JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 2, 559–564 (1989)

SOLUTE–SOLVENT INTERACTIONS IN CHEMICAL AND BIOLOGICAL SYSTEMS. IV. CORRELATIONS OF ΔG, ΔH AND $T\Delta S$ OF TRANSFER OF ALIPHATIC AND AROMATIC SOLUTES FROM 2,2,4-TRIMETHYLPENTANE TO AQUEOUS SOLUTION

RICHARD FUCHS
Department of Chemistry, University of Houston, Houston, TX 77004, USA
MICHAEL H. ABRAHAM
Chemistry Department, University College London, 20 Gordon Street, London WC1H 0AJ, UK
MORTIMER J. KAMLET*
Naval Surface Weapons Center, White Oak Laboratory, Silver Spring, MD 20910, USA
ROBERT W. TAFT
Department of Chemistry, University of California, Irvine, CA 92717, USA

ABSTRACT

ΔG, ΔH and $T\Delta S$ of transfer of 25 aliphatic and aromatic solutes from 2,2,4-trimethylpentane to aqueous buffer (pH 7) at 298 K have been examined in terms of intrinsic volumes and the solvatochromic parameters π^*, δ, β and α of the pure solutes Correlations of the form

$$XYZ = XYZ_0 + mV_I/100 + s\pi^* + d\delta + b\beta + a\alpha$$

indicate that the thermodynamic quantities of transfer are unequally affected by solute properties; most notably, for aromatic solutes the cavity term $mV_I/100$ is a principal (unfavorable) factor affecting $T\Delta S$, but has little effect on ΔH. Transfer to water is favored by increasing solute π^* (dipolarity–polarizability), β (H-bond basicity) and α (H-bond acidity), because water has greater dipolarity, H-bond acidity and H-bond basicity than trimethylpentane. Hydrogen bonding contributes exothermically to ΔH, but unfavorably to $T\Delta S$, as would be expected from a loss of transitional entropy. Correlations of ΔG, ΔH and $T\Delta S$ with solute $V_I/100$, β, α, μ^2 and polarizability function $[(n^2-1)/(n^2+2)]$ give closely comparable results.

INTRODUCTION

The most important of all solvents, water, is highly atypical. The polarizability is low, the cohesiveness is very high and extensive three-dimensional hydrogen bonding occurs. The solubility of non-polar substances in water is very low. The corresponding positive standard

*Deceased.

0894–3230/89/070559–06$05.00

Received 29 June 1988
Revised 26 October 1988

free energies of solvation [$\Delta G^0(v \rightarrow w)$] are largely the result of unfavorable negative entropy terms [$T\Delta S^0(v \rightarrow w)$], which outweigh the enthalpy contribution [$\Delta H^0(v \rightarrow w)$] to $\Delta G^0(v \rightarrow w)$. Frank and Evans[1] proposed in 1945 the existence of enhanced water structure around non-polar solutes to account for the abnormal entropy of solution. More recently, several workers have suggested that $\Delta S^0(v \rightarrow w)$ and $\Delta H^0(v \rightarrow w)$ consist of two components, one of which contributes *only* to the 'fluctuation' of water from more structured clusters (promoted by nonpolar solutes) to less structured arrangements.[2-5] The enthalpy and entropy of 'fluctuation' cancel one another, and therefore do not contribute to the observed free energy and low alkane solubility. The origin of these contributions is still debatable. Grunwald[5] suggests perterbation of the solvent network, whereas other studies, both statistical mechanical simulations[6-8] and experimental,[9,10] point merely to an increase in water–water interactions in the solvent close to the solute. Jorgensen *et al.*[7] have noted that $\Delta S^0(v \rightarrow w)$, $\Delta H^0(v \rightarrow w)$ and $\Delta G^0(v \rightarrow w)$ of alkanes are linearly dependent on the number of water molecules in the first hydration shell. Whatever the origin, the existence of these contributions to $\Delta H^0(v \rightarrow w)$ and $\Delta S^0(v \rightarrow w)$, but not $\Delta G^0(v \rightarrow w)$, should be reflected in linear free energy relationships (LFERs) involving solvation in or transfers to water, most likely in the term related to solute size, mV_I. We shall consider this point in the Discussion section.

