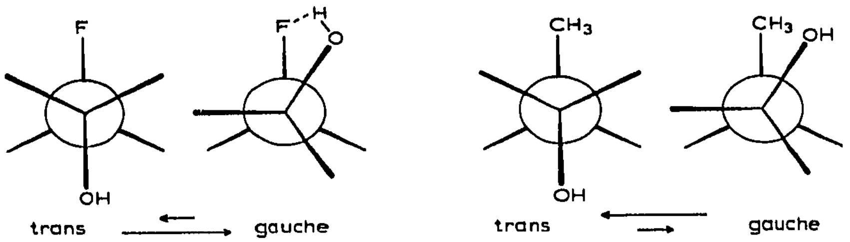

Fig. 1. The *trans*⇄*gauche* equilibria for 2-fluoroethanol (*gauche* conformation internally hydrogen-bonded) and propanol.

As regards alkyl chlorides, the enthalpy of propyl chloride is slightly lower in the *gauche* than in the *trans* conformation, due to attraction between the negative –Cl and the positive $-CH_3$ groups. In substituted alkyl chlorides, the *trans* conformation is favoured, because of steric and electrostatic repulsion of the two negative groups. Table IV shows some interesting data on the conformations of alcohols and alkyl chlorides.

Nothing is known about the influence of the preferred conformation of these compounds on their dipole–dipole interaction with polar solvents, which governs the magnitude of F.

The influence on their interaction with apolar solvents is small, as judged from the relative retention volumes for hexadecane and octadecane in Table I. These are all between 0.6 and 0.7, except for the substituents ≡N and –CN. However, their deviating behaviour can not be caused by differences in conformation of the alcohol and the alkyl chloride, as the former substituent can only occur in one conformation and the latter forms only a weak hydrogen bond with a –OH group.

It will be shown that any errors in F of substituted alcohol–alkyl chloride pairs cause, at most, a standard deviation of 3% in K.

TABLE IV

THERMODYNAMIC DATA ON THE CONFORMATION CHANGE *trans→gauche* FOR β-SUBSTITUTED ALCOHOLS AND ALKYL CHLORIDES, IN CARBON TETRACHLORIDE AND AT 25°, EXCEPT WHERE NOTED OTHERWISE*

Substituent	*Alcohols*			*Alkyl chlorides*
	$-\Delta H^0$ (*kcal mole*$^{-1}$)	$-\Delta S^0$ (*cal mole*$^{-1}$ *deg*$^{-1}$)	K''	$-\Delta H^{0**}$ (*kcal mole*$^{-1}$)
$-CH_3$	0.55	4.0	0.26	0.05
$-C_2H_5$			0.28	
$-C_5H_{11}$	0.44	4.2	0.26	
–F	2.07	3.6	5.2	−0.5
–Cl	1.20	3.9	1.1	−1.2
–Br	1.25	4.7	0.76]	−1.4
–I	0.81	5.1	0.30	
$-OCH_3$	2.20	3.0	8.9	
$=CH_2$			1.2	
$-C_2H_3$			0.59	
–CN	0.14	0.9	0.81	

* See refs. 17–19 and 21–24.

** In the vapour.

Comparison of the proton acceptors

Strictly, the data on the various proton acceptors cannot be compared, as they are related to different reference states. However, these states are so similar that interpretation to a limited extent is possible.

The data in Tables II and III show that hydrogen bonds were formed with all proton acceptors investigated. As far as we are aware, the ability of the disulphide group to act as a proton acceptor has not been demonstrated before. This group, as well as some other investigated groups (sulphide, amine and carbonyl) occurs in proteins, and hydrogen bonding to these groups may be an important factor in stabilizing the conformation of protein molecules in the organism.

From the mean values of the enthalpy data in Table III, the following order of decreasing acceptor strength results: $-NCH_3$, $-CN$, $>CO$, $-O-$, $-C(CH_3)O$, $-S-$, $-Br$, $-F$, $-I$, $-Cl$, $-S_2-$. The mean values of the entropy data in Table III yield the same order of acceptor strength, except for inversion of the $-C(CH_3)O$ and $-S-$ groups.

