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Local composition models in pharmaceutical chemistry. II. Differentiation of hydrophobic fragmental constants

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Summary

A method of analysis based on the UNIQUAC model, has been developed to examine in more detail the hydrophobic fragmental constants for three different organic solvent/water systems. The three organic solvents, i.e. 2,2,4-trimethylpentane, chloroform and octan-1-ol, have been chosen to represent different chemical characteristics. This analysis allows one to differentiate fragmental values into a non-specific size term, which is due to the possible arrangment that a fragment has in space, and specific interaction effects both with water and the organic phase. This differentiation of fragmental values permits the design of a universal scale of interaction terms relative to 2,2,4-trimethylpentane as a standard reference solvent. The interaction terms are discussed in terms of proton donating–accepting abilities of both the solvent and the fragment.

Introduction

The distribution coefficient of a solute between two immiscible liquids, K_d, has a use in many areas of science, e.g. toxicology, bioaccumulation studies, chemical engineering, drug design and membrane transport. It has been well recognized that the distribution coefficient can be of fundamental importance in quantitative structure activity relationships (QSAR), as well as being an indicator of the absorption rate of a solute from an aqueous phase to a biological lipid (organic) phase (de Meere, 1985).

Since the measurement of distribution coefficients of solutes can be tedious and difficult (Brändström, 1982; Smith et al., 1975), many attempts have been made to calculate K_d values from simple structural elements. Hansch et al. (1962) were the first to recognize the approximate additive constitutive molecular property of the $\log K_d$ value, which led them to the concept of hydrophobic substituent constants or ¶-value. The parameter ¶ has been defined as:

$$\P_x = \log K_{d,x} - \log K_{d,H} \qquad (1)$$

where $K_{d,x}$ is the distribution coefficient of the derivative and $K_{d,H}$ that of the parent aromatic compound.

By starting with $\log K_d$ values for a large num-

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ber of structures, Rekker used a reductionist approach to calculate hydrophobic fragmental constants (Nijs and Rekker, 1973; Rekker, 1977; Rekker and de Kort, 1979). Their system is based on the following equation:

$$\log K_d = \Sigma a_i \cdot f_i + \Sigma kn \cdot CM \qquad (2)$$

where a is the number of occurrences of fragments f being of type i. In more complex structures, summation of fragments alone can lead to spurious values. The necessary correction is given in the second part of Eqn. 2. This term is given as a discrete number of incidences (i.e. a key number, k_n) of a ‘magic’ constant (CM).

In contrast to the method of Rekker, Leo and Hansch began by using a few carefully measured distribution coefficients for simple structures, and then adapted these derived fragmental constants to larger molecules by means of numerous correction factors (Leo et al., 1975; Hansch and Leo, 1979). Their constructionist approach is given by:

$$\log K_d = \Sigma a_n \cdot f_n + \Sigma b_m \cdot F_m \qquad (3)$$

where F_m is a correction factor, which rather than being a simple multiple of a constant, can have many kinds of different values.

The ¶-concept, as well as the various fragmental systems, are based on empirically established relationships between observed distribution coefficients and the structures of the distributed molecules *alone*. The physicochemical properties of the two liquid phases involved are not explicitly specified in the fragmental systems, which is the reason why the ultimate effect of a particular organic solvent/water system on the distribution process can be evaluated only a posteriori. This characteristic feature of the fragmental systems makes it difficult to reveal the relative importance of the different forces acting during the distribution process on a solute (and consequently on its fragments).

Rekker (1977) has suggested a relation between his magic constant and the clustering of water molecules. Similarly, van der Waterbeemd and Testa (1983) have attempted to describe the correction factors of Hansch and Leo (1979) in terms of hydration phenomena. Both groups considered their view to be in agreement with the classical picture of hydrophobic effects (Frank and Evans, 1945; Tanford, 1973) according to which the main driving force for the transfer of solutes from an aqueous to an organic phase results from the entropy gain consequent upon releasing structured water of solvation into bulk water. This classical view is supported by linear relationships found between distribution coefficients and size parameters of apolar solutes (Testa and Seiler, 1981; Kühne et al., 1981; Bultsma, 1980).

More recently, however, it has been shown that the enthalpic contribution to the transfer of a solute from water to an organic phase can be more important for the distribution process than the corresponding change in entropy (Shinoda, 1977; Abraham, 1980; Riebesehl and Tomlinson, 1984). In addition, no clear relationship has been found between the molar volume of a solute and the entropic change associated with phase transfer (Riebesehl et al., 1984).

Contrary to the hydrophobicity concept, that interactions with water are of decisive importance in the distribution process, some reports indicate that the solvation of a solute in the organic phase is more important than the repulsive interaction with water (Amidon et al., 1975; Cramer, 1977; Kühne et al., 1981).

In order to elucidate these conflicting interpretations of the distribution process, a method of analysis has been designed which clearly accounts for the different factors affecting the distribution of a compound. Firstly, it should be noted that hydrophobic fragmental constants, as suggested by their name, do not represent pure hydrophobic effects, but merely reflect the relative preference of a fragment (and thus a solute) for a particular organic over an aqueous phase. As a consequence, the distribution is dependent upon the physicochemical properties of the organic solvent involved. Rytting et al. (1972) have argued that from a thermodynamic standpoint a nonpolar inert solvent, such as 2,2,4-trimethylpentane (TMP), should provide an appropriate standard for reference purposes. This suggestion has been followed here, and fragmental constants (and its derivatives) referring to octan-1-ol and chloroform as organic phases have been normalized using TMP as a standard reference.

