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Free Energies of Solution of Rare Gases and Alkanes in Water and Nonaqueous Solvents. A Quantitative Assessment of the Hydrophobic Effect

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Abstract: Standard free energies of solution of the rare gases and alkanes in water and in over 16 nonaqueous solvents are tabulated. It is shown that it is difficult to reach unambiguous conclusions about the existence of the hydrophobic effect from plots of $\Delta G_s°$ against solute radius or solute volume, partly because of inherent uncertainties in the values of the solute radius. It is found that $\Delta G_s°$ values for both rare gases and alkanes in all nonaqueous solvents are well correlated through linear equations: $\Delta G_s°(\text{solvent}) = m\Delta G_s°(\text{benzene}) + c$ and $\Delta G_s°(\text{solvent}) = lR + d$, where R is a solute parameter related to solute radius. When applied to $\Delta G_s°$ values for solution in water, these equations show conclusively that the solution of alkanes (but not rare gases) in water is quite anomalous. The $-CH_2-$ increment for partition of *n*-alkanes between hexane and water is 0.92 kcal mol^{-1} in favor of hexane, and can be separated into a favorable gas → hexane contribution of 0.74 kcal mol^{-1} and an unfavorable gas → water contribution of 0.18 kcal mol^{-1}. The latter is further dissected into a true (unfavorable) hydrophobic contribution of 0.54 kcal mol^{-1} and a favorable normal solvent effect of 0.36 kcal mol^{-1}. Methods for the estimation and prediction of $\Delta G_s°$ values in nonaqueous solvents are discussed.

Liszi and I have tabulated data on the free energy of solution of rare gases and the lower alkanes in a variety of solvents.[1] We observed that, when the $\Delta G_s°$ values for a series of solutes in a given solvent were plotted against the solute radius, reasonable straight lines were obtained for every solvent studied except water. In the latter case, a straight line was found only for solution of the rare gases and it was suggested[1] that the solution of alkanes in water gave rise to anomalous free energies. While this work was in the press, Cramer[2] showed that, when $\Delta G_s°$ values for rare gases and *n*-alkanes in water and 1-octanol were plotted against solute molecular volume, quite similar patterns of behavior were observed for the two solvents. Cramer[2] concluded that the mechanism of solvation of the above solutes by water and 1-octanol was fundamentally similar and hence that prevailing descriptions of the hydrophobic effect could not be correct.

It is obviously of great importance to establish whether or not water is unique with respect to the solution of hydrocarbons, and I thought it useful to assemble results on the free energy of solution of rare gases and an extended series of alkanes, and to explore the observed patterns of the $\Delta G_s°$ values. The latter are expressed as standard free energies of solution in kcal mol^{-1}, and refer to the process

$$\text{solute (gas, 1 atm)} \rightarrow \text{solute (solution, unit mole fraction)} \qquad (1)$$

Values for the rare gases and the C_1 to C_4 alkanes in water are from the review by Wilhelm, Battino, and Wilcock;[3] those for solution of the higher *n*-alkanes in water are from results compiled by Hine and Mookerjee.[4] Data on the rare gases in nonaqueous solvents are mainly from the work of Battino et al.,[5] supplemented by values given by de Ligny et al.[6] and by Linford and Thornhill.[7] For the rare gases in methanol, the results of Beckwith and of Law were used.[8] Numerous workers[9-25] have reported data from which were calculated $\Delta G_s°$ values for alkanes in nonaqueous solvents. Values of $\Delta G_s°$ for the rare gases and *n*-alkanes in various solvents are in Table I, together with values for solvent 1-octanol, used by Cramer.[2]

Inspection of Table I shows that, for any given nonaqueous solvent, $\Delta G_s°$ decreases with increasing solute size. This trend is not easy to quantify, because there is no unambiguous measure of solute size for the nonelectrolytes involved. In Table II are given some values of solute radii (Å) used by various workers. The rare gas radii used by Abraham and Liszi[1] were taken from Huheey[26] and differ considerably from those used by Cramer,[2] taken from the work of Bondi.[27] Other sets of rare-gas radii[6,28] agree with those used by Abraham and Liszi, but yet others[29] are close to those used by Cramer. It seems clear that any analysis of $\Delta G_s°$ values and solute size will suffer from the inherent difficulty of assigning solute radii (and hence molecular volume). This is illustrated in Figures 1 and 2, where are given plots of $\Delta G_s°$ for rare gases and C_1 to C_5 *n*-alkanes in benzene, 1-octanol, and water against solute radius; in Figure 1 are used the radii of Abraham and Liszi and in Figure 2 the radii of Cramer are used. Although there is considerable scatter, especially in Figure 1, a fairly straight line can be drawn through all the points in benzene and in 1-octanol. The discrepancies, although apparently quite large, are actually within the uncertainty in solute radius. This can be demonstrated by the construction of a set of solute radii, R, designed so that plots of $\Delta G_s°$ against R yield straight lines for the case of the nonaqueous solvents. These constructed radii are in