Comparison of ethanol, propanol and butanol

From the enthalpy and entropy data in Table III, it follows that propanol invariably forms weaker hydrogen bonds than does ethanol or butanol. This leads to smaller association constants for propanol than for ethanol or butanol (see Table II), which is reminiscent of the minimum in the dissociation constants of the carboxylic acids in water for propionic acid[25] and the minimum in the protonation constants of the primary alkylamines in water and ethanol–water mixtures for propylamine[26].

It is tempting to ascribe these phenomena to stabilization of the reactants (propanol, propionic acid and propylamine, respectively) due to a weak electrostatic interaction between the positive $-CH_3$ group and the negative $-OH$, $-COOH$ or $-NH_2$ group in the *gauche* conformation[26]. However, this explanation suffers from two weak points, *viz.*:

(1) It follows from Table IV that the enthalpy of the *gauche* conformation of propanol is 0.55 kcal $mole^{-1}$ lower than that of the *trans* conformation, and that about 20% of the propanol molecules are in the *gauche* conformation. When it is assumed that the *trans* conformation of propanol has the same tendency towards hydrogen-bond formation as does ethanol, it can be deduced from these data that the enthalpy and standard entropy of hydrogen-bond formation for propanol should be 0.11 kcal $mole^{-1}$ and 0.8 cal $mole^{-1}$ deg^{-1}, respectively, higher than the corresponding values for ethanol. The ratio of the association constants should be 0.79. However, it follows from Tables II and III that the actual (mean) effects are much larger: 0.8 kcal $mole^{-1}$, 2.4 cal $mole^{-1}$ deg^{-1} and 0.94, respectively.

(2) In ethanol, interaction between the $-CH_3$ and $-OH$ groups is impossible on steric grounds. For butanol, no data are available on the enthalpy or entropy for the *trans*→*gauche* conformation change. However, from the value of the equilibrium constant for butanol and from the enthalpy and entropy data for heptanol in Table IV, it follows that the *gauche* conformation of butanol and higher homologues is probably stabilized by interaction between the γ-CH_2 and $-OH$ groups to the same extent as with propanol. Thus, it is not clear why propanol should form weaker hydrogen bonds than does butanol.

Comparison of inter- and intra-molecular hydrogen bonding

It is clear that, when an alcoholic species is stabilized by an intra-molecular hydrogen bond in the *gauche* conformation, its ability to form inter-molecular hydrogen bonds must be decreased. A negative correlation between the K values for inter-molecular hydrogen bonding in Table II and the K'' values for the *trans*→*gauche* conformation change in Table IV can be expected; Fig. 2 shows that this result was indeed observed.

It is also instructive to compare the enthalpy of formation of an inter-molecular hydrogen bond in Table III (*e.g.*, for butanol) with the enthalpy of the conformation change *trans*→*gauche* in Table IV for the same proton-accepting group; the latter appears always to be less negative. For the proton-accepting groups $-F$, $-Cl$, $-Br$,

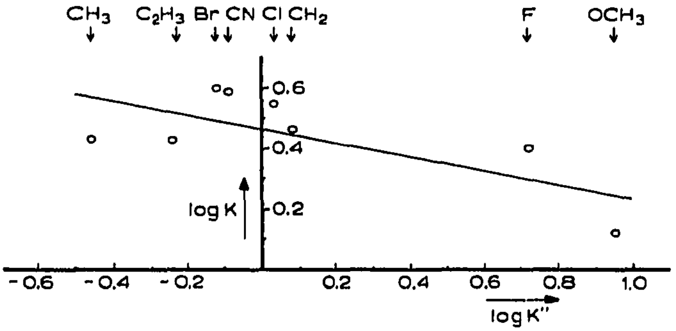

Fig. 2. Negative correlation of log K (for inter-molecular hydrogen bonding, with hexadecyl cyanide as proton acceptor and solvent) and log K'' (for the *trans*→*gauche* conformation change) for β-substituted alcohols.