Another problem with the analysis of distribution coefficients is of thermodynamic origin, i.e. K_d values comprise both enthalpic and entropic contributions. Therefore, since fragmental constants are not solely attributable to interactions (the enthalpic part), a finite part of the fragmental value must be ascribed to a factor dependent upon both the size and shape of the fragment itself and the solvents employed. Theoretically, such a nonspecific mixing factor can be considered as a size contribution accounting for the fact that the space available to solvent molecules diminishes upon the introduction of a solute or fragment into the system (Ashworth and Everett, 1960; Wilson and Deal, 1962). The size contribution is independent of the chemical characteristics of the fragments or solvents, and should be accounted for in the fragmental values before these values can be discussed in terms of specific interaction terms. In this present study, an estimation of the magnitude of the size effect on a fragmental value is obtained by using the UNIQUAC model (Abrahams and Prausnitz, 1975). The calculated size contribution refers to a hypothetical distribution process without fragment–solvent interactions. The contributions of specific solvation forces are subsequently derived by subtracting the size contributions from experimental fragmental values.

Such a method of analysis allows both mixing and interaction effects to be distinguished, and specific solvation effects in water, chloroform and octan-1-ol relative to TMP to be studied. Therefore, such an approach should provide a better understanding of the nature of the different forces responsible for a phase transfer of a solute or a fragment thereof.

Method of Analysis

The thermodynamic distribution coefficient K_d^x of a solute (component i) between water and an organic solvent on the mole fraction scale is given by:

$$K_d^x = x_i'/x_i = \gamma_i/\gamma_i' \quad (4)$$

where x and γ represent the mole fraction and activity coefficient (based on Raoult's law), respectively. Quantities in the organic phase are indicated by primes.

According to the UNIQUAC model (Abrahams and Prausnitz, 1975), the activity coefficient of component i in a mixture is composed of a combinatorial part of entropic origin, arising from the arrangments of molecules in space and a residual part which reflects the energetic interaction between component i and its neighbouring molecules, i.e.

$$\ln \gamma_i = \ln \gamma_{\mathrm{comb},i} + \ln \gamma_{\mathrm{res},i} \quad (5)$$

where

$$\ln \gamma_{\mathrm{comb},i} = \ln \frac{\Phi_i}{x_i} + \left(\frac{z}{2}\right) q_i \ln \frac{\theta_i}{\Phi_i} + l_i - \frac{\Phi_i}{x_i} \sum_j x_j l_j \quad (5a)$$

and

$$\ln \gamma_{\mathrm{res},i} = -q_i \ln\left(\sum_j \theta_j \tau_{ji}\right) + q_i - q_i \sum_j \frac{\theta_j \tau_{ij}}{\sum_k \theta_k \tau_{kj}} \quad (5b)$$

with

$$l_j = (z/2)(r_j - q_j) - (r_j - 1) \quad (5c)$$

$$\tau_{ij} = \exp\{-(u_{ij} - u_{jj})/RT\} \quad (5d)$$

$$A_{ij} = (u_{ij} - u_{jj})/R \quad (5e)$$

$i = 1,3 \; j = 1,3$

and where the average area θ and volume fractions Φ are defined by:

$$\theta_i = \frac{q_i x_i}{\sum_j q_j x_j} \quad (5f)$$

$$\Phi_i = \frac{r_i x_i}{\sum_j r_j x_j} \quad (5g)$$

In these equations z represents a lattice coordination number, which is usually set equal to 10. The structural parameters r_i and q_i are (relative) measures of the van der Waals volume and area of molecule i, respectively. The interaction energy u_{ij} between two neighbouring molecules i and j are taken into account by $\ln \gamma_{i,res}$, using the interaction parameters A_{ij} and A_{ji} per pairwise interaction.

Note that the combinatorial part of Eqn. 5 is dependent upon volume and area fraction only, whilst the residual part is a function of the area fraction and the interaction parameters, but not of the volume fraction. Therefore, the combinatorial part of the activity coefficient can be calculated a priori from a knowledge of the composition of the system and the structural parameters of the components. Residual contributions can only be calculated when reliable values for the interaction parameters, A_{ij} and A_{ji}, are available. The latter are always derived from experimental data. A compilation of the available interaction parameters is given by Sørensen and Arlt (1980). The interaction parameters used in this study are given in Table 1.

The distribution coefficient (molar concentration scale), K_d, is readily obtained by taking the solute activity coefficients at infinite dilution (γ^{∞}), i.e. the limit for $x_i \rightarrow 0$. The molar distribution coefficient becomes (Grünbauer and Tomlinson, 1984):

$$\log K_d = \log \gamma_i^{\infty} - \log \gamma_i'^{\infty} + C \tag{6}$$

where the conversion factor is given by:

$$C = \log\{(r_1 x_1 + r_2 x_2)/(r_1 x_1' + r_2 x'_2)\} \tag{6a}$$

and where subscripts 1 and 2 refer to water and the organic phase, respectively.

Combining Eqns. 5 and 6 it can be seen that the distribution coefficient is composed of a part due to the arrangments of molecules in space and of a residual contribution, which arises from the difference in interaction of the compound with water and the organic solvent.

Similarly, a hydrophobic fragmental constant f_i can be given by:

$$f_i = f_{size,i} + f_{res,i} \tag{7}$$

In Eqn. 7 $f_{size,i}$ represents the contribution of fragmental size to the transfer process of a fragment from water to organic solvent.

