Substitution at Saturated Carbon. Part XIX.[1] The Effect of Alcohols and Water on the Free Energy of Solutes and on the Free Energy of Transition States in S_N and S_E Reactions

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Standard free energies of transfer from methanol to other alcohols and to water are reported for nearly 40 solutes, ranging from hydrocarbons to amino-acids. These transfer free energies from methanol to alcohols are negative for nonpolar inert solutes, but quite positive for amino-acids and ion pairs; from the assembled data it is predicted that linear free energy relationships between $\Delta G^‡$ values for substitution reactions in alcohols will in general be approximate only. By combination of initial-state effects with values of $\Delta G^‡$ previously determined, free energies of transfer from methanol to alcohols have now been calculated for 20 different substitution reactions involving electrically neutral reactants. The various values of $\Delta G^{\circ}_{t}(\mathrm{Tr})$ are by no means linearly related, but by comparison with values for polar species such as amino-acids and ion pairs it is shown that the polarity of transition states increases in the order $[R_4Pb–I_2]^‡ < [R_3N–RI]^‡ \leqslant [R_4Sn–I_2]^‡ < [R_4Sn–HgX_2]^‡ < [Bu^tX]^‡ \leqslant [PhCHMeCl]^‡ \leqslant [Ph_2CHCl]^‡$. The α-amino-acids are shown to be suitable model solutes for highly polar transition states, especially when any differences in molar volume between solute and transition state are taken into account.

In recent years, the effects of solvents on rate constants for a number of reactions involving neutral molecules have been dissected into initial- and transition-state contributions (see ref. 2).* Generally, it appears that the accelerating effect of water in aqueous–organic solvents is largely due to destabilisation of the initial state in the more aqueous media, but that for reactions taking place in nonaqueous solvents both initial- and transition-state effects may be of importance.[2] Studies of the effect of solvents on the free energy of transition states have shown that it is possible to deduce such transition-state properties as solubility parameter, dipole moment, and the extent of charge separation.[2] Other work [2,4] has involved the comparison of solvent effects on transition states with the effect of solvents on the thermodynamic properties of various solutes. The number of studies hitherto reported is still quite small, so that few generalisations are possible. One difficulty has been the lack of systematic data on the influence of solvents on simple solutes of different chemical type.

The effect of typical alcoholic solvents on rate constants for a large number of substitution reactions has recently been documented.[1] In the present work we set out to dissect these effects into initial- and transition-state components, and to compare the determined transition-state effects with those for a wide range of solutes, hoping in this way to assess the nature and properties of the various transition states.

Solvent Effects on the Free Energies of Solutes.—For a volatile solute, the most convenient way of determining solvent effects on the free energy of the solute is through the limiting values of the Raoult's law activity coefficient (γ_∞) of the solute in the various solvents. Quite recently, data have been published by Rohrschneider [5] and by Yaacobi and Ben-Naim [6] from which we have calculated γ_∞ values for methane, ethane, dioxan, nitromethane, butan-2-one, and toluene in alcohols (Table 1). We ourselves have used our g.l.c. method [7,8] to determine γ_∞ values for benzyl chloride, benzyl bromide, ethyl iodide, pyridine, and triethylamine, which together with some of our previous measurements,[9] and other literature data, are in Table 1. Thus values of γ_∞ are now available for a wide range of volatile solutes in typical alcohols, and in water.[10]

In the case of involatile solid solutes, recourse has

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* Parker [3] has reviewed the area of solvent effects on anion–molecule reactions.

[1] Part XVIII, M. H. Abraham and P. L. Grellier, *J.C.S. Perkin II*, 1975, 623.

[2] M. H. Abraham, *Progr. Phys. Org. Chem.*, 1974, **11**, 1.

[3] A. J. Parker, *Chem. Rev.*, 1969, 69, 1.

[4] P. Haberfield, *J. Amer. Chem. Soc.*, 1971, **93**, 2091; E. M. Arnett in 'Physico-chemical Processes in Mixed Aqueous Solvents,' ed. F. Frank, Heinemann, London, 1967.

[5] L. Rohrschneider, *Analyt. Chem.*, 1973, **45**, 1241.

[6] M. Yaacobi and A. Ben-Naim, *J. Phys. Chem.*, 1974, **78**, 175.

[7] M. H. Abraham, *J. Chem. Soc.* (*A*), 1971, 1061.

[8] M. H. Abraham, P. L. Grellier, and J. Mana, *J. Chem. Thermodynamics*, 1974, **6**, 1175.

[9] M. H. Abraham, *J.C.S. Perkin II*, 1972, 1343.

[10] H. D. Nelson and C. L. de Ligny, *Rec. Trav. chim.*, 1968, **87**, 623; D. Wauchope and R. Haque, *Canad. J. Chem.*, 1972, **50**, 133.

TABLE 1

Limiting Raoult's law activity coefficients of volatile solutes in water and alcohols at 298 K

Solvent	H_2O	MeOH	EtOH	Pr^{n}OH	Pr^{i}OH	Bu^{n}OH	*iso*-C_5H_{11}	Bu^{t}OH	Ref.
CH_4	158	4.61	3.15	2.55	2.78 [a]	2.16	1.92 [b]		6
C_2H_6	776	6.55	3.96	3.01		2.44	2.13 [b]		6
C_3H_8	3 910	11.65	6.36		4.41				*c*
C_4H_{10}	1.92×10^4	14.8	7.41		4.91				*c*
C_5H_{12}	1.00×10^5	27.0	10.5						*d*
C_6H_{14}	2.97×10^5	27.4	12.8						*d*
C_7H_{16}	2.52×10^6	28.2	13.2	7.8	8.5	6.3			*d*
C_8H_{18}	4.12×10^6	53.5	17.9	10.6	10.2	7.9	6.1	6.4	5, 10
Me_4Sn	4.0×10^5	31.0	15.14	8.36	8.00	6.13		3.30	This work, 9
Et_4Sn	7.6×10^7	65.0	26.6	15.0	12.7	10.7		4.70	This work, 9
Et_4Pb	8.4×10^7	85.0	23.3	13.5					9
Benzene	2 505	7.8	5.9	4.6	4.6	3.6			e
Toluene	8 150	10.8	5.0	4.6	5.4	3.5	3.7	4.4	5, 10
Benzyl chloride	3.6×10^4	7.5	6.7	6.1	7.0	5.7		5.8	This work
Benzyl bromide	4.0×10^4	10.0	8.3	7.1	7.9	5.9		5.9	This work
EtI	2 165	7.98	5.00	3.88	3.85	3.16	2.28	4.04	This work
Bu^{t}Cl	2.2×10^4	10.0	6.40	5.59	6.04	4.62		4.60	9
Bu^{t}Br	3.0×10^4	14.0	7.25		6.20			5.04	9
Me_3N	2.62	0.39	0.41	0.32			0.27		18
Et_3N	67.5	0.98	1.26	0.90	1.45	0.84	0.66	1.79	8
Pyridine	17.9	1.20	1.00	0.93	1.31	0.92		1.05	*f*
Dioxan	5.1	3.2	3.2	2.8	3.0		2.3	1.8	5
$MeNO_2$	25.4	4.4	5.8	7.5	7.7	7.3	7.7	7.6	5
MeCOEt	24.3	2.3	2.4	2.5	2.0	2.2	2.1		5