–I, –OCH_3 and –CN the differences in the enthalpies (for intra- and inter-molecular hydrogen bonding) are 0.4, 1.0, 1.1, 1.1, 1.8 and 3.3 kcal $mole^{-1}$, respectively. A plausible explanation of the observed enthalpy differences is increasing steric strain in the *gauche* conformation. In fact, for the substituents –F, –Cl and –Br the enthalpy differences are about equal to the enthalpies of the conformation change *trans*→*gauche* for the substituted alkyl chlorides, *i.e.*, to the energy increase of the *gauche* conformation due to steric strain. In the case of the –CN substituent, it is probable that in inter-molecular hydrogen bonding its n-electrons are involved, whereas in intra-molecular hydrogen bonding this is sterically impossible and only a weak hydrogen bond with the π-electrons can be formed.

Influence of substituents on the association constants

The influence of substituents on equilibrium constants can often be described by the Hammett[27] equation:

$$\log K/K_{\mathrm{H}} = \varrho\sigma \tag{8}$$

where K_{H} is the equilibrium constant of the unsubstituted compound, ϱ is a parameter that depends only on the reaction (in the present instance: the proton acceptor) and σ is a known constant that depends only on the substituent.

In the present case, the substituents are isolated from the reaction centre by at least one –CH_2 group. Accordingly, they can only have an inductive effect on the electron density in the –OH group, and use of the inductive substituent constants σ_I (see ref. 28) in eqn. 8 seems to be appropriate.

However, Fig. 3 shows that, for two proton acceptors, there is no correlation between log K/K_{H} and σ_I.

Surprisingly, the data can be well described by the Taft equation[29]:

$$\log K = c + \varrho_I\sigma_I + \varrho_R\sigma_R \tag{9}$$

where the last term on the right-hand side accounts for the effect of substituents on resonance structures ("mesomeric" or "delocalization" effects).

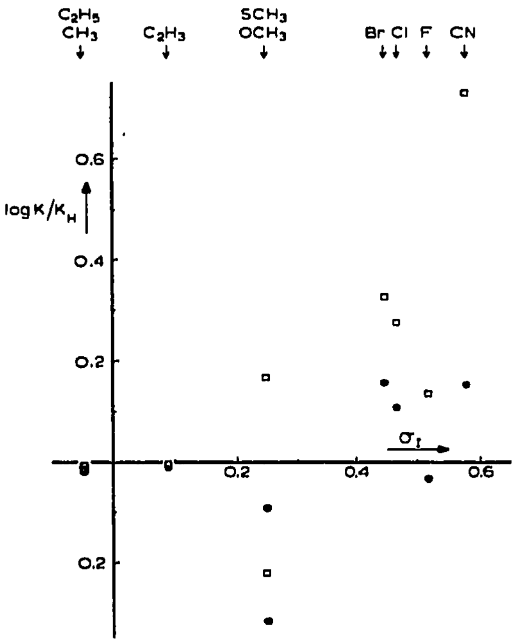

Fig. 3. No correlation of log K/K_H and σ_I. ●, Hexadecyl cyanide (proton acceptor and solvent); □, dioctylmethylamine.

Calculations were made for the substituents $-CH_3$, $-F$, $-Cl$, $-Br$ and $-OCH_3$, for which accurate values of σ_I and σ_R are available.

For the five strongest proton acceptors, the calculated standard deviations of log K ranged from 0.012 to 0.022 (corresponding to standard deviations of 2.5 to 5% in K) and the correlation coefficients were better than 0.998. Even for the weakest proton acceptor (dioctyl disulphide), the standard deviation in log K was better than 0.058.

It is probable that such a good correlation is not fortuitous. Another argument for this belief is the good correlation between c and log K_H (see eqn. 8): $c = 1.12 \log K_H + 0.10$.