The residual fragment constant, $f_{res,i}$, is given by:

$$f_{res,i} = \frac{-(\mu_{res,i} - \mu'_{res,i})}{2.303\ RT} \tag{8}$$

Eqn. 8 states that the residual fragmental value is dependent upon the difference in free energy, $\mu_{res,i}$, due to the interaction of the fragment in the aqueous and organic phase. If we assume that the free energy of a fragment in TMP is not the result of specific interactions, such as H-bond formation or dipole–dipole interactions (Taft et al., 1985), then the TMP phase can be used as a reference. As a consequence the residual fragmental values of a TMP/water system give an indication of the specific aqueous interaction terms. For solvent/water systems with negligible solubility on the mole fraction scale of the organic solvent in water, the free energy of a fragment in water is independent of the organic solvent, i.e. the aqueous interaction term of those solvent/water systems can be taken from the TMP/water system. A fragmental constant then can be given by:

$$f_i = f_{size,i} + f_{w,i} + f_{o,i} \tag{9}$$

Eqn. 9 offers a means to differentiate a fragmental value into a size term and aqueous, $f_{w,i}$, and organic, $f_{o,i}$, interaction terms relative to the free energy of a fragment in TMP. The difference between the experimental determined fragmental value for a TMP/water system and the calculated

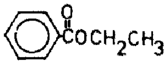
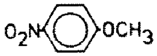
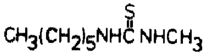
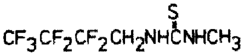
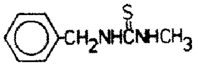
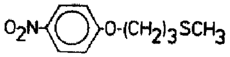
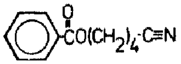
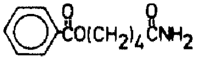
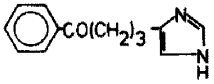
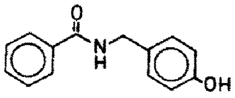
TABLE 1

INTERACTION PARAMETERS, A_{ij}, AND MOLE FRACTION SOLUBILITY

Water(1)	A_{12}	A_{21}	x_1'
TMP	498.64	1283.1	0
$CHCl_3$	356.84	793.15	$5.86.10^{-3}$
Octan-1-ol	295.79	193.59	0.207

TABLE 2

DISTRIBUTION COEFFICIENTS

Compound no.	Structure	log K_d		
		TMP [a]	$CHCl_3$	Oct. [b]
1		2.34	2.89	2.64 [c]
2		1.32	3.18	2.03 [c]
3		−1.76	1.00	0.86 [c]
4		−1.10	1.54	
5	 $CH_3(CH_2)_5NH\overset{S}{C}NHCH_3$	−0.94	2.36	2.31
6	 $CF_3CF_2CF_2CH_2NH\overset{S}{C}NHCH_3$	−1.17	1.25	1.99
7		−1.12	2.23	2.67
8		−2.13	1.45	
9		1.85	2.96	3.24
10		1.03	3.10	2.04
11		−2.53	2.00	0.93
12		−1.84	2.49	1.10
13		−3.11	0.68	0.97
14		−2.13	1.68	1.39
15		−1.92	1.99	
16		−2.61	0.68	1.87

[a] TMP = 2,2,4-Trimethylpentane.

[b] Oct. = Octan-1-ol.

[c] Literature values.

size fragmental constant is a measure of the specific interaction of the fragment with water. Subtracting the aqueous interaction term and the size part of a fragment from the fragment values for other organic/water systems provides a quantity of the interaction term of the fragment with a particular organic solvent relative to TMP as a standard reference.

Although the differentiation of the fragment values into aqueous and organic interaction terms suffers from the same limitations which apply to the fragmental constant system, it offers a convenient way of unravelling the relative importance of the different forces acting in the distribution process. This method of analysis results in the development of a universal scale of interaction terms of fragments with solvents relative to TMP as a standard reference. This makes it possible from a knowledge of the distribution coefficients to characterize any organic solvent in terms of interactions.

Experimental

The compounds used in this study, together with the values of the distribution coefficients for different organic solvents are given in Table 2. Compound 2 is from Fluka (ex. Hicol b.v. Rotterdam, The Netherlands), compound 3 from Janssen Chemicals, (Beerse, Belgium) and compound 4 from Pfaltz and Bauer, (ex. Rijnland Industrie en Handelmij, Capelle a/d IJssel, The Netherlands) and all other compounds have been kindly synthesized and supplied by ICI Pharmaceuticals Division (Macclesfield, U.K.). All these compounds have been used as received.

The distribution coefficient of every solute between the aqueous buffer phase (phosphate buffer, pH 7, having an ionic strength of 0.01 mol · dm^{-3}, except for compound 15 ($pK_a = 7.35$) where a borate buffer (pH 9.3) was used) and TMP or $CHCl_3$ was determined by a shake flask method at 298.2 K in 6-fold at three different concentrations. The relative standard deviations of the values presented in Table 2 varied by less then 5%. The available values for octan-1-ol were measured by Leahy et al. (1985).

The r and q parameters of Eqn. 8 are defined as the van der Waals volumes (cm^3 · mol^{-1}) and the Van der Waals area (cm^2 · mol^{-1}) as given by Bondi (1968) divided by 15.17 and 2.5.10^9, respectively. The r and q parameters of the fragments are presented in Table 3. The fragment parameters indicated have been estimated from the values given in the study by Testa and Seiler (1981), in

TABLE 3

RELATIVE VOLUME (r) AND AREA (q) PARAMETERS

Fragment	r	q	q/r
C_6H_5	3.022	2.13	0.706
C_6H_4	2.856	1.86	0.651
CH_3	0.901	0.85	0.941
CH_2	0.674	0.54	0.801
CH	0.447	0.23	0.510
C	0.220	0 [b]	0
H	0.227	0.31	1.368
$CF_3CF_2CF_2$	3.427	3.22	0.940
$CH_3CH_2CH_2$	2.250	1.93	0.857
$C_6H_4NO_3$ [a]	4.066	2.98	0.733
(ar)NO_2	0.999	0.90	0.905
(al)CN	0.969	0.88	0.904
(al)S	0.712	0.52	0.730
(al)NH	0.533	0.40	0.744
(ar)NH_2	0.695	0.70	1.002
(ar)O	0.211	0.22	1.024
(al)O	0.244	0.24	0.984
(al)OH	0.530	0.58	1.102
(ar)OH	0.530	0.58	1.102
(al)CO	0.771	0.64	0.839
(ar)CO [c]	0.706	0.53	0.756
(ar)CO_2	1.002	0.88	0.878
(al)CO_2H [c]	1.277	1.11	0.866
(ar)CO_2H [c]	1.242	1.08	0.866
(al)CONH [c]	1.174	0.92	0.778
(ar)CONH [c]	1.138	0.88	0.776
(al)$CONH_2$	1.450	1.24	0.857
(al)NHCSNH	2.276	1.95	0.856
(al)SO	1.024	0.78	0.758
(al)SO_2	1.338	1.04	0.777
(al)SO_2NH_2 [c]	1.958	1.61	0.820
Pyridinyl	2.833	1.72	0.607
Water	0.92	1.4	1.52
TMP	5.846	5.01	0.857
$CHCl_3$	2.87	2.41	0.839
Octan-1-ol	6.152	5.21	0.847