In previous papers[11,12] we have shown that the solubility properties (*SP*) of organic non-electrolytes in water are well correlated by equations of the form

$$SP = SP_0 + m\bar{V}/100 + s\pi^* + d\delta + b\beta_m + a\alpha_m$$

which include an endoergic solvent cavity term related to the solute molar volume, exoergic dipolarity and polarizability terms ($s\pi^*$, $d\delta$) (δ is the 'polarizability correction term,' with values of 0 for aliphatic 'select' solvents, 0·5 for polychlorinated aliphatics and 1·0 for aromatics; δ is related to the dipolarity/polarizability blend in the solvent effect on property *XYZ*.[13]) and exoergic hydrogen bonding terms ($a\alpha$, $b\beta$) describing hydrogen bond donation by solute to water acting as hydrogen bond acceptor (HBA) and solute acting as HBA from the hydrogen bond donor (HBD) water (π^*, δ, β_m and α_m refer to solute properties). Self-associated solutes require π_m^*, α_m and β_m values, which refer to the monomeric (unassociated) state present in dilute aqueous solution. To accommodate aromatic and carbocyclic species, it was necessary to add 10 cm^3 to the molar volume in the cavity term ($m\bar{V}$) of the earlier correlations.[14] More recently, computer-calculated intrinsic (van der Waals) molecular volumes[15] (V_I) of the pure solutes have been used without the need for corrections, and are available for solid solutes for which $\bar{V}$ cannot be measured at 25 °C. If *SP* represents the solubility of a solid compound in water, rather than partitioning between water and another solvent, an additional term must be added to the correlation to account for the entropy of fusion to the (supercooled) liquid at 25 °C.[12]

Solubility and partitioning are free energy related phenomena. We are generally unaware in correlations whether a particular solute property primarily affects the ΔH or $T\Delta S$ contribution to ΔG. It is likely that the recent observation[12] that aliphatic and aromatic solute solubilities in water are differently affected by the $s\pi^*$ and $b\beta_m$ contributions could be more readily rationalized if separate ΔH and $T\Delta S$ correlations were available. For this reason we were particularly interested in recent data on ΔG, ΔH and $T\Delta S$ of transfer of aliphatic and aromatic solutes from 2,2,4-trimethylpentane to aqueous buffer solution (pH 7) at 25 °C,[16,17] although the choice of solute is not ideal. Of the 25 compounds for which the required solvatochromic parameters are known, only eight (alcohols and ketones) are aliphatic; no hydrocarbons are included, and the range of β_m values is limited (0·23–0·55). Nevertheless, it is a uniform group of values measured in a single laboratory (by flow microcalorimetry and separate partitioning

experiments), furnishing all three thermodynamic quantities of transfer, and therefore worth examining in detail.

RESULTS

Solute solvatochromic parameters, $V_I/100$, and ΔG, ΔH and $T\Delta S$ of transfer[16,17] (kJ mol^{-1}) from 2,2,4-trimethylpentane to aqueous phosphate buffer (pH 7) at 25 °C are listed in Table 1. Correlations of ΔG, ΔH and $T\Delta S$ in terms of V_I, π^*, δ, β_m and α_m, and in terms of V_I, the polarizability function (PF) $(n^2-1)/(n^2+2)$, β_m, α_m and dipole moment (μ^2, D) are given in Table 2.