The ϱ_I and ϱ_R values are all positive, indicating that the association constants are larger as the substituents are more electron-attracting. The ratio ϱ_R/ϱ_I is 1.3 for dioctyl sulphide and dioctylmethylamine and 2.2 for all other proton acceptors. This shows that the effect of the substituents on resonance structures is fairly important in these hydrogen-bonding equilibria: in the dissociation of *p*-substituted benzoic acids ϱ_R/ϱ_I is only 1.

The positive sign of the ϱ_I values is in accord with other investigations of the influence of substituents on hydrogen bonding[30]. The occurrence of a $\varrho_R\sigma_R$ term and the positive sign of ϱ_R can probably be explained as follows.

As already mentioned, the substituted alcohols are all, more or less, internally hydrogen-bonded. For the hydrogen-bonded structure of, *e.g.*, 2-fluoroethanol*,

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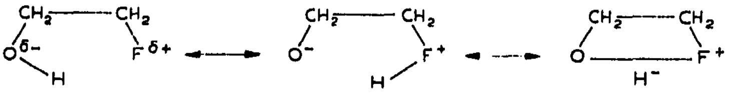
* Recently, the occurrence of hydrogen bonding in the *gauche* conformation of 2-fluoroethanol was challenged[32,33]. In the first paper, it is concluded that "small electronegative atoms, particularly

some of the resonance forms contributing to the stability of the hydrogen bond are as follows[31]:



The stability of these resonance forms increases with the availability of an electron pair on the proton-acceptor group, of which $-\sigma_R$ is a measure. As the stability of the intra-molecular hydrogen bond increases, the association constant for inter-molecular hydrogen bonding will decrease. Thus the latter will decrease with decreasing values of σ_R, hence ϱ_R will be positive,

It is remarkable that the Taft equation describes our data so well. Normally, this equation is used to describe the influence of substituents on a remote reaction centre; here, the substituent is part of the reaction centre.

Finally, all data except those on hydrogen bonding with hexadecyl cyanide in the solvent hexadecane (a somewhat exceptional case) and the incomplete data on the substituents $=CH_2$ and $\equiv N$ were analyzed by the technique of factor analysis by the equation:

$$\log K/K_H = \Sigma_i r_i s_i \tag{10}$$

where both r and s are adjustable parameters, r depending only on the proton acceptor and s only on the substituent[34]. The values of r_1 and s_1 are optimized with a view to explain as much of the variance of the data as possible by the first term r_1s_1. Then, the values of r_2 and s_2 are optimized with a view to explain as much of the residual variance as possible by the second term r_2s_2, and so on. The first term is able to account for 79.8% of the variance, and the second term for an additional 17.4%; further factors add only 1.4, 0.9, 0.3 and 0.2% to the explained variance (see Table V, column 2). Thus, it is probable that 97.2% of the variance in the data is caused by two real physical factors and further mainly by experimental error.

The two factors may be identified with linear combinations of the inductive and mesomeric effects of the substituents.

The 2.8% of unexplained variance corresponds to a standard deviation of 5.5% in K, and the average experimental error has been estimated at 4.5%. This leaves a standard deviation of 3% in K, which can be attributed partly to the inadequacy of eqn. 10 and partly to errors made in the calculation of F for substituted alcohol–alkyl chloride pairs.

F and O, show an overall attractive interaction". This conclusion is based on data on the standard free enthalpy of the conformation change *trans*→*gauche* for a number of substances. These data are interpreted as ΔH values, *i.e.*, the approximation is made that $\Delta S^0 = 0$. However, the third column of Table IV shows that this approximation is unjustified. In the second paper, it is concluded that, in the *gauche* conformation of 2-fluoroethanol, no intra-molecular hydrogen bond is formed, because of the similarity of the NMR chemical shifts of the -OH protons of 2-fluoroethanol and ethanol in dilute carbon tetrachloride solution. Ethanol, of course, can not form an intra-molecular hydrogen bond. However, in dilute carbon tetrachloride solution, it will probably form weak O–H–Cl inter-molecular hydrogen bonds, and it is probable that the chemical shift of the proton in this bridge is similar to that of the proton in an intra-molecular O–H–F bridge.