[a] *p*-Nitrophenoxy.

[b] A value of 0.001 has been used in the calculation of the size fragment.

[c] Estimated from the parameters of Testa and Seiler (1981).

which they found a linear relationship between their size parameters and those of Bondi.

Results

The main concern in the analysis of hydrophobic fragmental constants is to obtain a set of reliable values. Such a set has been given by Hansch and Leo (1979) for the octan-1-ol/water solvent pair and has been deduced from over 1000 data points by Rekker and de Kort (1979) for octan-1-ol/water fragmental values. The values given by Leo have been used in his computer program for calculating distribution coefficients (CLOGP). Since the source of distribution coefficients material for chloroform and TMP is much smaller than that for octan-1-ol, the fragment values for those systems are less reliable. The fragment values for chloroform have been obtained from Rekker (1977), and his recent unpublished hydrocarbon fragment listing has been assumed applicable to TMP (Seiler, 1974).

The fragment values are given in Table 4. Fragment values which are not available in the literature have been deduced from the log K_d values of the compounds and will be discussed in more detail.

The fragmental constants of Leo (CLOGP) are not interchangeable with the values of Rekker, due to the different basis of calculation arising from the introduction of Leo's bond factor $F_b = -0.12$. The alkyl fragment values of Table 4 all incorporate the F_b term for ease of comparison.

It is a prerequisite of this treatment that for compounds from which polar fragments are to be deduced, there must be no intramolecular interactions. Furthermore, the hydrocarbon values must be soundly based. For octan-1-ol and TMP Rekker's fragmental hydrocarbon values are considered acceptable, but those for chloroform have been re-assessed. From the log $K_d = 2.80$ and 3.41 for benzene and toluene, respectively, a value of $f(C_6H_5) = 2.6$ and $f(C_6H_4) = 2.4$ can be deduced for the $CHCl_3$/water system. Since alkyl f-values in hydrocarbon solvents are unlikely to be exceeded for any other system, the $f(CH_3)$ in chloroform/water appears to be overestimated. To counter this the $f(CH_3)$ and f(CH) values determined in chloroform/water have been simply scaled to fit to $f(CH_2)$ — i.e. the most soundly based value of all f-values. Because of the above approximation of the alkyl fragments for chloroform all the experimental deduced polar fragments are rounded off to ± 0.05.

An additional argument, in favour of the hypothesis that the alkyl f-values are largest in hydrocarbon solvents, arises from the fact that Hildebrand-Scatchard solubility parameter of $CHCl_3$ is larger than that of TMP (Barton, 1983).

From compound 1 values of $f(ar)CO_2$ of -1.27 and -1.1 have been obtained for TMP and $CHCl_3$, respectively. The value for TMP seems to be more reasonable than the value quoted by Rekker for hydrocarbon solvents (i.e. -0.739), since the ester group, being a proton acceptor, should have a less negative value towards $CHCl_3$ than towards TMP. Thus, this value has been used throughout the present study. The values of f(al)CN have been deduced from compound 10. Further, the values of f(ar)CONH deduced from compounds 3 and 4 are quite similar, and from compounds 5 and 8 a value for f(al)NHCSNH of -5.68 and -5.74 for TMP, and -2.25 and -2.5 for $CHCl_3$ can be obtained. Anomalous values do arise, however, from adamantyl thiourea (7), which gives rise to a f(al)NHCSNH value of -7.01 and -3.6 for TMP and $CHCl_3$, respectively. These values probably arise from an overestimation of the value for the hydrocarbon moiety, resulting from an inadequacy of Rekker's system to be able to account for branching.

The f value of perfluoropropyl (compound 6) can be determined from the f(al)NHCSNH values obtained from compounds 5 and 8. However, since compound 6 does not fulfil the requirements of having no intramolecular electronic interactions the NHCSNH fragment will be more positive, because of the electron-withdrawing effect of the heptafluorobutyl group. The value for perfluoropropyl, obtained by Leo with octan-1-ol/water as solvent pair, required a complicated process for calculating an interaction term in multihalogenated species. His value, derived from a large number of compounds, is regarded as being realistic. From compound 6 a fragment value of