[a] W. Gerrard, *J. Appl. Chem. Biotechnol.*, 1973, **23**, 1. [b] Value for n-pentanol. [c] C. B. Kretschmer and R. Wiebe, *J. Amer. Chem. Soc.*, 1952, **74**, 1276; the values in water are from ref. 10.[d] H. Wolff and H.-E. Hoppel, *Ber. Bunsengesellschaft. Phys. Chem.*, 1968, **72**, 710; C. J. Pierotti, C. H. Deal, and E. L. Derr, *Ind. and Eng. Chem.*, 1959, **51**, 95; M. Benedict, C. A. Johnson, E. Solomon, and L. C. Rubin, *Trans. Amer. Inst. Chem. Engineers*, 1945, **41**, 371; H. C. Van Ness, C. A. Soczek, G. L. Peloquin, and R. L. Machado, *J. Chem. and Eng. Data*, 1967, **12**, 217; ref. 10. [e] C. Black, *Amer. Inst. Chem. Engineers J.*, 1959, **5**, 249; ref. 10. [f] Value in water from R. J. L. Andon, J. D. Cox, and E. F. G. Herington, *J. Chem. Soc.*, 1954, 3188; values in MeOH, EtOH, Pr^{n}OH, and Bu^{n}OH from A. Orszagh and T. Kasprzycka-Guttman, *Bull. Acad. Polon. Sci.*, 1972, **20**, 349, 355, and V. Bandani, *Ind. and Eng. Chem.* (*Fundamentals*), 1974, **13**, 154; values in Pr^{i}OH and Bu^{t}OH determined in this work.

to be made to studies on the solubility of the solutes [2,11,12] noting that freee energies of solution or of transfer cannot be directly obtained from solubilities if the solute forms solid solvates with the solvents concerned.[11] The solubilities of various mercury(II) salts are given in Table 2, both in terms of molar concentration and as mole fractions (we determined the concentration of the solute in the saturated solution both by volume and by weight); where comparisons can be made, there is good agreement between our data and those of previous workers.[13,14]

Although the mercury(II) salts, and some of the solutes in Table 1, may be regarded as having some polar character, we felt that data on more polar solutes was desirable. Accordingly, we investigated the solubilities of two α-amino-acids, which, since they exist in the zwitterion form, are interesting model solutes for highly polar transition states.[15] The solubility of glycine in alcohols has been determined by Cohn and his co-workers [16] and more recently by Needham,[17] but there are marked discrepancies between the two sets of data (Table **3**). Our own results agree quite well with the older data of Cohn, and it appears that the solubility data of Needham must be in error especially with regard to the higher alcohols.* The other amino-acid we chose

TABLE 2

Solubilities of mercury(II) salts in water and alcohols [a] at 298 K

Solvent	Salt	Concentration (M)	Mole fraction
H_2O	$HgCl_2$ [b]	0.2659	0.004 84
	HgI_2 [c]	9.7×10^{-5}	1.75×10^{-6}
	$Hg(OAc)_2$		0.0235 [d]
MeOH [e]	$HgCl_2$	1.768 [f]	0.1690 [g]
	HgI_2	0.0702	0.002 86
	$Hg(OAc)_2$ [h]	0.278	0.0113
EtOH	$HgCl_2$	1.291	0.0731
	HgI_2	0.0211	0.002 23
	$Hg(OAc)_2$ [h]	0.0710	0.004 17
Pr^{n}OH	$HgCl_2$	0.606	0.0449
	HgI_2	0.0252	0.001 93
	$Hg(OAc)_2$ [h]	0.0427	0.003 23
Bu^{n}OH	$HgCl_2$	0.462	0.0413
	HgI_2	0.0224	0.002 03
	$Hg(OAc)_2$	0.0434	0.003 89
Bu^{t}OH [i]	$HgCl_2$	0.152	0.0144
	HgI_2	0.0039	0.00 037
	$Hg(OAc)_2$ [h]	0.0140	0.001 33

[a] This work, except where indicated. [b] H. C. Thomas, *J. Amer. Chem. Soc.*, 1939, **61**, 920. [c] J. A. de Bruijn, *Rec. Trav. chim.*, 1941, **60**, 309. [d] In the presence of acetic acid, 0.22M, but solid phase is still HgO + $Hg(OAc)_2$. E. G. Long and K. A. Kobe, *Ind. and Eng. Chem.*, 1951, **43**, 2366. [e] Ref. 11. [f] Observed solubility. [g] Solubility corrected for solvate formation. [h] In presence of acetic acid, 0.07M. [i] M. H. Abraham and F. J. Dorrell, *J.C.S. Perkin II*, 1973, 444.

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* Unlike Cohn and ourselves, Needham determined the solubility of glycine in alcohols by evaporating aliquot portions of the saturated solutions to constant weight. Using our data, a 100 ml portion from t-butyl alcohol would contain only 0.000 76 g of glycine, so that the error introduced by such an analytical method must be considerable.

[11] M. H. Abraham, J. F. C. Oliver, and J. A. Richards, *J. Chem. Soc.* (*A*), 1970, 203.

[12] M. H. Abraham, *J. Chem. Soc.* (*B*), 1971, 299.

[13] F. Madaule-Aubry, *Ann. Chim.* (*France*), 1965, **10**, 367.

[14] V. A. Mikhailov and É. F. Grigor'eva, *Zhur. strukt. Khim.*, 1968, **9**, 788; M. Étard, *Ann. Chim. Phys.*, 1894, **2**, 503; W. Herz and M. Knoch, *Z. anorg. Chem.*, 1905, **45**, 262.

[15] D. G. Oakenfull, *Austral. J. Chem.*, 1974, **27**, 1423.

[16] T. L. McMeekin, É. J. Cohn, and J. H. Weare, *J. Amer. Chem. Soc.*, 1936, **58**, 2173.

[17] T. E. Needham, jun., A. N. Paruta, and R. J. Gerraughty, *J. Pharm. Sci.*, 1971, **60**, 565.