DISCUSSION

General observations concerning the correlations

The two types of linear solvation energy relationships examined are

$$XYZ = XYZ_0 + mV_I/100 + s\pi^* + d\delta + b\beta_m + a\alpha_m$$

Table 1. Solute solvatochromic parameters and ΔG, ΔH and $T\Delta S$ of transfer from 2,2,4-trimethylpentane to aqueous buffer (pH 7) at 298 K (kj mol^{-1})

Solute	$V_I/100$	π^*	δ	β_m	α_m	$PF \times 10$	$\mu^2/10$	ΔG^a	ΔH^a	$T\Delta S^a$
CH_3CH_2OH	0·305	0·40	0	0·45	0·33	2·213	0·289	−11·40	−34·99	−23·99
1-PrOH	0·408	0·40	0	0·45	0·33	2·338	0·289	−8·09	−33·11	−25·04
1-BuOH	0·499	0·40	0	0·45	0·33	2·420	0·289	−4·93	−31·49	−26·56
1-PeOH	0·593	0·40	0	0·45	0·33	2·478	0·289	−0·89	−29·56	−28·67
1-HexOH	0·690	0·40	0	0·45	0·33	2·519	0·289	3·09	−27·48	−30·58
Acetone	0·380	0·71	0	0·48	0·03	2·200	0·784	−4·58	−19·80	−15·22
Butanone	0·477	0·67	0	0·48	0·03	2·310	0·729	−1·04	−18·99	−17·95
Pentan-2-one	0·574	0·65	0	0·48	0·03	2·368	0·729	2·95	−17·56	−20·51
ϕCH_2OH[b]	0·634	0·99	1·0	0·52	0·35	3·136	0·289	−4·36	−25·72	−21·36
ϕCH_2CH_2OH	0·732	0·97	1·0	0·55	0·33	3·101	0·289	−2·04	−26·25	−24·21
$\phi(CH_2)_3OH$	0·830	0·95	1·0	0·55	0·33	3·078	0·289	1·05	−26·85	−27·90
ϕOH	0·536	0·72	1·0	0·33	0·61	3·190	0·210	−5·48	−19·40	−13·92
4-$CH_3\phi OH$	0·634	0·68	1·0	0·34	0·58	3·095	0·256	−2·26	−18·85	−16·59
4-ClϕOH	0·626	0·72	1·0	0·23	0·69	3·262	0·484	−2·77	−17·20	−14·43
ϕNH_2	0·562	0·73	1·0	0·50	0·16	3·357	0·225	−1·19	−13·61	−12·42
4-$CH_3\phi NH_2$	0·660	0·69	1·0	0·51	0·13	3·251	0·196	1·94	−14·77	−16·71
4-ClϕNH_2	0·652	0·73	1·0	0·40	0·20	3·337	0·900	2·74	−10·30	−13·04
$\phi NHCH_3$	0·660	0·73	1·0	0·47	0·12	3·273	0·289	5·92	−10·56	−16·48
ϕOCH_3	0·630	0·73	1·0	0·32	0	3·030	0·169	11·56	0·00	−11·56
$\phi COCH_3$	0·690	0·90	1·0	0·49	0·03	3·124	0·900	6·35	−8·86	−15·21
ϕNO_2	0·631	1·01	1·0	0·30	0	3·215	1·600	8·15	−2·82	−10·97
ϕCN	0·590	0·90	1·0	0·37	0	3·084	1·681	5·63	−6·05	−11·68
ϕCHO	0·606	0·92	1·0	0·44	0	3·168	0·784	5·99	−4·16	−10·15
$\phi COOCH_3$	0·736	0·76	1·0	0·39	0	3·022	0·324	10·40	−3·42	−13·82
$\phi COOEt$	0·834	0·74	1·0	0·41	0	2·966	0·361	13·78	−3·09	−16·48

[a] From Refs 16 and 17. The standard deviations in ΔG were 0·1–0·6 kJ mol^{-1} and averaged 0·14 kJ mol^{-1}. The standard deviations in ΔH were 0·1–2·9 kJ mol^{-1} and averaged 0·5 kJ mol^{-1}.
[b] ϕ = phenyl.