TABLE 4

FRAGMENT VALUES

Fragment	Octan-1-ol		TMP Rekker	$CHCl_3$ Rekker
	Leo [a]	Rekker		
C_6H_5	1.855	1.840	2.164	2.348
				2.6 [c]
C_6H_4	1.628	1.658	1.946	2.123
				2.4 [c]
CH_3	0.756 [b]	0.701	0.833	0.965
				0.8 [c]
CH_2	0.529 [b]	0.519	0.615	0.628
				0.6 [c]
CH	0.302 [b]	0.337	0.397	0.163
				0.4 [c]
C	0.195 [b]	0.155	0.179	0.2 [c]
H	0.227	0.182	0.218	0.2 [c]
$CF_3CF_2CF_2$	2.10	1.47	3.06 [c]	2.1 [c]
			(2.6) [c]	(1.6) [c]
$CH_3CH_2CH_2$	1.934	1.739	2.063	2.0 [c]
$C_6H_4NO_3$ [d]	1.27 [c]	1.33 [c]	0.5 [c]	2.4 [c]
(ar)NO_2	−0.03	−0.05	−0.704	0.279
(al)CN	−1.27	−1.04	−1.804	−1.13
			−2.32 [c]	−0.8 [c]
(al)S	−0.79	−0.51	−1.32 [c]	−1.95 [c]
	−0.31 [c]	−0.35 [c]		
(al)NH	−2.15	−1.814	−2.648	−2.386
(ar)NH_2	−1.00	−0.842	−2.149	−0.981
(ar)O	−0.61	−0.439	−0.758	−0.25
(al)O	−1.82	−1.581	−1.688	
(al)OH	−1.82	−1.470	−3.560	−2.367
(ar)OH	−0.44	−0.314	−2.94	−2.049
			−2.58 [c]	−2.57 [c]
(al)CO	−1.90	−1.643	−2.323	−1.14
(ar)CO	−1.09	−0.776	−1.393	−0.818
(ar)CO_2	−0.56	−0.384	−0.739	
			−1.27 [c]	−1.1 [c]
(al)CO_2H	−1.11	−0.938	−3.862	−2.485
(ar)CO_2H	−0.03	−0.071	−2.932	−1.849
(al)CONH	−2.71	−2.446	−5.550	
(ar)CONH	−1.81	−1.579	−4.78 [c]	−2.4 [c]
			−4.71 [c]	−2.35 [c]
(al)$CONH_2$	−2.18	−1.975	−5.022	−2.98
			−5.48 [c]	−2.2 [c]
(ar)$CONH_2$	−1.26	−1.108		−2.21
(al)NHCSNH	−1.97 [c]	−1.69 [c]	−5.68 [c]	−2.25 [c]
			−5.74 [c]	−2.5 [c]
			−7.01 [c]	−3.6 [c]
(al)SO	−3.01	−2.75		
		−2.66 [e]	−5.70 [c]	−2.9 [c]
(al)SO_2	−3.05	−2.49 [e]	−5.01 [c]	−2.4 [c]
(al)SO_2NH_2	−2.4	−1.92 [e]	−5.45 [c]	−3.4 [c]
Pyridinyl	0.42	0.52	−0.495	0.899
Imidazolyl	−0.28	−0.08	−4.66 [c]	−1.3 [c]

[a] Values used in CLOGP program.

[b] Corrected with bond factor $F_b = -0.12$.

[c] See discussion in text. Literature values are all those not otherwise indicated.

[d] *p*-Nitrophenoxy.

[e] Calculated by difference and incorporating a correction of +0.16 to compensate for an inadequacy in the system of Rekker to

f(al)NHCSNH of −1.495 can be predicted using the perfluoropropyl fragment value obtained by Leo — which is +0.48 units greater than the value obtained from compound 5. Hence, it is suggested that the perfluoropropyl f-values for TMP and $CHCl_3$ should be adjusted to 2.6 and 1.6, respectively.

The f-values for (ar)OH have been obtained from compound 16. However, it should be noted that the value of f(ar)CONH used in this calculation may need some adjustment for its benzylic position. The f(al)$CONH_2$ value has been deduced from compound 14.

Using the (revised) f-values of Rekker for *p*-nitroanisole (compound 2) a log K_d value of 1.32 (found 1.32) for TMP and 3.23 (found 3.18) for $CHCl_3$ can be calculated. Remarkably, there is an apparent absence of an electron interaction term, which for the octan-1-ol/water system is +0.16 (= 2.03−1.87). Further, the fragment value for *p*-nitrophenoxy, (which appears in many compounds), is directly calculated from *p*-nitroanisole. Finally, the fragmental values of (al)S, (al)SO, (al)SO_2, (al)SO_2NH_2, and imidazolyl have been deduced from compounds 9, 11, 12, 13 and 15, respectively, upon using the fragmental value of *p*-nitrophenoxy.

Discussion

The calculated size parts of the fragmental values, f_{size}, for the three organic solvent/water systems are given in Table 5, from which it becomes clear that the hypothetical distribution coefficient of a fragment in the absence of interactions is not related to the chemical characteristics of the fragment. For example, the size fragmental value in the chloroform/water system of CH (0.227) nearly equals the value of (al)SO_2 (0.229). An interesting feature is that with increasing size parameters, as from −C to CH_3, the size fragment values decrease. However, as shown for propyl, since an alkyl group consists of CH_3 and CH_2 units having opposing signs, an alkyl group will not necessarily exhibit a smaller size fragment value than that of CH_3. It can readily be seen that with increasing chain length the size fragmental values of hydrocarbons become larger. A closer investigation of the results reveals that the magnitude of a size fragment is not only determined by the absolute size (area or volume) of that fragment, but is dependent also upon the ratio of area-to-volume. For fragments with comparable volumes an increase in the size fragmental value is observed at a decrease of the area to volume ratio. In addition, the size fragmental values are largest for the organic solvent/water systems with the lowest area-to-volume ratio of the organic solvent. The size fragmental values for octan-1-ol and chloroform/water given in Table 5 are composed partly of small, but finite, interaction terms, which result from the slight mutual solubility of the solvents and tend to increase the size fragmental values (see Eqn. 5b).

In general, the size fragment values contribute significantly to the apolar fragmental values, whereas for polar functional groups the size values are not significantly different from zero. This means that the polar fragmental values represent principally interaction effects.

The large negative size fragmental value for the perfluoroalkyl fragment might result from an inadequacy of the system of Bondi (1968) to calculate the volume and the area of this fragment correctly. Using van der Waals radii compiled by Allinger (1976) r and q parameters of 4.32 and 3.42, respectively, can be calculated, which will result in an even positive size fragmental value of 0.26.