TABLE 3

Solubilities of α-amino-acids in water and alcohols, in mol l^{-1} at 298 K

	Glycine			DL-α-Phenylalanine	DL-α-Aminocaproic acid
	Needham[17]	Cohn[16]	This work	This work	Cohn[16]
H_2O	2.90	2.886			0.0866
MeOH	0.009	0.004 26	0.004 50	0.007 80	0.008 54
EtOH	0.004	0.000 39	0.000 65	0.001 27	0.001 04
Pr^nOH	0.011		0.000 23	0.000 48	
Pr^iOH	0.004		0.000 18	0.000 31	
Bu^nOH		0.000 0959	0.000 12	0.000 37	0.000 336
Bu^tOH	0.004		0.000 10	0.000 14	

was DL-α-phenylalanine; our results (Table 3) cannot be compared with those of Needham[17] on L-α-phenylalanine (because solubilities of racemic and active forms need not be the same) but follow the general trend of solubilities of DL-α-aminocaproic acid.[16]

A solute of moderate polarity is *p*-nitrobenzyl chloride (dipole moment, $\mu = 3.94$ D); solubilities have been determined by von Halban[18] and we have carried out further experiments. Results are in good agreement with each other and are in Table 4. We also redetermined the solubility of iodine in alcohols, and extended the solvents used. Details are in Table 5.

TABLE 4

Solubility of *p*-nitrobenzyl chloride in alcohols, in terms of mole fraction at 298 K

	von Halban[18]	This work
MeOH	0.0163	0.0158
EtOH	0.0187	0.0184
Pr^nOH	0.0196	0.0192
Pr^iOH		0.0154
Bu^nOH		0.0203
Bu^tOH		0.0156
iso-$C_5H_{11}OH$	0.0245	

From the data in Table 1, standard free energies of transfer on the mole fraction scale from a reference solvent 1 (methanol) to any other solvent 2 may be calculated for the volatile solutes through equation (1). For the involatile solutes listed in Tables 2—5, the

$$\Delta G^x_t = RT\ln(\gamma 2^{\infty}_2/\gamma 1^{\infty}_1) \qquad (1)$$

$$\Delta G^x_t = -RT\ln(X_2/X_1) \qquad (2)$$

corresponding equation is (2), where X_1 and X_2 are the mole fraction solubilities of the solute in solvents 1 and 2. In equation (2) we have implied that the term in the secondary medium activity coefficients is unity, and, of course, that the solid forms no solvates with the solvents. Mercury(II) chloride does indeed form a solvate with methanol, and we have used in equation (2) the hypothetical mole fraction solubility of mercury(II) chloride in methanol at 298 K were no solvates to be formed. We have taken the secondary medium activity coefficient term as unity for the α-amino-acids, reasoning that although the secondary medium activity coefficient for glycine in its saturated solution in water is only[19,20] *ca.* 0.88, there will probably be some compensation in the other solvents.

In Table 6 are given values of ΔG^x_t for transfer of nearly 40 solutes from methanol to alcohols and to water. For nonpolar nonelectrolytes, ΔG^x_t for transfer to water is always large and positive, this being due to the so-called nonelectrostatic effect (see ref. 21). Although ΔG^x_t values for these nonpolar solutes for transfer from methanol to alcohols are numerically much smaller than for transfer to water, they are still significant quantities by comparison to values of $\delta\Delta G^{\ddagger}$ for many reactions. The nonelectrostatic (ΔG^x_n) and electrostatic (ΔG^o_e) contributions to ΔG^x_t may be treated through equation (3). We shall calculate ΔG^x_t and ΔG^x_n on the mole fraction scale, but ΔG^o_e is independent of any such

$$\Delta G^x_t = \Delta G^x_n + \Delta G^o_e \qquad (3)$$

standard state. As a measure of ΔG^x_n for a given solute, we take the value of $\Delta G^x_t = \Delta G^x_n$ for a nonpolar solute of the same molar volume. Values of ΔG^x_n for transfer from methanol to water have been calculated by the method of Abraham and Johnston[21] (after conversion from the molar to the mole fraction scale), and hence knowing ΔG^x_t a value for ΔG^o_e may be calculated. Details are in Table 7. It can be seen that for the nonpolar solutes the calculated ΔG^x_n values agree well with the observed ΔG^x_t values (as required by theory, since ΔG^o_e is zero for a nonpolar solute); the average difference in the two sets of values for the alkanes is only 0.27 kcal mol^{-1}. The polar solutes in Table 7 all give rise to marked negative values of ΔG^o_e, those for the α-amino-acids being not far short of values calculated

TABLE 5

Solubility of iodine, in terms of mole fraction, at 298 K

	This work	Previous work	
H_2O		2.36×10^{-5} [a]	2.40×10^{-5} [b]
MeOH	2.65×10^{-2}	2.56×10^{-2} [c]	2.86×10^{-2} [d]
EtOH	4.72×10^{-2}	4.31×10^{-2} [a]	4.72×10^{-2} [e]
Pr^nOH	6.23×10^{-2}		
Pr^iOH	6.40×10^{-2}		
Bu^nOH	5.11×10^{-2}		

[a] C. Barraqué, J. Vedal, and B. Trémillon, *Analyt. Chim. Acta*, 1969, **46**, 263. [b] Average value from several investigations given in 'Solubilities of Inorganic and Metal Organic Compounds,' ed. W. F. Linke, Van Nostrand, New York, 1958, 4th edn., vol. I, p. 1254. [c] Ref. 9. [d] J. Mahieu, *Bull. Soc. chim. belges.*, 1936, **45**, 667. [e] Data in footnote *b*.

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[18] H. von Halban, *Z. phys. Chem.*, 1913, **84**, 129.

[19] 'Proteins, Amino Acids, and Peptides,' eds. E. J. Cohn and J. T. Edsall, Reinhold, New York, 1943.

[20] J. P. Greenstein and M. Winitz, 'Chemistry of the Amino Acids,' Wiley, New York, 1961, vol. 1.

[21] M. H. Abraham and G. F. Johnston, *J. Chem. Soc.* (*A*), 1971, 1610.

TABLE 6

Standard free energies of transfer [a] from methanol to other solvents of solutes, on the mole fraction scale, in kcal mol^{-1} at 298 K