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Table I. Standard Free Energies of Solution of Gaseous Solutes (kcal mol^{-1}) at 298 K

solvent	He[a]	Ne[a]	Ar[a]	Kr[a]	Xe[a]	Rn	CH_4[b]	C_2H_6[b]	C_3H_8	n-C_4H_{10}	n-C_5H_{12}	n-C_6H_{14}	n-C_7H_{16}	n-C_8H_{18}[c]
decane	4.91	4.70	3.55	2.92	2.43[7]	1.49[6]	3.21[7]	1.97[9]	1.16[9]	0.42[9]	−0.25[13]	−0.98[13]	−1.68[13]	−2.53
hexane	4.89	4.67	3.54	2.94	2.16[7]	1.55[6]	3.14	2.06[9]	1.30[9]	0.55[9]	−0.20[d]	−0.96[d]	−1.66[d]	−2.36
cyclohexane	5.34	5.13	3.86	3.18	2.30[7]		3.39[11]	2.22[11]	1.40[7]					−2.43
CCl_4			3.91[7]	3.43[7]	2.79[7]		3.47[7]	2.28[9]	1.46[9]	0.61[9]		−0.79[14]	−1.47[15]	−1.97
toluene	5.47	5.26	4.05	3.37	2.50	1.81[6]	3.67[7]	2.47[7]	1.55[7]					−2.16
benzene	5.61	5.39	4.17	3.49	2.64	1.92[6]	3.66	2.49[9]	1.72[9]	0.93[9]	0.20[d]	−0.52[19]	−1.17[16]	−2.02
PhCl	5.67	5.47	4.19	3.49	2.60		3.71	2.50	1.60[7]					−1.91
PhBr	5.81	5.61	4.32	3.60	2.70		3.83	2.59	1.80					−1.95
PhI	6.02	5.82	4.51	3.78	2.80		4.02[7]	2.58[7]	1.68[7]					
acetone	5.41	5.19	4.15	3.53	2.75		3.73	2.75	2.05		0.75[20]	0.15[10]		−0.93
$PhNO_2$	6.09	5.78	4.58	3.89	3.05		4.06[10]	2.88[10]	2.24[10]	1.55[10]	0.92[10]	0.26[10]	−0.38[10]	−0.93
NMPyrrol[e]							4.10[10]	2.96[10]	2.40[10]	1.73[10]	1.17[20]	0.54[18]	0.08[10]	−0.35
MeCN										2.12[24]	1.54[17]	0.96[10]	0.42[17]	0.06
PC[e]							4.17[10]	3.23[10]	2.77[10]	2.16[10]	1.84[10]	1.38[18]	0.82[10]	0.32
$MeNO_2$	6.02	5.82	4.77	4.20	3.55						2.12[20]	1.33[10]		0.47
Me_2SO[e]	6.20	6.05	5.20	4.57	3.78		4.62[10]	3.53[10]	3.10[10]	2.47[10]	2.21[10]	1.67[10]	1.18[10]	0.62
1-octanol[f]	5.61	5.49	4.20	3.66	2.81		3.68	2.53	1.98	1.43	0.92			−1.61
isobutyl alcohol	5.45	5.21	4.12	3.54										
1-butanol							3.73[11]	2.69[11]			0.60[10]		−0.69[10]	−1.14
1-propanol							3.83[11]	2.82[11]					−0.45[21]	−0.96
ethanol	5.61	5.41	4.38			2.56[6]	3.90[11]	2.98[11]	2.35[12]	1.65[22]	1.15[22]	0.52[10]	−0.13[22]	−0.66
methanol	5.76[8]	5.58[8]	4.57[8]	4.02[8]			4.18[11]	3.28[11]	2.71[12]	2.06[12]	1.71[20]	1.00[10]	0.31[23]	−0.01
$(CH_2OH)_2$							5.13[10]	3.81[10]	3.56[10]	3.31[10]		2.91[10]	2.46[10]	
water[g]	7.03	6.94	6.27	5.93	5.60	5.15[6]	6.28	6.11	6.23	6.35	6.61	6.82	6.89	7.16

[a] Values from ref 1 and 5 unless shown otherwise. [b] From ref 1 unless shown otherwise. [c] All values for n-octane calculated from data by Rohrschneider.[25] [d] Calculated from vapor pressures. [e] Abbreviations: NMPyrrol (N-methylpyrrolidone), PC (propylene carbonate), and Me_2SO (dimethyl sulfoxide). [f] Values used by Cramer.[2] If the $\Delta G_s°$ values for water were taken as those used in the present paper, then the resulting $\Delta G_s°$ values for 1-octanol calculated from 1-octanol/water partition coefficients[2] would be slightly different. The value for n-octane is a direct determination from ref 25. [g] Values from ref 3 and 4. The value for n-octane is from ref 4.

Table II. Radii[a] of Solutes (Å)

	Abraham and Liszi[1,b]	Cramer[2,c]	Day and Selbin[28]	Hirschfelder[29]	de Ligny[6]	R[d]
He	1.29	1.40	1.28	1.44	1.29	1.32
Ne	1.40	1.54	1.39	1.56	1.41	1.39
Ar	1.71	1.88	1.71	1.92	1.72	1.75
Kr	1.80	2.02	1.80	2.02	1.80	1.96
Xe	2.03	2.16	2.00	2.27	2.03	2.20
Rn			2.20		2.18	2.39
CH_4	1.90	1.89		2.14	1.90	1.90
C_2H_6	2.21	2.21		2.48	2.20	2.26
C_3H_8	2.53	2.46		2.84	2.53	2.48
n-C_4H_{10}	2.76	2.67		2.80		2.71
n-C_5H_{12}	2.89	2.84				2.89
n-C_6H_{14}	3.01				2.99	
n-C_7H_{16}	3.13				3.13	
n-C_8H_{18}	3.24				3.29	

[a] These are the van der Waals or Lennard-Jones radii. [b] Values for the rare gases were taken from ref 26. [c] All values were taken from ref 27. [d] Values that give rise to the linear eq 3, $\Delta G_s° = lR + d$ (see text).