Table 2. Correlations of thermodynamic quantities for solute transfer from 2,2,4-trimethylpentane to aqueous buffer (pH 7) at 298 K (kJ mol^{-1})[a]

		$XYZ = XYZ_0 + mV_I/100 + s\pi^* + d\delta + b\beta_m + a\alpha_m$								
Equation	Solute set	XYZ_0	m	s	d	b	a	r	SD	n
1a	ΔG, all solutes	1·38	33·79	−5·80	*0·97*	−29·13	−21·67	0·9903	0·97	25
		±1·70	±2·18	±1·84	±0·87	±2·83	±1·06			
1b	Aromatics only	5·08	29·30	−6·28		−27·57	−21·73	0·9871	1·07	17
		±2·83	±3·58	±2·45		±3·23	±1·20			
3a	ΔH, all solutes	6·94	*6·59*	*−3·55*	11·29	−58·91	−36·01	0·9758	2·59	25
		±4·50	±5·76	±4.86	±2·29	±7.49	±2.79			
3b	Aromatics only	29·68	*−2·43*	−14·13		−52·21	−34·36	0·9860	1·64	17
		±4·46	±5·64	±3·86		±5·09	±1·88			
5a	$T\Delta S$, all solutes	5·55	−26·89	*2·12*	10·33	−29·90	−14·45	0·9442	2·27	25
		±3·92	±5·02	±4·25	±2·00	±6·54	±2·45			
5b	Aromatics only	24·33	−31·03	−7·94		−24·79	−12·79	0·9640	1·48	17
		±3·89	±4·92	±3·37		±4·45	±1·65			
		$XYZ = XYZ_0 + mV_I/100 + q\mu^2/10 + pPF \times 10 + b\beta_m + a\alpha_m$								
		XYZ_0	m	q	p	b	a	r	SD	n
2a	ΔG, all solutes	3·98	32·18	−2·0	*−0·53*	−34·56	−22·58	0·9898	1·00	25
		±2·39	±2·23	±0·6	±0·71	±2·97	±1·24			
2b	Aromatics only	9·59	25·88	−2·1	*−1·14*	−33·11	−23·32	0·9904	0·97	17
		±10·10	±4·02	±0·6	±2·79	±3·18	±1·28			
4a	ΔH, all solutes	−17·61	*6·01*	*−2·6*	12·25	−66·66	−39·98	0·9785	2·44	25
		±5·80	±5·43	±1·5	±1·74	±7·22	±3·02			
4b	Aromatics only	5·97	*−1·17*	−3·3	*6·07*	−65·22	−37·09	0·9817	2·02	17
		±21·11	±8·41	±1·3	±5·84	±6·64	±2·67			
6a	$T\Delta S$, all solutes	−21·42	−25·82	*−0·6*	12·72	−32·39	−17·52	0·9335	2·47	25
		±5·86	±5·48	±1·6	±1·76	±7·29	±3·05			
6b	Aromatics only	−3·65	−26·43	*−1·2*	*7·15*	−32·45	−13·87	0·9584	1·65	17
		±17·23	±6·86	±1·1	±4·76	±5·42	±2·18			

[a] Values in italics are not statistically significant at the 95% confidence level by Student's t-test.

and

$$XYZ = XYZ_0 + mV_I/100 + q\mu^2/10 + pPF \times 10 + b\beta_m + a\alpha_m$$

We shall be primarily concerned with the first type, but the second will be considered for additional information and verification. The terms $V_I/100$, $\mu^2/10$ and $PF \times 10$ have been scaled to put the contributions to XYZ on a more comparable basis. In spite of the limited range of β_m values, the hydrogen bonding terms ($b\beta_m$, $a\alpha_m$) (Table 2) are consistent between the 'all solutes' and corresponding 'aromatics only' correlations, and also between the π^*, δ and PF, μ^2 correlations. This leads us to believe that $a\alpha_m$ and $b\beta_m$ contributions are largely independent of the other parameters. The cavity term ($mV_I/100$) is also relatively consistent in the various ΔG and $T\Delta S$ correlations. All the terms are transfer quantities, and represent differences between trimethylpentane and water. In the ΔH correlations the values are much smaller and inconsistent, but the m coefficients are not statistically significant by Student's t test at the 95% confidence level (these values are in italics in Table 2). In these correlations the endoergic cavity