Solute	H_2O	MeOH	EtOH	Pr^nOH	Pr^iOH	Bu^nOH	*iso*-C_5H_{11}	Bu^tOH
CH_4	2.09	0	−0.23	−0.35	−0.30	−0.45	−0.52	
C_2H_6	2.83	0	−0.30	−0.46		−0.59	−0.67	
C_3H_8	3.45	0	−0.36		−0.58			
n-C_4H_{10}	4.25	0	−0.41		−0.65			
n-C_5H_{12}	4.87	0	−0.56					
n-C_6H_{14}	5.50	0	−0.45					
n-C_7H_{16}	6.75	0	−0.45	−0.76	−0.71	−0.89		
n-C_8H_{18}	6.67	0	−0.65	−0.96	−0.98	−1.13	−1.29	−1.26
Me_4Sn	5.60	0	−0.43	−0.78	−0.80	−0.96		−1.33
Me_4Pb	5.38	0	−0.5 [b]	−0.8 [b]				
Et_4Sn	8.28	0	−0.53	−0.87	−0.97	−1.07		−1.56
Et_4Pb	8.18	0	−0.77	−1.09				
Benzene	3.42	0	−0.17	−0.31	−0.31	−0.46		
Toluene	3.93	0	−0.46	−0.51	−0.41	−0.67	−0.63	−0.53
$PhCH_2Cl$	5.02	0	−0.07	−0.12	−0.04	−0.16		−0.15
$PhCH_2Br$	4.91	0	−0.11	−0.20	−0.14	−0.31		−0.31
p-$NO_2C_6H_4CH_2Cl$		0	−0.10	−0.12	+0.02	−0.15	−0.26	+0.01
Naphthalene	5.04	0	−0.30			−0.58		
EtI	3.32	0	−0.28	−0.43	−0.43	−0.55	−0.74	−0.40
Bu^tCl	4.56	0	−0.26	−0.34	−0.30	−0.46		−0.46
Bu^tBr	4.54	0	−0.39		−0.48			−0.61
Me_3N	1.13	0	+0.03	−0.12			−0.22	
Et_3N	2.51	0	+0.15	−0.05	+0.23	−0.09	−0.23	+0.36
Pyridine	1.60	0	−0.11	−0.15	+0.05	−0.16		−0.08
Iodine	4.15	0	−0.34	−0.50	−0.52	−0.39		
Dioxan	0.28	0	0.00	−0.08	−0.04		−0.20	−0.34
MeCOEt	1.40	0	+0.03	+0.05	−0.08	−0.03	−0.05	
$MeNO_2$	1.04	0	+0.16	+0.32	+0.33	+0.30	+0.33	+0.32
$HgCl_2$	2.11	0	0.50	0.79	0.97 [g]	0.83		1.46
HgI_2	4.38	0	0.15	0.23		0.20		1.21
$Hg(OAc)_2$		0	0.59	0.74		0.63		1.27
Glycine [c]	−3.41	0	1.22	1.39	1.52	1.65		1.74
DL-α-Phenylalanine	−0.93 [d]	0	0.86	1.29	1.53	1.32		1.88
DL-α-Aminocaproic acid	−0.90	0	1.03			1.44		
Et_4NI [e]	0.1	0	1.1	1.4	2.0	1.6	1.9	3.3
Et_4NBr [e]	−0.7	0	1.4	1.6	2.3	1.8	2.2	3.6
Et_4NCl [e]	−1.8	0	1.6	1.9	2.6	2.1	2.5	3.9
$Et_4N^+ + I^-$ [f]	−0.9	0	2.1	3.0	4.2	3.7	4.5	7.3

[a] From data in Tables 1—5 (after conversion, where necessary, to the mole fraction scale) together with previous data from ref. 9. [b] Estimated values, ref. 9. [c] Using Cohn's values [16] for the mole fraction solubility of glycine in water (0.0566) and ethanol (2.3×10^{-5}), the average mole fraction solubility in methanol (1.80×10^{-4}) found in this work and by Cohn, and the remaining solubilities from this work. [d] Using the mole fraction solubility in water (1.54×10^{-3}) found by J. B. Dalton and C. L. A. Schmidt, *J. Biol. Chem.*, 1933, **103**, 549. [e] Ion pairs (ref. 9). [f] Dissociated pair of ions (ref. 9). [g] From data in ref. 14.

for ion pairs.[2,9] There is not enough data on the amino-acids to discuss in more detail these ΔG^o_e values, but much more data is available on transfers of amino-acids from ethanol to water, and summarised in Table 8. When the observed ΔG^x_t values are corrected for the nonelectrostatic effect, all the α-amino-acids listed give rise to very similar ΔG^o_e values, a forceful demonstration that for transfers involving aqueous solvents, the solute volume effect must be taken into account. The ΔG^o_e values for the α-, β-, and ε-amino-acids show that increase in solute dipole moments leads to an increase in ΔG^o_e; these increases in ΔG^o_e are not large, however, and it seems as though ΔG^o_e depends mainly on the extent of charge separation and only secondarily on the dipolar distance.

From the ΔG^x_t values for the solutes in Table 6, we can predict the effect of solvents on values of $\Delta G^{\ddagger}$ or on ΔG^x_t(Tr) for reactions in which relatively nonpolar reactants lead to more polar transition states, Tr. The variation in $\Delta G^{\ddagger}$ with solvent is given by equation (4) so

$$\delta\Delta G^{\ddagger} = \Delta G^x_t(\text{Tr}) - \Delta G^x_t(\text{Reactants}) \qquad (4)$$

that the quantity [ΔG^x_t (Polar solute) − ΔG^x_t (Nonpolar solute)] will provide an indication of the expected

TABLE 7

Calculated values of the nonelectrostatic contribution to free energies of transfer from methanol to water, on the mole fraction scale in kcal mol^{-1} at 298 K

Solute	V [a]	ΔG^x_t(obs) [b]	ΔG^x_n(calc) [c]	ΔG^o_e(calc) [d]
C_2H_6	55	2.83	2.46	0.37
C_3H_8	89	3.45	3.61	−0.16
n-C_4H_{10}	101	4.25	4.03	0.22
n-C_5H_{12}	116	4.87	4.67	0.20
n-C_6H_{14}	132	5.50	5.33	0.17
n-C_7H_{16}	148	6.75	6.02	0.73
n-C_8H_{18}	164	6.67	6.69	−0.02
EtI	81	3.32	3.32	0.00
Benzene	89	3.42	3.61	−0.19
Toluene	107	3.93	4.31	−0.38
Naphthalene	124	5.04	5.00	0.04
$MeNO_2$	54	1.04	2.43	−1.39
MeCOEt	90	1.40	3.65	−2.25
Dioxan	86	0.28	3.50	−3.22
Glycine	57 [e]	−3.41	2.52	−5.93
DL-α-Aminocaproic acid	122 [e]	−0.90	4.92	−5.82
DL-α-Phenylalanine	135 [e]	−0.93	5.46	−6.39
Average ion-pair				−7.5 [f]

[a] Solute molar volume in ml mol^{-1} (see ref. 21). [b] From Table 6. [c] Calculated by the method of Abraham and Johnstone,[2] and converted from the molar to the mole fraction scale. [d] Electrostatic contribution, given by $\Delta G^x_t - \Delta G^x_n$. [e] Molar volumes from ref. 19. [f] Ref. 2, this is the average value for a number of ion pairs of type $R_4N^+X^-$.