The aqueous interaction fragmental values can be calculated from the fragmental values obtained in TMP/water, and these are denoted in Table 5 by f_w. Since the values are referred to TMP as a standard reference, with no specific interactions, then a positive value indicates a hydrophobic interaction, whereas a negative sign indicates a hydrophilic interaction. As expected, the hydrophobicity for apolar fragments increases with increasing size parameters from −C to CH_3. However, the hydrophobic interaction term for the fragment −C nearly equals zero. Therefore, it appears that the apparent hydrophobic fragment value of C merely results from its size contribution, and not from any hydrophobic interaction/effect. This seems reasonable, since a quaternary

TABLE 5

DIFFERENTIATION OF FRAGMENT VALUES INTO SIZE AND AQUEOUS-ORGANIC INTERACTION TERMS

fragment	f_{size}			f_w	f_o		I_H [c]	H-bond [d]
	TMP [a]	Oct [b]	$CHCl_3$		$CHCl_3$	Oct [b]		
C_6H_5	0.50	0.60	0.80	1.66	0.14	−0.43		
C_6H_4	0.67	0.75	0.95	1.28	0.18	−0.37		
CH_3	−0.12	−0.07	−0.03	0.95	−0.11	−0.18		
CH_2	0.03	0.06	0.10	0.58	−0.05	−0.12		
CH	0.18	0.19	0.23	0.21	−0.04	−0.07		
C	0.23	0.23	0.25	−0.05	0.00	−0.02		
H	−0.15			0.37				
$CF_3CF_2CF_2$	−0.43	−0.25	−0.12	3.03	−1.32	−0.68		
$CH_3CH_2CH_2$	−0.05	0.05	0.16	2.12	−0.22	−0.43		
$C_6H_4NO_3$ [e]	0.54	0.68	0.93	−0.04	1.41	0.69		
(ar)NO_2	−0.08	−0.03	0.01	−0.62	0.89	0.60	0.45	−0.30
(al)CN	−0.08	−0.03	0.01	−2.24	1.43	1.23	0.23	−0.37
(al)S	0.09	0.12	0.16	−1.42	−0.70	0.95		
(al)NH	0.06	0.08	0.11	−2.71	0.21	0.81	0.61	−0.54
(ar)NH_2	−0.14	−0.10	−0.08	−2.00	1.11	1.26	1.18	−1.65
(ar)O	−0.05	−0.04	−0.03	−0.71	0.49	0.31		−0.91
(al)O	−0.04	−0.03	−0.02	−1.64		0.09	0.11	−0.84
(al)OH	−0.17	−0.14	−0.13	−3.39	1.15	2.06	1.82	−3.42
(ar)OH	−0.17	−0.14	−0.13	−2.61	−0.02	2.40	2.60	−3.42
(al)CO	0.01	0.04	0.08	−2.41	1.19	0.72		−0.58
(ar)CO	0.07	0.10	0.14	−1.47	0.51	0.59	0.31	−0.58
(ar)CO_2	−0.05	−0.00	0.04	−1.22	0.08	0.84		−0.58
(al)CO_2H	−0.04	0.02	0.07	−3.82	1.26	2.87	2.88	−2.02
(ar)CO_2H	−0.04	0.02	0.07	−2.89	0.97	2.80	2.87	−1.65
(al)CONH	0.09	0.13	0.20	−5.64		3.06	2.56	
(ar)CONH	0.09	0.13	0.20	−4.84	2.24	3.13		
(al)$CONH_2$	−0.03	0.03	0.10	−5.45	3.34	3.44		
(al)NHCSNH	−0.05	0.05	0.16	−5.66	3.13	3.92		
(al)SO	0.10	0.14	0.20	−5.80	2.70	3.00		
(al)SO_2	0.10	0.16	0.23	−5.11	2.48	2.47		
(al)SO_2NH_2	0.05	0.13	0.23	−5.50	1.87	3.45		
Pyridinyl	0.82	0.89	1.10	−1.31	1.12	0.94		
Imidazolyl [f]				(−4.66)	(3.4)	(4.6)		

[a] 2,2,4-Trimethylpentane.

[b] Octan-1-ol.

[c] Hydrogen bonding parameter of Seiler (1974).

[d] H-bond parameters calculated by dividing the parameters of Hansen and Beerbower (1971) by 5707 (= 2.303 · RT).

[e] *p*-Nitrophenoxy.

[f] The r and q parameters have not been estimated.

C is never exposed to solvent.

In Table 6 a collection of linear regression equations are given for the relationships between fragmental values or aqueous interaction terms and size parameters. As suggested by the UNIQUAC model, the hydrophobic interaction terms of the apolar fragments are correlated better with the (relative) van der Waals areas than with the (relative) volumes of the fragments. If the aromatic fragments C_6H_5 and C_6H_4 are excluded from the regression analysis, (since there might be hydrophilic interactions between water and the aromatic ¶-cloud), the statistics of the regression equation are improved. These results suggest that apolar

TABLE 6

LINEAR REGRESSION ANALYSIS OF (AQUEOUS INTERACTION) FRAGMENTAL VALUES WITH SIZE PARAMETERS

Dependent variable	Independent variable	Slope ± S.E.	Intercept ± S.E.	n	r	s
Apolar						
f_w	q	0.888 ± 0.080	0.036 ± 0.128	9	0.9727	0.249
f_w	q	0.968 ± 0.044	0.052 ± 0.064	7	0.9949	0.124
f_w	r	0.682 ± 0.129	0.065 ± 0.256	9	0.8944	0.471
f	q	0.854 ± 0.065	0.174 ± 0.104	9	0.9806	0.200
f	r	0.718 ± 0.045	0.105 ± 0.089	9	0.9868	0.166
Polar						
f	r	−2.455 ± 0.565	−0.785 ± 0.625	21	0.7058	1.297
f	q	−2.825 ± 0.725	−0.831 ± 0.677	21	0.6668	1.354
f_w	r	−2.493 ± 0.576	−0.736 ± 0.636	21	0.7048	1.310
f_w	q	−2.834 ± 0.744	−0.813 ± 0.696	21	0.6579	1.391

fragments exhibit the same mechanism of interaction with water, which most likely can be ascribed to hydrophobic hydration (Rouw, 1982).