TABLE V

PERCENTAGE OF THE VARIANCE OF THE DATA ON log K_X/K_H, ON log J_X/J_H AND ON log I_X/I_H, AND OF THE THREE SETS OF DATA TOGETHER, THAT CAN BE EXPLAINED BY SUCCESSIVE FACTORS i IN EQUATION 10 OR 17

i	log K_X/K_H	log J_X/J_H	log I_X/I_H	log K_X/K_H, log J_X/J_H, log I_X/I_H
1	79.8	72.6	83.6	69.3
2	17.4	22.0	9.4	18.4
3	1.4	3.8	6.3	9.2
4	0.9	1.0	0.6	2.0
5	0.3	0.3	0.1	0.6
6	0.2	0.2	0.0	0.3
7	0.0	0.1	0.0	0.2
8	0.0	0.0	0.0	0.0

Influence of substituents on the partition equilibria

Several authors have described chromatographic[35–39] and liquid–liquid partition[40,41] data by the Hammett equation without extracting chemical equilibrium constants from their data first.

Indeed, close analogy exists between partition equilibrium constants and chemical equilibrium constants, as will be demonstrated in the following. Consider the chemical equilibrium:

$$\mathrm{XNY} + \mathrm{R} \rightleftharpoons \mathrm{XNZ} \tag{11}$$

where X is a variable substituent, N a common hydrocarbon skeleton, Y a common reaction centre and R a common reactant. For the equilibrium constant K_X:

$$2.3RT \log K_X = \mu^0_{XNY} + \mu^0_R - \mu^0_{XNZ} \tag{12}$$

where μ^0 is the standard chemical potential.

When X = H, a similar relationship holds, and subtraction gives:

$$\log K_X - \log K_H = \frac{1}{2.3RT}(\mu^0_{XNY} - \mu^0_{HNY} - \mu^0_{XNZ} + \mu^0_{HNZ}) = \Sigma_i r_i s_i \tag{10}$$

For another solvent, a similar relationship holds, and subtraction gives:

$$\begin{aligned}\Delta \log K_X - \Delta \log K_H &= \frac{1}{2.3RT}(\Delta\mu^0_{XNY} - \Delta\mu^0_{HNY} - \Delta\mu^0_{XNZ} + \Delta\mu^0_{HNZ})\\ &= \Sigma_i \Delta r_i s_i\end{aligned} \tag{13}$$

Now, consider the phase equilibrium:

$$\mathrm{XNY(phase\ 1)} \rightleftharpoons \mathrm{XNY(phase\ 2)} \tag{14}$$

For the partition coefficient (P_X) it holds that:

$$2.3RT \log P_X = \Delta\mu^0_{XNY} \tag{15}$$

Subtraction of the similar expression for the case when X = H, gives:

$$\log P_X - \log P_H = \frac{1}{2.3RT}\left(\Delta\mu^0_{XNY} - \Delta\mu^0_{HNY}\right) \tag{16}$$

For the partition equilibrium of XNZ, where Z is another functional group, a similar relationship holds, and subtraction gives:

$$\log \frac{P_{X(Y)}}{P_{X(Z)}} - \log \frac{P_{H(Y)}}{P_{H(Z)}} = \frac{1}{2.3RT}\left(\Delta\mu^0_{XNY} - \Delta\mu^0_{HNY} - \Delta\mu^0_{XNZ} + {}\right.$$
$$\left. + \Delta\mu^0_{HNZ}\right) = \Sigma_i \Delta r_i s_i \tag{17}$$

Equations 13 and 17 appear to be formally identical. The only difference, in practice, is in the nature of the groups Y and Z that one expects to encounter in chemical equilibria and phase equilibria, respectively. In the first case, Y can be transformed into Z by a reversible reaction (*e.g.*, Y = COO^- and Z = COOH): in the second case, this is not required (*e.g.*, Y = OH and Z = Cl), and this may make some difference.