Table II and are just as reasonable as any of the other sets of radii. Thus, in terms of solute radius, it can plausibly be argued that the solutions of rare gases and n-alkanes in benzene (a typical nonaqueous solvent) and 1-octanol follow the same pattern of behavior. On the other hand, no adjustment of solute radii will yield a single linear plot for both rare gases and n-alkanes in water. Use of the solute radius as a measure of solute size therefore leads to the conclusion that the solution of n-alkanes in water is in some way anomalous.

In Figures 3 and 4 are given, following Cramer, plots of $\Delta G_s°$ against solute molecular volume; in Figure 3 are used volumes from Abraham and Liszi's radii and in Figure 4 volumes used by Cramer.[2,30] Cramer's method of analysis is illustrated in the plots for 1-octanol and water: he constructs a straight line for the rare gases and then, omitting the point for methane, constructs another straight line for the C_2 to C_5 n-alkanes. The resulting V shape for 1-octanol is quite similar to the V shape obtained for water, again by leaving out the point for methane. Cramer argues that the two lines of different slope obtained for 1-octanol require two different modes of solute-solvent interaction, one for rare gas-solvent and one for n-alkane-solvent interaction. Furthermore, because both 1-octanol and water give rise to the V-shaped lines, he suggests that solvation by 1-octanol and water must have many common features. However, another method of dealing with the selection of points in Figures 3 and 4 for the nonaqueous solvents is merely to draw a smooth curve through them all; this is illustrated for solvent benzene in the two figures. If a smooth curve can be drawn through the points for benzene or 1-octanol, it implies that the mechanism of solvation of the rare gases

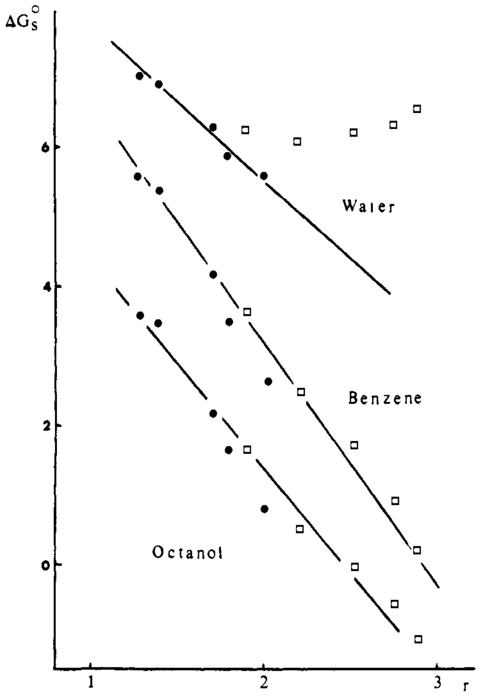


Figure 1. Plot of ΔG_s°/kcal mol^{-1} against solute radius r/Å (taken from Abraham and Liszi); the ΔG_s° values in 1-octanol have been reduced by 2 kcal mol^{-1} on the graph. Rare gases, ●; n-alkanes, □.

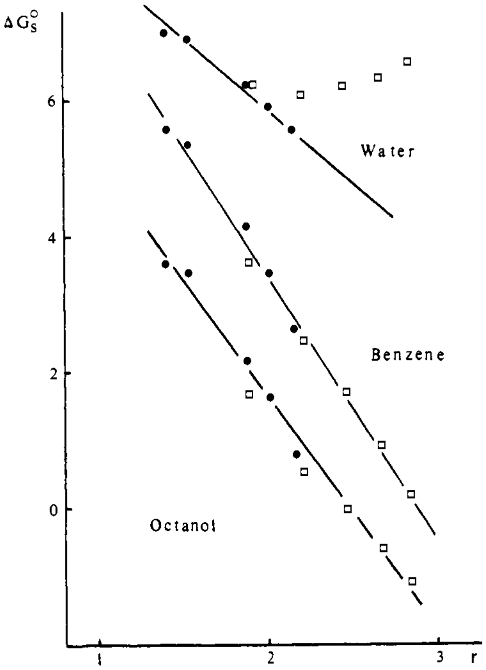


Figure 2. Plot of ΔG_s°/kcal mol^{-1} against solute radius r/Å (taken from Cramer); the ΔG_s° values in 1-octanol have been reduced by 2 kcal mol^{-1} on the graph.

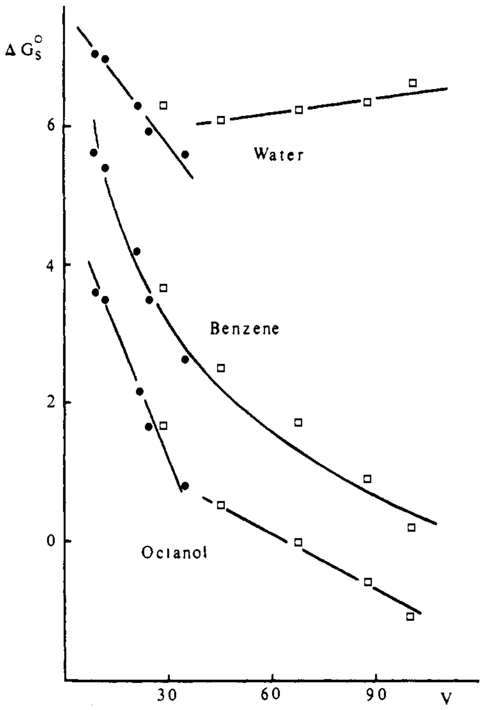


Figure 3. Plot of ΔG_s°/kcal mol^{-1} against solute molecular volume V/Å^3 (using the radii of Abraham and Liszi); the ΔG_s° values for 1-octanol have been reduced by 2 kcal mol^{-1} on the graph.