contribution to ΔG is determined largely by the cavity term in $T\Delta S$. It should be noted, however, that because of an insufficient variety and number of aliphatic solutes (8 of 25), there are no independent correlations of aliphatic solutes only. It is likely that for aliphatics the $mV_I/100$ contribution to ΔH would be substantially endothermic, and would make an important contribution to the ΔG cavity term. An unfavorable cavity term is expected whenever a solute is transferred from a less cohesive to a more cohesive solvent (Hildebrand δ_H: trimethylpentane, 6·9; water, 23·4). Transfers of aliphatic solutes from alkanes to polar organic solvents[18] such as from cyclohexane to propylene carbonate also show unfavorable cavity terms in ΔG, with appreciable contributions from both ΔH and $T\Delta S$. The overall cavity contribution to this ΔG is, as expected, smaller than that for transfers to water.

The very different $mV_I/100$ terms in equations (1a) (Table 2) (33·8 kJ mol^{-1}) and (3a) (6·6 kJ mol^{-1}) are an example of possible effects resulting from 'structural' contributions to the ΔH^0 term, which would lead to more exothermic ΔH^0 values. Our LFER fits to ΔH^0 and $T\Delta S^0$ are significantly poorer than the fits to ΔG^0, but we believe that this probably reflects the much greater experimental errors in ΔH^0 and $T\Delta S^0$, rather than any intrinsic difficulty in handling 'structural' contributions within the LFER framework.

Free energies of transfer

The ΔG values are the most accurate experimentally, and are expected to be the most readily interpreted. Equation (1a), the 'all solutes' ΔG of transfer correlation, is only marginally improved by the $d\delta$ term,[13] which is included for comparison. Equations (1a) and (1b) ('aromatic solutes only') are very similar [$\delta = 1·0$ for all aromatics, so a $d\delta$ term cannot be evaluated in equation (1b)]. Transfer to water is favored by increasing π^*, β_m and α_m, as is expected for solutes which can interact with water (but not 2,4,4-trimethylpentane) by dipole–dipole effects and by hydrogen bonding. π^* terms appear in ΔG correlations (1a) and (1b), and both aliphatic and aromatic solutes show a dependence. This is in contrast to aqueous solubility data,[12] for which the π^* term is appreciable for aliphatic but not aromatic solutes. The large s/d ratio [equation (1a)] and the large q/p ratios [equations (2a) and (2b)] suggest that the π^* dependence describes a predominantly dipolar effect. However, this is the resultant of enthalpic and entropic contributions, which considered separately (see below) give a different picture. It is not surprising that there is a substantial term in $a\alpha_m$, because water is much more basic than 2,2,4-trimethylpentane. This is unlike the situation for octan-1-ol–water partitioning,[19] where water seems to be about as basic as octanol saturated with water, giving rise to a small or zero term in $a\alpha_m$. The sizes of the coefficients b and a give no exact indication of the acidity difference between water and 2,2,4-trimethylpentane (the solute b coefficient) compared with the basicity difference between the solvents (the a coefficient), because β_m and α_m are not entirely comparable. This results from the derivation of β_m and α_m from two completely independent measurements, and there is no way of determining whether the basicity of a solute with, for example, $\beta_m = 0·50$, is equal to the acidity of a solute with $\alpha_m = 0·50$.

Enthalpies and entropies of transfer

For solutes with HBD or HBA behavior towards water one expects and observes the ΔH contribution to be negative, the $T\Delta S$ effect to be negative as a result of the loss of translational entropy and the ΔG term to be negative but less so than ΔH. There is essentially no difference in behavior between the aliphatic and aromatic solutes, which suggests that hydrogen bonding involves the extra-ring functional groups of the latter in preference to the aromatic ring. The