TABLE 8

Effects of amino-acid structure on free energies of transfer from ethanol to water, on the mole fraction scale, in kcal mol^{-1} at 298 K

Amino-acid	Structure	V [a]	ΔG^{x}_{t} [b]	ΔG^{x}_{n} [c]	ΔG^{o}_{e}	μ [d]
Glycine	$NH_2CH_2CO_2H$	57	−4.63	2.82	−7.45	13.5
DL-α-Alanine	$CH_3CH(NH_2)CO_2H$	73	−3.90	3.37	−7.27	13.9 [e]
DL-α-Aminobutyric acid	$CH_3CH_2CH(NH_2)CO_2H$	90	−3.24	4.01	−7.25	(13.5)
DL-Valine	$Me_2CHCH(NH_2)CO_2H$	106	−2.94	4.69	−7.63	(13.5)
DL-α-Aminovaleric acid	$MeCH_2CH_2CH(NH_2)CO_2H$	106	−2.73	4.69	−7.42	(13.5)
L-Leucine	$Me_2CHCH_2(NH_2)CO_2H$	122	−2.21	5.37	−7.58	(13.5)
DL-α-Aminocaproic acid	$MeCH_2CH_2CH_2CH(NH_2)CO_2H$	122	−1.93	5.37	−7.30	(13.5)
DL-α-Phenylalanine	$PhCH_2CH(NH_2)CO_2H$	135	−1.79	5.91	−7.70	(13.5)
Glycine	$NH_2CH_2CO_2H$	57	−4.63	2.82	−7.45	13.5
β-Alanine	$NH_2CH_2CH_2CO_2H$	73	−4.28	3.37	−7.65	16.7
ε-Aminocaproic acid	$NH_2(CH_2)_5CO_2H$	122	−4.05	5.37	−9.42	24.1

[a] Molar volume in ml mol^{-1} from refs. 19 and 20. [b] Oberved free energy of transfer from Table 6 and ref. 19. [c] Calculated as in Table 7 for MeOH $\longrightarrow$ water, and from values for the alkanes in Table 6 for EtOH $\longrightarrow$ MeOH. [d] Dipole moment of the amino-acid, E. E. Schrier and R. A. Robinson, *J. Biol. Chem.*, 1971, **246**, 2870; the various α-amino-acids all have about the same dipole moment (see ref. 20). [e] Dipole moment of L-α-alanine, E. E. Schrier and R. A. Robinson, *J. Solution Chem.*, 1974, **3**, 493.

variation in $\delta\Delta G^{\ddagger}$. Inspection of Table 6 shows that the various combinations of [ΔG^{x}_{t}(Polar solute) − ΔG^{x}_{t} (Nonpolar solute)] are only approximately linearly related, there being many anomalies and exceptions even for transfers amongst the alcoholic solvents. Thus from the properties of simple solutes, it may be deduced that $\Delta G^{\ddagger}$ values for reactions in a series of alcohols will in general not be well correlated by linear free energy relationships (l.f.e.r.s). Again, since the various values of ΔG^{x}_{t} (Polar solute) do not fall into well correlated l.f.e.r.s, it is predicted that l.f.e.r.s will not generally be applicable to various ΔG^{x}_{t}(Tr) values in alcoholic solvents.

One reason for the lack of l.f.e.r.s lies in the non-electrostatic effect, which creates difficulties when solutes or transition states of different molar volumes are compared. Suppose, for example, glycine is selected as a model for a highly polar transition state such as that in the solvolysis of t-butyl chloride, [$Bu^{t}Cl$]‡. Since the molar volumes of glycine (57 ml mol^{-1}) and the transition state (116 ml mol^{-1}) differ considerably, it is inappropriate merely to compare values of ΔG^{x}_{t} (glycine) with ΔG^{x}_{t}([$Bu^{t}Cl$])‡; the correct comparison must be between the two sets of ΔG^{o}_{e} values. The molar volumes of t-butyl chloride and its transition state are close in value, so that $\Delta G^{x}_{n}(Bu^{t}Cl) \simeq \Delta G^{x}_{n}([Bu^{t}Cl]^{\ddagger})$ and it may be deduced from equations (3) and (4) that for the solvolysis, $\delta\Delta G^{\ddagger} \simeq \Delta G^{o}_{e}([Bu^{t}Cl]^{\ddagger})$. The molar volume of glycine is close to that of ethane so we may take ΔG^{x}_{n} (glycine) $\simeq \Delta G^{x}_{n}$(ethane) $= \Delta G^{x}_{t}$(ethane). Hence ΔG^{o}_{e} (glycine) $=$ [ΔG^{x}_{t}(glycine) − ΔG^{x}_{t}(ethane)] and the two quantities to be compared are [ΔG^{x}_{t}(glycine) − ΔG^{x}_{t}(ethane)] and $\delta\Delta G^{\ddagger}$. In Table 9 are the relevant values in the final two columns. Except for solvent acetone, there is good agreement between the two sets of data, whereas, as predicted earlier, there is much less correlation between the sets of data ΔG^{x}_{t}(glycine) : ΔG^{x}_{t}([$Bu^{t}Cl$]‡) and ΔG^{x}_{t}(glycine) : $\delta\Delta G^{\ddagger}$.

TABLE 9

Comparison of values of $\Delta G^{\ddagger}$ for the solvolysis of t-butyl chloride with ΔG^{o}_{e} values for glycine in kcal mol^{-1} at 298 K

Solvent	ΔG^{x}_{t} (Glycine) [a]	ΔG^{x}_{t} (Ethane) [a]	ΔG^{o}_{e} (Glycine) [b]	$\delta\Delta G^{\ddagger}$ [c]
Water	−3.41	2.83	−6.24	−6.22
Formamide	−1.73 [d]	($\simeq$0.0) [e]	−1.73	−2.31 [f]
MeOH	0	0	0	0
EtOH	1.22	−0.30	1.52	1.32
$Pr^{n}OH$	1.39	−0.46	1.85	1.68
$Pr^{i}OH$	1.52	(−0.45) [g]	1.97	2.24
$Bu^{n}OH$	1.65	−0.59	2.24	1.94
$Bu^{t}OH$	1.74	(−0.65) [g]	2.39	2.96
Acetone	2.57 [d]	−0.68	3.25	5.38

[a] From Table 6 unless indicated. [b] Calculated as ΔG^{x}_{t} (Glycine) − ΔG^{x}_{t}(Ethane). [c] Values for solvolysis of t-butyl chloride from ref. 9; $\delta\Delta G^{\ddagger} = \Delta G^{\ddagger}$ (Solvent) − $\Delta G^{\ddagger}$ (MeOH). [d] Ref. 19. [e] Estimated value. [f] A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, 1956, **78**, 2770. [g] Estimated from values in Table 6.