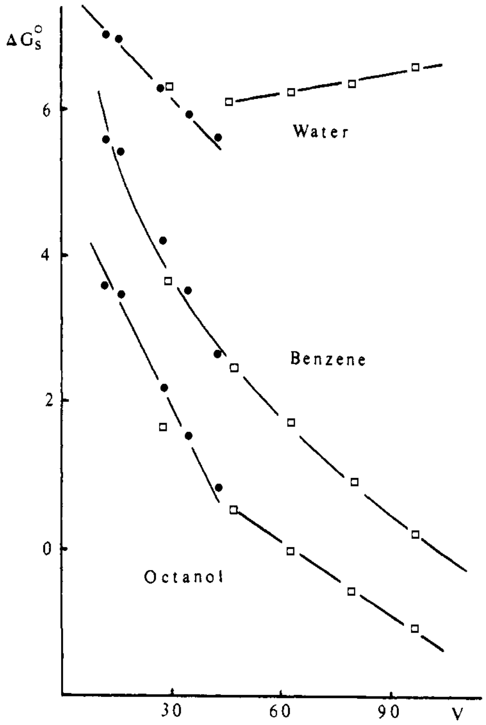


Figure 4. Plot of ΔG_s°/kcal mol^{-1} against solute molecular volume V/Å^3 (using the radii of Cramer); ΔG_s° values for 1-octanol have been reduced by 2 kcal mol^{-1} on the graph.

and the n-alkanes could be similar. Inspection of Figures 3 and 4 shows that there is no clear-cut distinction between a smooth curve and the V-shaped lines. In addition, since it is possible to construct radii, R, to produce a single straight line for rare gases and n-alkanes in terms of plots of ΔG_s° against R, it follows that use of these radii must result in a smooth curve when ΔG_s° is plotted against $4\pi R^3/3$ for the nonaqueous solvents.

Because different conclusions can be drawn from plots of ΔG_s° against solute radius or solute molecular volume, and because these conclusions seem to be quite critically dependent on the numerical values of the solute radii used, it seemed advisable to investigate other methods of analysis.

Linear Relationships in Nonaqueous Solvents. If any given nonaqueous solvent, for example, benzene, is arbitrarily taken as a reference solvent, a set of linear equations can be constructed of type $y = mx + c$:

$$\Delta G_s^\circ(\text{in solvent}) = m\Delta G_s^\circ(\text{in benzene}) + c \qquad (2)$$

Table III. An Analysis of $\Delta G_s°$ Values Based on Equation 2

	rare gases					*n*-alkanes					rare gases and *n*-alkanes				
solvent	no.[a]	m	c	σy	ρ	no.[a]	m	c	σy	ρ	no.[a]	m	c	σy	ρ
decane	6	0.895	−0.13	0.11	0.9968	8	1.001	−0.50	0.04	0.9998	14	0.978	−0.47	0.11	0.9989
hexane	6	0.907	−0.22	0.02	0.9999	8	0.985	−0.42	0.05	0.9996	14	0.958	−0.41	0.07	0.9995
cyclohexane	5	1.025	−0.41	0.01	0.9999	4	1.026	−0.36	0.01	0.9999	9	1.018	−0.36	0.02	0.9999
CCl_4	3	0.733	0.86	0.01	0.9998	7	0.981	−0.20	0.12	0.9983	10	1.002	−0.17	0.16	0.9973
toluene	6	0.996	−0.11	0.01	0.9999	4	1.024	−0.12	0.06	0.9997	10	1.003	−0.12	0.06	0.9997
benzene	8	1	0			8	1	0			14	1	0		
PhCl	5	1.037	−0.13	0.01	0.9999	4	0.984	0.04	0.09	0.9993	9	1.000	0.02	0.07	0.9996
PhBr	5	1.051	−0.07	0.01	0.9999	4	1.014	0.08	0.03	0.9999	9	1.020	0.07	0.03	0.9999
PhI	5	1.083	−0.03	0.03	0.9998	3	1.208	−0.41	0.02	0.9999	8	1.114	−0.16	0.06	0.9992
acetone	5	0.889	0.42	0.02	0.9999	6	0.830	0.65	0.07	0.9993	11	0.839	0.64	0.06	0.9995
$PhNO_2$	5	1.013	0.36	0.03	0.9997	8	0.884	0.74	0.07	0.9992	13	0.922	0.73	0.10	0.9989
NMPyrrol						8	0.792	1.06	0.11	0.9974					
MeCN						5	0.718	1.39	0.10	0.9930					
PC						8	0.665	1.65	0.07	0.9984					
$MeNO_2$	5	0.836	1.31	0.03	0.9997	3	0.717	1.87	0.14	0.9846	8	0.722	1.82	0.14	0.9977
Me_2SO	5	0.806	1.73	0.07	0.9974	8	0.679	1.98	0.11	0.9968	13	0.735	1.97	0.14	0.9970
1-octanol	5	0.953	0.29	0.05	0.9991	6	0.904	0.44	0.20	0.9940	11	0.921	0.42	0.15	0.9976
isobutyl alcohol	4	0.896	0.40	0.02	0.9997										
1-butanol						5	0.879	0.48	0.11	0.9986					
1-propanol						4	0.858	0.67	0.09	0.9993					
ethanol	4	0.825	0.97	0.02	0.9999	8	0.821	0.93	0.05	0.9994	12	0.828	0.94	0.05	0.9998
methanol	4	0.822	1.15	0.00	0.9999	8	0.757	1.40	0.11	0.9972	12	0.767	1.40	0.09	0.9989
$(CH_2OH)_2$						6	0.479	2.96	0.28	0.9522					
water	6	0.503	4.21	0.04	0.9987	8	−0.180	6.67	0.14	−0.9227	14	−0.049	6.48	0.56	−0.2030

All Solutes in Tables I and IV

acetone	16	0.8342	0.651	0.069	0.9997
1-octanol	13	0.9076	0.476	0.146	0.9977
ethanol	20	0.8307	0.923	0.053	0.9997
methanol	20	0.7747	1.369	0.092	0.9991
water	22	−0.067	6.337	0.537	−0.0345

[a] Number of solutes used.