In an attempt to establish a relationship between size parameters and hydrophobic fragmental constants, Testa and Seiler (1981) were unable to factor out a size contribution from the fragmental values and therefore needed to force the relation through the origin. However, the present analysis clearly shows that the relationships between the total fragmental values and size parameters lead to a significant intercept, whereas the intercept term of the linear relation between the deduced aqueous interaction terms of the apolar fragments and the area is nearly nil.

Negative aqueous interactions, (i.e. hydrophilic interactions), suggest proton donor–acceptor (H-bonding) or dipole–dipole interactions with water. The aqueous interaction terms of polar fragments are poorly related to area or volume (see Table 6). In contrast to non-polar fragments, the aqueous interaction terms of the polar fragments seem to decrease with an increase in surface area of the fragment. However, this trend is complicated by the existence of various kinds of interaction effect in the aqueous phase.

The differing abilities of the various functional groups to interact with water, follow the same pattern as found in the solubility study of Amidon et al. (1975) with the order being ($-CO_2H$) > ($-OH$) > ($>C{=}O$) > ($-O-$).

Group contribution values for H-bonding are scarce. The H-bonding parameters, derived from solubility data, given in Table 5 have been recalculated from the system described by Hansen and Beerbower (1971) (given as $J \cdot mol^{-1}$). Since parameters derived from solubility data take account of crystal forces, it is expected that they correlate poorly with the hydrophilic interaction parameters. The largest discrepancy arises when comparing aryl with alkyl fragments. Hansen and Beerbower found little differences between aryl and alkyl fragments, whereas values obtained by us indicate a stronger hydrophilic interaction for alkyl fragments.

Subtracting the size fragment values and the aqueous interaction terms from the fragmental values for octan-1-ol/water and $CHCl_3$/water result in organic interaction terms, f_o (see Table 5), relative to TMP as a standard reference phase. A positive value indicates a dipolar interaction with the organic phase, whereas a negative sign represents a repellent interaction with the specific organic solvent, i.e. a preference for an even less polar environment.

As can be seen in Table 5, the alkyl fragments have a slight preference for TMP over that of $CHCl_3$ or octan-1-ol. Since the interactions of apolar alkyl fragments with solvents will not be specific, these (repellent) values give an indication of the difference in dispersion forces of the organic phases. In contrast to the values for octan-1-ol, the $CHCl_3$ interaction terms for C_6H_5 and C_6H_4 are somewhat positive, which might reflect the bonding of this proton donor solvent to the aromatic ¶-cloud.

As expected, the dipolar interaction terms of the fragments for octan-1-ol correspond well with the I_H hydrogen bonding parameters of Seiler (1974) (see Table 5), with only the organic interaction term of (al)CN (1.23) significantly different from the value obtained by Seiler (0.23).

The absolute organic interaction terms (lipophilic or repulsive) of the fragments are smaller than the corresponding absolute aqueous interaction terms, suggesting that the interactions taking place in the aqueous phase are more important than those occurring in the organic phase. Thus, the more alike the aqueous and organic interaction terms of a fragment are, then the more will the physicochemical behaviour of the organic solvent approximate that of water.

Although the aqueous interactions of the fragments are stronger than those in the organic phase, the hydrophobic and hydrophilic interactions of the fragments of a compound might be such that they cancel out each other, whereas the organic interactions do not cancel out. The result of this could be that despite the large interactions of the individual fragments in water, the distribution of a compound is driven completely by the sum of the interactions in the organic phase. An example of this is seen with by *p*-nitrophenoxy, where the $CHCl_3$/water distribution is nearly solely due to the result of a proton acceptor–donor interaction of the solute with the organic phase.

The interaction terms of the fragmental values of Table 5 are now examined in more detail.

The perfluoropropyl group is strongly repelled by water ($f_w = 3.03$) due to its characteristic surface of lone pair electrons, which repel other lone pairs but are incapable of forming hydrogen bonds. Octan-1-ol contains fewer polar groups containing lone pairs than does water; thus, perfluoropropyl is repelled less by octan-1-ol (0.68) than by water. $CHCl_3$ also has a surface of lone pairs, so it repels perfluoroalkyl more than octan-1-ol, but less than water does, because water has the additional complication of a very high molar density.

If the postulate is made that for proton donors no attractive interactions with the pure proton donating solvent $CHCl_3$ will occur, then the interaction terms of the fragments with $CHCl_3$ will give some indication of the proton accepting ability of the fragments. On this basis, we find that the strongest acceptors are thiourea, alkyl-amide and imidazole, followed by SO, SO_2, and aryl-amide. Sulfonamide is weaker, with (al)CN, (al)CO, and pyridinyl weaker again, and finally followed by (ar)NO_2, aryl-ester and (ar)OH, which has a value close to zero. The fragments with proton-accepting ability can be divided into pure proton acceptors and amphiprotic groups.

The organic interaction terms of pure weak proton acceptors, such as (ar)NO_3 and (ar)O, are smaller than those of the stronger proton acceptors (al)CN, (al)CO and pyridinyl. In general, the interaction of pure proton acceptors are stronger with $CHCl_3$ than with octan-1-ol, although there exist a few apparent exceptions to this rule. For example, for (ar)CO_2 the interaction with octan-1-ol is clearly stronger than with $CHCl_3$. This may result from the presence of excess lone pair electrons on the etheric O, which do not form hydrogen bonds but can repel the lone pair of $CHCl_3$. This might also explain the extraordinary value of the chloroform interaction term of (al)S (-0.70).