Solvent Effects on the Free Energies of Transition States.—Combination of ΔG^{x}_{t} values for reactants (Table 6) with values of $\delta\Delta G^{\ddagger}$ for substitution reactions given in ref. 1 leads to values of the free energy of transfer of transition states, ΔG^{x}_{t}(Tr), through equation (5). Here $\delta\Delta G^{\ddagger} = \Delta G^{\ddagger}$ (solvent 2) − $\Delta G^{\ddagger}$ (solvent 1, methanol), with all second-order rate constants expressed as mole fraction^{-1} s^{-1}. We have incorporated in Table 10 a number of solvolyses of alkyl halides not dealt with in ref. 1 and have also included the results of Reutov and his co-workers[22] on the S_E2 substitution of diethylmercury by mercury(II) chloride in alcohols. The errors in the ΔG^{x}_{t}(Tr) values in Table 10 vary considerably from reaction to reaction, and we have indicated the less reliable values by rounding-off the figures to the nearest 0.1 kcal mol^{-1}.

$$\Delta G^{x}_{t}(\mathrm{Tr}) = \Delta G^{x}_{t}(\mathrm{Reactants}) + \delta\Delta G^{\ddagger} \qquad (5)$$

Since transfers from methanol to water have been dealt with in detail before[2,7,9,21] we confine our comments to transfers from methanol to the other alcohols. As predicted from the behaviour of simple solutes, values of ΔG^{x}_{t} for the various transition states are only approximately linearly related, and so the dissection of $\delta\Delta G^{\ddagger}$ values into initial- and transition-state contributions has not led to any significant improvement in terms of l.f.e.r.s.

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[22] A. N. Kashin, I. P. Beletskaya, V. A. Milyaev, and O. A. Reutov, *Zhur. org. Khim.*, 1974, **10**, 1561.

TABLE 10

Standard free energies of transfer from methanol to other solvents of transition states in substitution reactions,[a] on the mole fraction scale in kcal mol^{-1} at 298 K

Reactants	H_2O	MeOH	EtOH	Pr^nOH	Pr^iOH	Bu^nOH	Bu^tOH
Ph_2CHCl [b]	2.21	0	1.3		2.6		
PhCHMeCl [c]	−0.48	0	1.2				
PhCHMeBr [d]	0.03	0	1.0				
Bu^tCl [e]	−1.65	0	1.06	1.34	1.94	1.48	2.50
Bu^tBr [e]	−1.37	0	0.82		1.62		2.18
$PhCH_2Cl$ [f]	1.88	0	0.7				
$PhCH_2Br$ [g]		0	0.4	0.6	1.4	0.8	
$Me_4Sn + I_2$		0	0.42	0.71	0.64		
$Et_4Sn + I_2$		0	0.27	0.52	0.07		
$Me_4Pb + I_2$		0	0.2	0.2			
$Et_4Pb + I_2$		0	−0.2	−0.2			
$Me_4Sn + HgI_2$		0	0.35	0.51		0.56	2.62
$Et_4Sn + HgI_2$		0	0.41	0.56		0.64	2.75
$Me_4Sn + HgCl_2$	(3.50) [h]	0	0.64	0.84		0.99	2.24
$Et_4Sn + HgCl_2$	(5.27) [h]	0	0.77	1.02		1.10	2.40
$Et_4Sn + Hg(OAc)_2$		0	0.67	0.66		0.54	2.65
$Et_2Hg + HgCl_2$ [i]		0	0.6		1.0		
$Me_3N + ArCH_2Cl$ [j]		0	0.53	0.67		0.65 [k]	
Pyridine + EtI		0	0.17	0.26	0.50	0.25	0.61
Et_3N + EtI	4.04	0	0.19	0.17	0.29	0.26	0.37

[a] Unless otherwise stated, calculated from $\delta\Delta G^{\ddagger}$ values in ref. 1, and ΔG°_{t} (Reactant) values in Table 6. [b] $\Delta G^{\mathrm{x}}_{\mathrm{t}}$ (Ph_2CHCl) for transfer to water calculated to be 7.37 kcal mol^{-1}, and estimated as −0.3 kcal mol^{-1} for transfer to EtOH and Pr^iOH. [c] $\delta\Delta G^{\ddagger}$ values from A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 1597. $\Delta G^{\mathrm{x}}_{\mathrm{t}}$ (PhCHMeCl) for transfer to water calculated to be 5.42 kcal mol^{-1} and for transfer to EtOH estimated as −0.2 kcal mol^{-1}. [d] $\delta\Delta G^{\ddagger}$ values from A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 1602. $\Delta G^{\mathrm{x}}_{\mathrm{t}}$ (PhCHMeBr) for transfer to water calculated to be 5.54 kcal mol^{-1} and for transfer to EtOH estimated as −0.2 kcal mol^{-1}. [e] Refs. 2 and 9. [f] $\delta\Delta G^{\ddagger}$ values from R. E. Robertson and J. M. W. Scott, *J. Chem. Soc.*, **1961**, 1596; R. A. Clement, J. N. Naghizadeh, and M. R. Rice, *J. Amer. Chem. Soc.*, 1960, **82**, 2449; G. Georgoulis, J. Landais, and G. Ville, *J. Chim. Phys.*, 1970, **67**, 450. [g] These values are regarded as approximate only. [h] Extrapolated value (ref. 2). [i] $\delta\Delta G^{\ddagger}$ Values from ref. 22 after conversion to units of mole $fraction^{-1}\ s^{-1}$. Values of $\Delta G^{\mathrm{x}}_{\mathrm{t}}$ (Et_2Hg) estimated to be −0.45 kcal mol^{-1} for transfer to EtOH and −0.70 kcal mol^{-1} for transfer to Pr^iOH. [j] Ar = p-$NO_2C_6H_4$, refs. 2 and 12. [k] iso-$C_5H_{11}OH$.

The seven solvolysis transition states (Table 10) behave as expected, with values of $\Delta G^{\mathrm{x}}_{\mathrm{t}}$(Tr) increasing as the polarity of the transition state increases. The values for transfer from methanol to ethanol may usefully be compared with $\Delta G^{\mathrm{x}}_{\mathrm{t}}$ values for ion pairs of about the same molar volume as the transition state and containing the appropriate halide ion. Details are in Table 11, together with the ratio $\Delta G^{\mathrm{x}}_{\mathrm{t}}(\mathrm{Tr})/\Delta G^{\mathrm{x}}_{\mathrm{t}}(\mathrm{Ion\ pair})$. Although these ratios are only approximate, they do provide an indication of the degree of polarity of the transition states. Thus diphenylmethyl, 1-phenylethyl, and t-butyl halide all seem to undergo solvolysis by quite polar (S_N1) transition states, whereas the benzyl halides seem to be nearer the S_N2 end of the solvolysis spectrum of mechanism.