Details of an analysis based on eq 2 are in Table III, in which are given the values of m and c together with the standard deviation in y, σy, and the correlation coefficient ρ. The outstanding feature is that for any nonaqueous solvent the values of m, σy, and ρ are almost the same for the rare gases only, the C_1 to C_8 *n*-alkanes, or the rare gases plus the *n*-alkanes. The simplest and at the same time the most general explanation is that in any given solvent the nature of the solution process of the rare gases and *n*-alkanes is similar, and that whatever is the nature of the solution process it is fundamentally the same in all 16 nonaqueous solvents for which there is extensive data. For the 15 nonaqueous solvents plotted against benzene, eq 2, ρ values for the rare gases plus *n*-alkanes range from 0.9999 to 0.9970 and the σy values average at only 0.09 kcal mol^{-1}. It is abundantly clear that the linear eq 2 applies to both the rare gases and the *n*-alkanes in these 15 solvents. Application of eq 2 to $\Delta G_s°$ values in water leads to quite different results. First of all the plot for the rare gases only is very good (ρ = 0.9987) with a slope that is of quite reasonable value by comparison with m values in the nonaqueous solvents, especially in the alcoholic solvents. Solution of the rare gases in water is thus not exceptional as compared to their solution in the nonaqueous solvents. However, although, when the *n*-alkanes are taken alone, there is also a quite good straight line (ρ = −0.9227), the slope of the line (m = −0.180) is very different from corresponding slopes in all the nonaqueous solvents. Solution of the *n*-alkanes in water thus gives rise to a very different pattern of $\Delta G_s°$ values than does solution of these solutes in the nonaqueous solvents. This analysis resolves the problem obtained by analyses in terms of solute radius or molecular volume and shows that the solution of *n*-alkanes in water must be fundamentally different from solution in the nonaqueous solvents. This conclusion is reinforced by the results of taking the rare gases and *n*-alkanes together (final five columns of Table III). Against benzene as the standard solvent, $\Delta G_s°$ values in the 15 other nonaqueous solvents are very well correlated by eq 2, with ρ values ranging from 0.9999 to 0.9970; yet in the case of water there is almost no correlation at all when the rare gases and *n*-alkanes are taken together (ρ = −0.2030). In Figure 5 are plotted $\Delta G_s°$ values for solvents acetone, methanol, and water against those for benzene. It is quite clear that the $\Delta G_s°$ values for the *n*-alkanes in water are much more positive than expected, or, in other words, a hydrophobic effect is operative. The observation of a hydrophobic effect does not depend on the selection of benzene as a reference solvent, and exactly the same conclusion would be reached were any other nonaqueous solvent chosen as the reference solvent.

The scope of eq 2 may be examined further through data on the solutes isobutane, cycloalkanes, and alkane-like solutes of type R_4M, results on which have been reported by de Ligny and van der Veen[31] and by myself.[32] Observed $\Delta G_s°$ values are in Table IV and an analysis for all solutes in Tables I and IV is given in Table III. All solutes in Table IV are well correlated by eq 2, with ρ values for the total data in Tables I and IV ranging from 0.9997 to 0.9977 for the four nonaqueous solvents used.[33] As might be expected, the alkane or alkane-like solutes in Table IV are not correlated by eq 2 when taken with the solutes in Table I, in the case of water. The ρ value of −0.0345 for the 22 solutes in Tables I and IV with solvent water is in complete contrast to the excellent correlations found with the nonaqueous solvents.

Correlations Using the *R* Values. It has been shown that, for the rare gases and the smaller *n*-alkanes, it is possible to construct a set of solute radii that give rise to linear correlations with $\Delta G_s°$ values in nonaqueous solvents. For the higher *n*-

Table IV. Standard Free Energies of Solution of Gaseous Alkane and Alkane-Like Solutes (kcal mol^{-1}) at 298 K[a]

solvent	isobutane	cyclopentane	cyclohexane	Me_4C	Me_4Si	Me_4Ge	Me_4Sn	Et_4C	Et_4Si	Et_4Sn	Et_4Pb
benzene	1.24[9]	−0.21[b]	−0.91[c]	0.84[d]			−0.66	−2.50		−4.05	−4.25
acetone				1.32			0.09	−1.42		−2.82	−2.76
1-octanol		0.33[2]	−0.19[2]								
ethanol	1.93[12]	0.79[e]	0.09[f]	1.51			0.46	−1.18	−1.35	−2.42	−2.63
methanol	2.33[12]	1.18[g]	0.48[h]	2.00	1.80	1.47	0.89	−0.50	−0.70	−1.89	−1.86
water	6.60[3]	5.48[4]	5.50[4]	6.78[3]	7.32	7.07[i]	6.36[i]	6.50	7.04	6.39	6.32

[a] All values from de Ligny and van der Veen[31] or from Abraham (ref 32 and unpublished work) unless shown otherwise. [b] With $\gamma^\infty = 1.69$, the same as cyclohexane. [c] J. A. V. Butler and P. Harrower, *Trans. Faraday Soc.*, **33**, 171 (1937). [d] E. W. Funk and J. M. Prausnitz, *Ind. Eng. Chem.*, **62**, No. 9, 8 (1970). [e] With $\gamma^\infty = 9.05$, the same as cyclohexane. [f] R. H. Stokes and M. Adamson, *J. Chem. Soc., Faraday Trans. 1*, **73**, 1232 (1977). [g] With $\gamma^\infty = 17.4$, the same as cyclohexane. [h] S. Madhavan and P. S. Murti, *Chem. Eng. Sci.*, **21**, 465 (1966). [i] Recalculated from data in ref 31 with more recent values for the vapor pressure of Me_4Ge and Me_4Sn.