$s\pi^*$ term in ΔH and $T\Delta S$ is less straightforward. If dipole–dipole interactions were dominant than (as with hydrogen bonding) ΔH would be more negative than ΔG and $T\Delta S$ would also be negative. This seems to be the case for 'aromatics only,' but not for 'all solutes', but the comparison may not be valid because of relatively large uncertainties in some of the s coefficients, and because we are comparing π^*, δ correlations ('all solutes') with correlations involving π^* alone ('aromatics only'). If one correlates ΔH and $T\Delta S$ ('all solutes') using π^* but not δ (the correlations are poorer), large positive s coefficients result, and a different conclusion would be drawn. Perhaps the best information can be derived from the μ^2, PF equations (2a), (2b), (4a), (4b), (6a) and (6b). The coefficient q of the dipolar term $q\mu^2/10$ is indeed more negative in the ΔH correlation than for the ΔG, and is also negative for $T\Delta S$, for 'all solutes' and 'aromatics only'. Again, however, there are substantial uncertainties in several q values. In ΔH and $T\Delta S$ correlations for both solute groups [equations (4a), (4b), (6a) and (6b)] the polarizability term $pPF \times 10$ is much larger than and of opposite sign to the dipolarity term $q\mu^2/10$. We tentatively propose that a small exoergic dipolar term favors water, whereas the larger endoergic polarizability term (an indication of dispersion interactions between solute and solvent) favors 2,2,4-trimethylpentane ($n_D = 1{\cdot}392$) over water ($n_D = 1{\cdot}333$). Overall, the polarizability term is much more important than dipolarity in determining ΔH and $T\Delta S$. The opposite applies to ΔG, because the polarizability contributions of ΔH and $T\Delta S$ nearly cancel, whereas the dipolarity contributions do not.

ACKNOWLEDGEMENT

The studies at the University of Houston were supported by the Robert A. Welch Foundation.

REFERENCES

1. H. S. Frank and M. W. Evans, *J. Chem. Phys.* **13**, 507 (1945).
2. T. H. Benzinger, *Nature (London)* **229**, 100 (1971).
3. R. Lumry, E. Battistel and C. Jolicoeur, *Faraday Symp. Chem. Soc.* No. 17, 93 (1982).
4. D. Mirejovsky and E. M. Arnett, *J. Am. Chem. Soc.* **105**, 1112 (1983).
5. E. Grunwald, *J. Am. Chem. Soc.* **108**, 5726 (1986).
6. W. L. Jorgensen, *J. Chem. Phys.* **77**, 5757 (1982).
7. W. L. Jorgensen, J. Gao and C. Ravimohan, *J. Phys. Chem.* **89**, 3470 (1985).
8. P. J. Rossky and D. A. Zichi, Ref. 3, p. 69.
9. H. Leiter, C. Albayrak and H. G. Hertz, *J. Mol. Liq.* **27**, 211 (1984).
10. E. Matteoli and L. Lepori, *J. Chem. Phys.* **80**, 2856 (1984).
11. M. J. Kamlet, R. M. Doherty, J.-L. M. Abboud, M. H. Abraham and R. W. Taft, *J. Pharm. Sci.* **75**, 338 (1986).
12. M. J. Kamlet, R. M. Doherty, M. H. Abraham, P. W. Carr, R. F. Doherty and R. W. Taft, *J. Phys. Chem.* **91**, 1996 (1987).
13. R. W. Taft, J.-L. M. Abboud and M. J. Kamlet, *J. Am. Chem. Soc.* **103**, 1080 (1981).
14. R. W. Taft, M. H. Abraham, G. R. Famini, R. M. Doherty, J.-L. M. Abboud and M. J. Kamlet, *J. Pharm. Sci.* **74**, 807 (1985).
15. D. E. Leahy, P. W. Carr, R. S. Pearlman, R. W. Taft and M. J. Kamlet, *Chromatographia* **21**, 473 (1986).
16. W. Riebesehl and E. Tomlinson, *J. Phys. Chem.* **88**, 4770 (1984).
17. W. Riebesehl, E. Tomlinson and H. J. M. Grünbauer, *J. Phys. Chem.* **88**, 4775 (1984).
18. M. H. Abraham, *J. Am. Chem. Soc.* **104**, 2085 (1982).
19. D. Leahy, *J. Pharm. Sci.* **75**, 629 (1986).