TABLE 11

Approximate values of $\Delta G^{\mathrm{x}}_{\mathrm{t}}$ for transfer of solvolysis transition states from methanol to ethanol, in kcal mol^{-1} at 298 K

Alkyl halide	$\Delta G^{\mathrm{x}}_{\mathrm{t}}$(Tr) [a]	Ion pair	$\Delta G^{\mathrm{x}}_{\mathrm{t}}$ [b]	Ratio [c]
Ph_2CHCl	1.3	Et_4NCl	1.6	0.8
PhCHMeCl	1.2	Et_4NCl	1.6	0.75
PhCHMeBr	1.0	Et_4NBr	1.4	0.7
Bu^tCl	1.1	Me_4NCl	1.5	0.7
Bu^tBr	0.8	Me_4NBr	1.3	0.6
$PhCH_2Cl$	0.7	Et_4NCl	1.6	0.4
$PhCH_2Br$	0.4	Et_4NBr	1.4	0.3

[a] From Table 10 unless indicated. [b] Refs. 2 and 9. [c] Calculated as $\Delta G^{\mathrm{x}}_{\mathrm{t}}(\mathrm{Tr})/\Delta G^{\mathrm{x}}_{\mathrm{t}}$ (Ion pair).

Values of $\Delta G^{\mathrm{x}}_{\mathrm{t}}$(Tr) in the iododemetallation of the tetra-alkyltins are reasonably large,* so that whatever the structure of the $[R_4Sn{-}I_2]^{\ddagger}$ transition states, they behave as solutes of moderate polarity. On the other hand, the $[R_4Pb{-}I_2]^{\ddagger}$ transition states have $\Delta G^{\mathrm{x}}_{\mathrm{t}}$ values that are surprisingly small in view of the polar nature of the transition states hitherto assumed (see ref. 23).

The S_E2 reactions of tetra-alkyltins with mercury(II) salts represent a quite well studied class of organometallic substitution reactions. Previous work [2,9,21,23] has suggested that the $[R_4Sn{-}HgX_2]^{\ddagger}$ transition states are intermediate in polarity between S_N1 solvolysis transition states, and S_N2 transition states in solvolyses and in Menschutkin reactions. The data in Table 10 by and large supports this interpretation. The only remarkable feature is the very large values of $\Delta G^{\mathrm{x}}_{\mathrm{t}}$(Tr) for transfer to t-butyl alcohol by comparison with transfers to the other alcohols. If the alcoholic solvents interact with the leaving R_3Sn^+ group in the transition state, it is possible that such interaction is inhibited sterically in the case of t-butyl alcohol, thus leading to an increase in the free energy of the transition state. Approximate values of $\Delta G^{\mathrm{x}}_{\mathrm{t}}$ for the transition state in the two-alkyl mercury exchange reaction between diethylmercury and mercury(II) chloride [22] are also in Table 10; these values suggest that the polar nature of the $[Et_2Hg{-}HgCl_2]^{\ddagger}$ transition state is similar to that of the $[R_4Sn{-}HgCl_2]^{\ddagger}$ transition states.

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* Note, however, that values in Pr^iOH are smaller than expected.

[23] M. H. Abraham, ' Electrophilic Substitution at a Saturated Carbon Atom,' in ' Comprehensive Chemical Kinetics,' eds. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1973, vol. 12.

In the Et_3N–EtI reaction, the determination of initial- and transition-state $\Delta G^x{}_t$ values has resolved a previous [1] anomaly. The very low value of $\Delta G^\ddagger$ in t-butyl alcohol can now be seen to be due mainly to initial-state effects, and the value of $\Delta G^x{}_t([Et_3N/EtI]\ddagger)$ is not abnormally low in this solvent. In fact all values of $\Delta G^x{}_t$ for the transfer of Menschutkin reaction transition states from methanol to the other alcohols are quite small. Towards change in alcohol solvent these transition states behave as solutes of only low or moderate polarity (compare, for example, values of $\Delta G^x{}_t$ for the $[Et_3N–EtI]^\ddagger$ transition state with values for nitromethane in Table 6). For the Et_3N–EtI reaction, a more complete comparison with reactants and product ion pair can be made (Table 12) and it is clear that the transition state more resembles the reactants than the product ion pair.

TABLE 12

Comparison of solvent effects on the $[Et_3N–EtI]^\ddagger$ transition state with those on reactants and products, on the mole fraction scale, in kcal mol^{-1} at 298 K

$\Delta G^x{}_t$	H_2O	MeOH	EtOH	Pr^nOH	Pr^iOH	Bu^nOH	Bu^tOH
Reactants [a]	5.8	0	−0.1	−0.5	−0.2	−0.6	0.0
$[Et_3N/EtI]\ddagger$ [b]	4.0	0	0.2	0.2	0.3	0.3	0.4
$Et_4\overset{+}{N}\overset{-}{I}$ [c]	0.1	0	1.1	1.4	2.0	1.6	3.3
$Et_4\overset{+}{N} + \overset{-}{I}$ [d]	−0.9	0	2.1	3.0	4.2	3.7	7.3

[a] From Table 6. [b] From Table 8. [c] Values for the ion pair from ref. 9. [d] Values for the pair of ions from ref. 9.

Conclusions.—From data on $\Delta G^x{}_t$ values for the transfer of solutes and transition states from methanol to other alcohols, we suggest that l.f.e.r.s between $\Delta G^\ddagger$ values of different types of substitution reaction in alcoholic solvents will be of only limited applicability. Dissection into initial-state and transition-state contributions is of little help since there are only poor or moderate l.f.e.r.s between different $\Delta G^x{}_t(Tr)$ values in these solvents.

Comparison of values of $\Delta G^x{}_t(Tr)$ with each other and with a number of simple solutes suggests that the order of increasing polar character of the transition states is $[R_4Pb–I_2]^\ddagger < [R_3N–RI]^\ddagger \leqslant [R_4Sn–I_2]^\ddagger < [R_4Sn–HgX_2]^\ddagger < [Bu^tX]^\ddagger \leqslant [PhCHMeX]^\ddagger \leqslant [Ph_2CHX]^\ddagger$. As models for highly polar transition states, both α-amino-acids and tetra-alkylammonium halide ion pairs may be used, but care must be taken to choose a model solute of about the same molar volume as the transition state to which it is to be compared.

APPENDIX

An Analysis of the Winstein–Grunwald mY *Equation*.—We have shown from the behaviour of simple solutes that in general l.f.e.r.s between values of $\Delta G^\ddagger$ for various reactions in alcoholic–hydroxylic solvents are not expected to obtain. However, the Winstein–Grunwald equation [24] is a classic example of a l.f.e.r. often applied to reactions in these solvents, so that it seems obligatory to analyse our data further in order to ascertain the conditions under which the Winstein–Grunwald equation would be expected to apply.