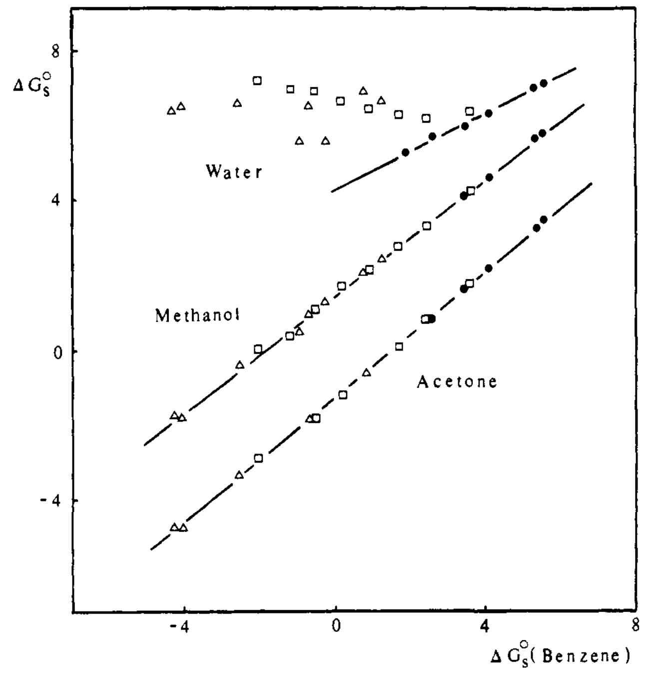


Figure 5. Plot of ΔG_s°/kcal mol^{-1} against ΔG_s° in benzene; the ΔG_s° values for acetone have been reduced by 2 kcal mol^{-1} on the graph. Solutes in Table IV, Δ.

alkanes, the R values chosen to yield linear correlations do not quite correspond to previous estimates of solute radii, and it is then better to regard such R values simply as empirical solute parameters (Table V), designed so that the linear relationship, eq 3, applies:

$$\Delta G_s^\circ(\text{in solvent}) = lR + d \qquad (3)$$

Of course, the R values themselves are obtained by analysis of ΔG_s° values in several solvents, but eq 3 should then be rather more reliable than eq 2 since the latter is tied to just one solvent. An analysis based on eq 3 is given in Table VI.[35] For the nonaqueous solvents there is no point in attempting to differentiate between the rare gases and the n-alkanes, because eq 3 is designed to include both of these sets of solutes in the same correlation. For all the nonaqueous solvents in Table VI there are excellent linear correlations with respect to eq 3, with ρ ranging from −0.9999 to −0.9976 (excluding ethylene glycol with $\rho = -0.9557$)[34] and with an average value of σy of only 0.08 kcal mol^{-1} over all the nonaqueous solvents. These correlations cover not only the rare gases and n-alkanes (Table I) but also the other alkane and alkane-like solutes in Table IV.[35]

Values of ΔG_s° for the rare gases in water are well correlated by eq 3, with $\rho = -0.9987$ and $\sigma y = 0.04$ kcal mol^{-1}; the slope l and intercept d are also quite reasonable in value by comparison to those for the nonaqueous solvents. Thus again, it is seen that solution of the rare gases in water must be quite similar in mechanism to solution in the nonaqueous solvents. If, however, the rare gases and n-alkanes (14 solutes) are taken together in water, there is almost no correlation through eq 3, and $\rho = +0.2002$ and $\sigma y = 0.56$ kcal mol^{-1}. This is in total contrast to results for the nonaqueous solvents and indicates quite strikingly that the n-alkanes give rise to ΔG_s° values in water that are not at all correlated by eq 3. The same is true for the solutes in Table IV and, if these are included, the total solutes (22 solutes) are again very badly correlated with the R values, $\rho = +0.0338$ and $\sigma y = 0.54$ kcal mol^{-1}. There can be no greater indication of the anomalous solution of alkanes and alkane-like solutes in water than the fact that for the 22 solutes (Tables I and IV) correlation with R is nonexistent ($\rho = 0.0338$) in the case of water but excellent for the nonaqueous solvents, $\rho = -0.9998$ in benzene (22 solutes), −0.9997 in acetone (16 solutes), −0.9976 in 1-octanol (13 solutes), −0.9999 in ethanol (20 solutes), and −0.9995 in methanol (20 solutes). If the ΔG_s° values are plotted against values of R (plots not shown) it is also evident that the ΔG_s° values for the alkanes and alkane-like solutes are all much more positive than expected. The analysis in terms of R yields results that are, if anything, even more conclusive than the analysis through eq 2, and confirms completely the existence of the hydrophobic effect.

Table V. Values of the Solute Parameter, R, for Use in Eq 3

solute	R	no.[a]	solute	R	no.[a]
He	1.32	9	isobutane	2.61	3
Ne	1.39	9	cyclopentane	3.01	4
Ar	1.75	9	cyclohexane	3.24	4
Kr	1.95	7	Me_4C	2.73	4
Xe	2.19	7	Me_4Sn	3.14	4
Rn	2.39	4	Et_4C	3.71	3
CH_4	1.90	11	Et_4Sn	4.16	4
C_2H_6	2.26	11	Et_4Pb	4.19	4
C_3H_8	2.47	11			
n-C_4H_{10}	2.70	10			
n-C_5H_{12}	2.89	11			
n-C_6H_{14}	3.11	10			
n-C_7H_{16}	3.32	9			
n-C_8H_{18}	3.52	10			

[a] Number of solvents used.