Compared to (al)SO_2, al(SO) is a much stronger acceptor for *one* hydrogen bond, whereas (al)SO_2 can accept twice as many. The fact that the hydrophilic interaction term of (al)SO is stronger than (al)SO_2 fits with the view that strong proton donors (water) prefer bonds with strong proton acceptors. The differences in the organic interaction terms between (al)SO and (al)SO_2 are larger for octan-1-ol than for $CHCl_3$. Furthermore, the organic interaction term of (al)SO is stronger for octan-1-ol than for chloroform, whereas the differences in (al)SO_2 disappear. These results suggest that octan-1-ol is a better proton donor towards strong acceptors and $CHCl_3$ towards weak ones.

Although the differences of the fragments in organic interaction terms for $CHCl_3$ and octan-1-ol might not be great, the summation of the fragments into, for example, compounds 11 and 12 clearly enlarge the differences between the two solvents.

Among the amphiprotic groups the proton

accepting ability of sulfonamide should be similar to SO_2. The difference between the organic interaction terms of SO_2NH_2 and SO_2 for $CHCl_3$, which is very negative, indicates that chloroform as a pure proton donating solvent itself, might repel other donors even more. The larger (positive) difference in the interaction terms of the fragments for octan-1-ol than for water, is consistent with the view that the proton accepting ability of octan-1-ol is superior to that of water (Lewis et al., 1983).

For amides, it is seen that the alkyl amide C=O is a better proton acceptor than aryl-amide C=O, and aryl NH is a better proton donor than alkyl NH. These trends are indicated in the interaction terms of the amide fragments. Thus, the stronger interaction of (al)$CONH_2$ over that of (al)CONH in octan-1-ol suggests that two NH donors are more effective than one. The stronger interaction with octan-1-ol of the amide fragment with the enhanced proton donating ability, (ar)CONH, over that of the fragment with the enhanced proton accepting ability, (al)CONH, agrees well with the view that the proton accepting ability of octan-1-ol is more important than its proton-donating ability. Similarly, it can be seen from a comparison of the hydrophilic interaction terms of alkyl and aryl CONH that water is a much stronger proton donor than acceptor. Also, though only two organic interaction terms for amide with $CHCl_3$ are available, these values are also consistent with the observation of an enhanced proton donating ability of chloroform relative to octan-1-ol.

The stronger interaction of aryl-OH with octan-1-ol and the apparent absence of it with chloroform suggest that aryl-OH is predominantly a proton donor.

The differences between the octan-1-ol and the $CHCl_3$ interaction terms of the fragments (which is largest for (ar)OH followed by CO_2H, SO_2NH_2, imidazole and amide), is likely to represent a measure of the proton-donating ability of the fragments.

Recently, Taft et al. (1985) have introduced the concept of linear solvation energy relationships (LSER), which can be regarded as a modified regular solution theory. In their model, the distribution of a solute is determined by an endoergic cavity term, an exoergic dipolar term and an exoergic hydrogen bonding term. Though the fundamentals of this model seem to resemble those of the present study, some important differences should be noted.

First, in the approach of Taft et al. (1985) cavity terms, defined as the energy required to make a hole, are calculated from enthalpies of vaporization, whereas the size contributions in this study, which essentially reflect the differences in free energy in creating and filling up a hole in either the aqueous or organic phase, is due merely to entropic mixing effects. The differences between the experimental determined fragmental values of hydrocarbons and the hypothetical size values, therefore should reflect a hydrophobic interaction effect, which is of enthalpic origin. These findings are in concordance with those of Shinoda (1977).

Second, the treatment of Taft et al. (1985) does not allow one to handle a range of amphiprotic solutes or to factor out separate interactions with each solvent. According to Taft et al. the specific interaction terms are predominantly determined by the hydrogen-donating characteristics of water and the hydrogen-accepting ability of the solute. Although the results presented in this study indicate that the aqueous donating characteristics are more important than their accepting abilities and that the specific interactions occurring in water dominate those in the organic phase, the specific interactions in the organic phase can not be neglected and are not proportional to the aqueous interaction terms.

Further, regular solution theory as a starting point for the analysis of distribution phenomena seems to be a less appropriate choice than the UNIQUAC model (Shinoda, 1977; Grünbauer and Tomlinson, 1984).

Conclusions

In this present study a method of analysis, based on the UNIQUAC model, has been used to differentiate the structural group-fragment values into aqueous and organic interaction terms as well as into a term which is due to a size term, which reflects the possible arrangments that a fragment has in space. This method has proven to be a useful approach for explaining the different patterns of distribution of solutes in different organic solvent/water systems.

A remarkable feature, which becomes clear using this method of analysis, is the apparent absence of interaction terms in the quaternary C atom/group fragment. Further, the repulsive (hydrophobic) interaction with water — which is a linear function of the area of an apolar fragment — might be associated with hydrophobic hydration in the aqueous phase.

The attractive interactions of a fragment with water or organic solvent can be explained in terms of proton donor–acceptor characteristics. The results indicate that octan-1-ol is a stronger proton–acceptor than water, whereas $CHCl_3$ has no proton-accepting ability. The proton donating ability of water is much stronger than those of $CHCl_3$ and octan-1-ol; the relative proton donor strength of octan-1-ol and $CHCl_3$ could be a function of the proton accepting ability of a fragment or compound.

Furthermore, it has been shown that although the interactions of fragment with water are stronger than with an organic solvent, in accord with Amidon et al. (1975) and Cramer (1977) the distribution of a solute might be driven by the total of the interactions in the organic phase.

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