Let two reactions proceed through transition states Tr^a and Tr^b, in solvents 1 (the standard) and 2. Then by methods we have dealt with above, we can dissect the values of $\delta\Delta G^\ddagger$ into $\Delta G^o{}_t$(Reactants) and $\Delta G^o{}_t(Tr)$ and can dissect $\Delta G^o{}_t(Tr)$ further into $\Delta G^o{}_n(Tr)$ and $\Delta G^o{}_e(Tr)$. Suppose for the two reactions we have equation (6).

$$\Delta G^o{}_e(Tr^a)/\Delta G^o{}_e(Tr^b) = \alpha \qquad (6)$$

Then since $\Delta G^o{}_t = \Delta G^o{}_e + \Delta G^o{}_n$, and since $\Delta G^o{}_t(Tr) = \Delta G^o{}_t(\text{Reactants}) + \delta\Delta G^\ddagger$ we may work backwards and calculate that equation (7) must hold. If the reactants

$$\begin{aligned}&\Delta G^o{}_t(\text{Reactants}^a) + \delta\Delta G_a{}^\ddagger - \Delta G^o{}_n(Tr^a)\\ &\quad = \alpha\Delta G^o{}_t(\text{Reactants}^b) + \alpha\delta\Delta G^\ddagger{}_b - \alpha\Delta G^o{}_n(Tr^b) \qquad (7)\end{aligned}$$

are reasonably nonpolar, as in the solvolysis of alkyl halides, we may write approximation (8) and since also

$$\Delta G^o{}_t(\text{Reactants}) \doteqdot \Delta G^o{}_n(\text{Reactants}) \qquad (8)$$

the molar volume of the reactants is usually close to the molar volume of the transition state, approximation (9)

$$\Delta G^o{}_t(\text{Reactants}) \doteqdot \Delta G^o{}_n(\text{Reactants}) \doteqdot \Delta G^o{}_n(Tr) \qquad (9)$$

also follows. Thus equation (7) is quite simply transformed into (10) which is an alternative statement of the Winstein-Grunwald equation, in which $\alpha = (m_a/m_b)$.

$$\delta\Delta G^\ddagger{}_a = \alpha\delta\Delta G^\ddagger{}_b \qquad (10)$$

For various solvent pairs, the Winstein–Grunwald *m* value will only remain constant if α is constant, in other words if the electrostatic part of $\Delta G^o{}_t(Tr)$ remains constant. Thus the extent of charge separation in the transition states must remain constant if the Winstein–Grunwald equation is to apply (in von Schleyer's terms,[25] the extent of nucleophilic solvent participation must remain constant). Furthermore, the Winstein–Grunwald equation will not apply at all unless $\Delta G^o{}_t$(Reactants) $\doteqdot \Delta G^o{}_n(Tr)$, that is unless the reactants behave as inert nonpolar solutes.*

There is thus no conflict between our conclusions and

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* This is for the case of relatively nonpolar reactions proceeding to a polar transition state; for polar reactants going to a nonpolar transition state, the transition state must behave as an inert nonpolar solute.

[24] E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 846.

[25] T. W. Bentley and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, in the press (personal communication from Dr. Bentley).

previous observations of l.f.e.r.s between *e.g.* values of $\Delta G^{\ddagger}$ for different reactions in hydroxylic solvents; special circumstances, as outlined here, are necessary for l.f.e.r.s to apply.

EXPERIMENTAL

The alcohols, and most of the solutes, were purified as described.[1]

Limiting values of the Raoult's law activity coefficients of volatile solutes were obtained at 298.15 ± 0.05 K using analytical g.l.c. to determine the concentration of the solute in the head-space above dilute solutions of the solute in the solvents concerned. The procedure was as described before;[7-9] the instrument was a Perkin-Elmer F-11 flame ionisation gas chromatograph. Activity coefficients of ethyl iodide were determined using columns of either 20% diglycerol on Celite or 10% Carbowax on Celite; the solute was eluted before the alcoholic solvents and reproducible values of γ_∞ were obtained. Pyridine was analysed using the 20% diglycerol column, and for the two benzyl halides a column of 15% diethylene glycol succinate on Celite was required. In these last three cases, the solutes were eluted after the large solvent peaks, so that the calculated values of γ_∞ are not as reliable as those for ethyl iodide and triethylamine.

Solubilities of solutes at 298.15 ± 0.10 K were obtained by equilibrating mixtures of the solute and solvent for several days. Equilibration was aided first by using an ultrasonic bath to agitate the mixture and then by gentle agitation from time to time. Finally the mixtures were left to settle, and aliquot portions of the saturated solutions carefully withdrawn. In the case of the more soluble solutes, the aliquot portions were quickly transferred to pre-weighed vessels, the vessel stoppered and reweighed, and the proportion of solute to solvent determined by weight. For the the less soluble solutes, the concentration in the aliquot portions was determined by volume, and the molar concentration of solute converted to mole fractions using the dilute solution approximation.

Analyses of the aliquot portions were carried out as follows. Mercury(II) chloride and mercury(II) acetate were determined using a back titration method involving ethylenediamine tetra-acetic acid.[11] Mercury(II) iodide was determined either spectrophotometrically[26] as HgI_3^- or directly by weight. The *p*-nitrobenzyl chloride was determined directly by weight after evaporation of the aliquot portions under vacuum. Iodine was determined volumetrically using sodium thiosulphate and the proportion of iodine to alcohol calculated by weight.

The amino acids were analysed by the ninhydrin method, using a freshly prepared reagent [ninhydrin (1 g) plus hydrandantin (0.15 g) made up to 50 ml with acetate buffer (10 ml) and methyl cellosolve; the buffer was prepared from sodium acetate trihydrate (272 g) plus glacial acetic acid (50 ml) made up to 500 ml with distilled water]. Aliquot portions (2 ml) of the saturated solutions were gently evaporated to dryness in test tubes, and distilled water (2 ml) then added. A series of test tubes containing various aqueous standard solutions of the particular amino-acid (2 ml) and also blank distilled water (2 ml) was prepared, and to all the test tubes was added the reagent solution (2 ml). The mixtures were heated in a boiling water bath for 15 min, cooled in ice, shaken for 15 s, made up to a given standard volume (usually either 25 or 10 ml) with 50 : 50 v/v H_2O–Pr^iOH, shaken for 30 s, and their optical densities then recorded using an SP 3000 spectrophotometer ($\lambda_{max.}$ 560 nm). The concentrations of the amino-acid were then calculated, taking into account the blank correction, from a (linear) plot of concentration against optical density constructed using the various standard solutions. Each time any amino-acid analyses were carried out, the above procedure was run through in its entirety, using the appropriate amino-acid standard solutions. As a check, following Cohn,[16] after the amino-acids had been equilibrated with solvent, the saturated solution was discarded and the residual undissolved solid then equilibrated with a fresh portion of solvent; within experimental error, the observed solubility was unchanged.

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[5/861 *Received, 7th May,* 1975]

[26] M. H. Abraham, G. F. Johnston, and T. R. Spalding, *J. Inorg. Nuclear Chem.*, 1968, **30**, 2167.