There are a number of reasons why the conclusions drawn from analyses of eq 2 and 3 are quite different from those reached by Cramer[2] from considerations of ΔG_s° and molecular volume. Firstly, considerably more data, both with regard to the number of solutes and the number of solvents, have been used in the present work. It may be noted also that the data for 1-octanol are probably not as reliable as those in many of the other nonaqueous solvents. Secondly, the analysis of Cramer relies very much on a given set of molecular radii

Table VI. An Analysis of $\Delta G_s°$ Values in Terms of R, Eq 3

solvent	no.[a]	l	d	σy	ρ
decane	14	−3.3707	9.507	0.12	−0.9987
hexane	14	−3.2991	9.358	0.09	−0.9993
cyclohexane	9	−3.5260	10.056	0.06	−0.9996
CCl_4	10	−3.4741	10.116	0.13	−0.9981
toluene	10	−3.4763	10.147	0.09	−0.9992
benzene	14	−3.4456	10.198	0.04	−0.9998
	22[b]	−3.4315	10.169	0.05	−0.9998
PhCl	9	−3.4662	10.257	0.05	−0.9997
PhBr	9	−3.5344	10.509	0.04	−0.9999
PhI	8	−3.7638	11.067	0.06	−0.9991
acetone	11	−2.9077	9.227	0.06	−0.9996
	16[b]	−2.8668	9.143	0.07	−0.9997
$PhNO_2$	13	−3.1774	10.135	0.08	−0.9994
NMPyrrol	8	−2.7662	9.244	0.09	−0.9984
MeCN	5	−2.5310	8.886	0.07	−0.9965
PC	8	−2.3244	8.528	0.06	−0.9990
$MeNO_2$	8	−2.5037	9.206	0.12	−0.9982
Me_2SO	13	−2.5351	9.477	0.12	−0.9977
1-octanol	11	−3.1881	9.845	0.15	−0.9976
	13[b]	−3.1336	9.746	0.15	−0.9976
isobutyl alcohol	4	−3.0242	9.426	0.02	−0.9999
1-butanol	5	−3.0700	9.567	0.08	−0.9993
1-propanol	4	−2.9956	9.548	0.05	−0.9998
ethanol	12	−2.8549	9.385	0.02	−0.9999
	20[b]	−2.8511	9.372	0.03	−0.9999
methanol	12	−2.6443	9.229	0.06	−0.9994
	20[b]	−2.6612	9.258	0.07	−0.9995
$(CH_2OH)_2$	6	−1.6547	7.876	0.27	−0.9557
water	6[c]	−1.7331	9.328	0.04	−0.9987
	14	0.1686	5.984	0.56	+0.2002
	22[b]	0.0226	6.270	0.54	+0.0338

[a] Number of solutes (rare gases and *n*-alkanes in Table I unless shown otherwise). [b] All solutes in Tables I and IV. [c] Rare gases only.

(or molecular volumes), and, as pointed out before, different sets of radii can lead to different conclusions. Thirdly, Cramer's analysis in terms of $\Delta G_s°$ and molecular volume is largely a personal judgment as to whether the plot of $\Delta G_s°$ against solute molecular volume for 1-octanol can (or should) be treated as two straight lines, or whether the plot is actually a smooth, continuous curve (see Figures 3 and 4). The present analysis avoids many of the above difficulties by taking a straight line as the datum line (either by use of eq 2 or eq 3). It is then much easier to see whether or not the results for water fit the straight-line correlation that applies to all the nonaqueous solvents. In the event, the deviations from the correlation are so large in the case of alkanes or alkane-like solutes that some special effect, such as the hydrophobic effect, must be invoked to explain these deviations.