The data in Table I correspond to:

$$\frac{P_{X(Y)}}{P_{X(Z)}} \equiv I_X \tag{18}$$

for partition of β-substituted ethanols (XNY) and ethyl chlorides (XNZ) between the liquid stationary phase and the gas phase.

We can also calculate the corresponding expression for partition between two stationary phases (supposed to be insoluble in each other):

$$\frac{P'_{X(Y)}}{P'_{X(Z)}} = \left(\frac{P_{X(Y)}}{P_{X(Z)}}, \text{solvent } p\right)\left(\frac{P_{X(Z)}}{P_{X(Y)}}, \text{solvent } q\right) \equiv J_X \tag{19}$$

where solvent q is hexadecane and solvent p is one of the polar stationary phases.

So, we can compare the applicability of eqn. 17 for partition between a liquid and a gas (from the values of $\log I_X/I_H$) and for partition between two liquids (from the values of $\log J_X/J_H$), and that of eqn. 10, for the case of hydrogen bonding (from the values of $\log K_X/K_H$). The results of the factor analyses are shown in Table V.

The results on $\log K_X/K_H$ have been discussed in the preceding section: the variance of the data seems to be caused by two real physical factors.

The variance of the data on $\log J_X/J_H$ and $\log I_X/I_H$ seems to be caused by three real physical factors, as the percentage of the variance explained by the third factor is rather large (3.8 and 6.3 %, respectively).

With three factors, eqn. 17 describes the data on $\log J_X/J_H$ and $\log I_X/I_H$ at least as well as eqn. 10 describes the data on $\log K_X/K_H$. The 1.6 and 0.7 % of unexplained variance corresponds with standard deviations of 2.5 % in J_X and 2.3 % in I_X. The experimental error is estimated to be 1.4 % and 1 %, respectively. It follows that the precision of eqn. 17 (with three factors) is 2.1 % in each case .

The three sets of data together can also be described by three factors. This shows that the factors governing the influence of substituents on chemical equilibria and on partition equilibria are closely related.

CONCLUSIONS

As a method for the determination of complex association constants, GC compares favourably with spectroscopic methods.

Hexadecyl derivatives and dioctyl compounds show the following order of decreasing proton-acceptor strength towards alcohols: $-NCH_3$, $-CN$, $>CO$, $-O-$, $-C(CH_3)O$, $-S-$, $-Br$, $-F$, $-I$, $-Cl$, $-S_2-$.

The differences of the enthalpies of intra- and inter-molecular hydrogen bonding of butanol, with the same proton-acceptor group, increase in the order $-F$, $-Cl$, $-Br$, $-I$, $-OCH_3$, $-CN$ from 0.4 to 3.3 kcal $mole^{-1}$, because of steric strain in the intramolecular hydrogen bond.

The association constants of the substituted alcohols can not be described by the Hammett equation, using inductive σ_I substituent constants; this is probably due to intra-molecular hydrogen bonding. A good description can be achieved by the Taft equation using the inductive and resonance substituent constants σ_I and σ_R.

Factor analysis shows that the variance of the data is caused by two factors, which may be identified as linear combinations of the inductive effect of the substituents on inter-molecular hydrogen bonding and their effect on the resonance structures involved in intra-molecular hydrogen bonding.

The effect of the intra-molecular interaction of two substituents on partition equilibria is, formally, fully analogous to the effect of intra-molecular interaction between a substituent and the reaction centre in chemical equilibria. From factor analysis, it follows that, in the present case, three physically significant factors are present. The data can be described with a precision of 2%.

The factors governing the effects of substituents on phase and chemical equilibria are closely related.

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