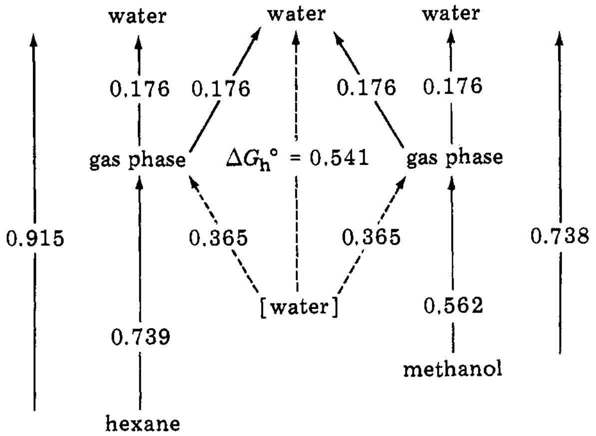
A Quantitative Assessment of the Hydrophobic Effect. Several authors have discussed quantitative aspects of the hydrophobic effect. One method is to define the hydrophobic free energy change as the free energy of transfer of a hydrocarbon from the pure liquid hydrocarbon to the dilute aqueous phase,[36] or to use the above definition for liquid hydrocarbons together[37] with the free energy of transfer from the gaseous phase at 1 atm pressure to the aqueous phase, for the hydrocarbons that are gaseous at 298 K. Using the standard state for liquid hydrocarbons of the pure liquid and the standard state for gaseous hydrocarbons of the gas at 1 atm, Gill and Wadsö[37] showed that the hydrophobic free energy change was linearly related to the number of hydrogen atoms in the hydrocarbon. Unfortunately, under the above definition, the hydrocarbon standard state differs for every liquid hydrocarbon, being, for example, the pure liquid hexane for solute hexane, but the pure liquid octane for solute octane; for gaseous hydrocarbons there is yet another standard state of 1 atm pressure.[38] It seems more preferable to use exactly the same standard state for all the hydrocarbon solutes. For example, a suitable standard state would be the infinitely dilute solution of the solute in a given nonaqueous solvent and the infinitely dilute solution of the solute in water, with concentrations expressed on the mole fraction scale. On this basis, the $-CH_2$ increment for transfer from hexane solvent to water can be obtained directly from the data in Table I as 0.915 kcal mol^{-1} for the C_2 to C_8 *n*-alkanes.[39] Wolfenden and Lewis[40] separated such an increment into a contribution due to favorable interaction in the nonaqueous phase and unfavorable (hydrophobic) interaction in the aqueous phase. To obtain the latter they used the $\Delta G_s°$ values for solution of alkane (gas) in water (see values in Table I), and calculated the $-CH_2-$ increment for the gas → water transfer. They obtained an unfavorable increment of 0.14 kcal mol^{-1} for the *n*-alkane series, and an average value of 0.15 for a number of homologous series. Cramer[2] calculated a value of 0.18 kcal mol^{-1} for the C_2 to C_5 *n*-alkanes in the same way. Using the data in Table I a value of 0.144 kcal mol^{-1} can be found for the C_1 to C_8 *n*-alkanes or one of 0.176 kcal mol^{-1} for the C_2 to C_8 *n*-alkanes,[41] since the $\Delta G_s°$ value for methane does not fit very well on plots of $\Delta G_s°$ in water against carbon number.[39] It may seem that this unfavorable $-CH_2-$ contribution of 0.176 kcal mol^{-1} for the gas → water transfer is very small for a hydrophobic effect, and that the unfavorable hexane → water transfer is mostly due to a favorable $-CH_2-$ contribution for the gas → hexane transfer (−0.739 kcal mol^{-1} for the C_2 to C_8 *n*-alkanes); similar results have been found by Wolfenden and Lewis[40] and by Cramer.[2] However, it is not correct to conclude from such results that the hydrophobic effect is very small, since the overall $-CH_2-$ contribution for the gas → water transfer includes not only the positive hydrophobic effect but also a negative effect that is due to a normal solution process. In order to calculate the actual hydrophobic effect, it is necessary to estimate the $\Delta G_s°$ values for the gas → water transfer that would be expected if there were no hydrophobic effect. Then the hydrophobic free

Table VII. A Quantitative Assessment of the Hydrophobic Effect (kcal mol^{-1}) at 298 K

solute	$\Delta G_s°$(obsd)[a]	$\Delta G_s°$(calcd)[b]	$\Delta G_h°$	$\Delta G_s°$(calcd)[c]	$\Delta G_h°$
CH_4	6.28	6.03	0.25	6.03	0.25
C_2H_6	6.11	5.45	0.66	5.41	0.70
C_3H_8	6.23	5.09	1.14	5.05	1.18
n-C_4H_{10}	6.35	4.67	1.68	4.65	1.70
n-C_5H_{12}	6.61	4.45	2.16	4.32	2.29
n-C_6H_{14}	6.82	3.99	2.83	3.94	2.88
n-C_7H_{16}	6.89	3.55	3.34	3.57	3.32
n-C_8H_{18}	7.16	3.34	3.82	3.23	3.93
isobutane	6.60	4.84	1.76	4.80	1.80
cyclopentane	5.48	4.11	1.37	4.11	1.37
cyclohexane	5.50	3.66	1.84	3.71	1.79
Me_4C	6.78	4.63	2.15	4.60	2.18
Me_4Sn	6.36	3.92	2.44	3.89	2.47
Et_4C	6.50	3.03	3.47	2.90	3.60
Et_4Sn	6.39	2.14	4.25	2.12	4.17
Et_4Pb	6.32	2.16	4.16	2.07	4.25

[a] Table 1. [b] Via eq 5. [c] Via eq 6.

Scheme I. An Analysis of the Hydrophobic Effect[a]



[a] Values for the $-CH_2-$ increment in C_2 to C_8 n-alkanes given in kcal mol^{-1}. The value of 0.365 kcal mol^{-1} favoring [water] over the gas phase indicates what the increment would be in the absence of the hydrophobic effect, $\Delta G_h°$.

energy, $\Delta G_h°$, may be obtained as

$$\Delta G_s°(\text{obsd}) = \Delta G_h° + \Delta G_s°(\text{calcd}) \qquad (4)$$

Since free energies of solution of the rare gases in water are quite normal and are well correlated with $\Delta G_s°$ values in nonaqueous solvents (see Table III), a possible method of obtaining $\Delta G_s°$(calcd) is to use results for the rare gases as a datum line. Of all the nonaqueous solvents, methanol is the nearest in type to water, and it may be calculated that

$$\Delta G_s°(\text{rare gas in water}) = 0.6406\Delta G_s°(\text{rare gas in methanol}) + 3.3505 \qquad (5)$$

Then, applying the constants in eq 5 to $\Delta G_s°$ values for n-alkanes in methanol, it is possible to calculate $\Delta G_s°$ values for the alkanes in water were there no hydrophobic effect.[42] Details are in Table VII. For the C_2 to C_8 n-alkanes the $-CH_2-$ increment in $\Delta G_h°$ is 0.537, much larger than the "total effect" increment of 0.176 kcal mol^{-1}. An alternative procedure may be based on the R values in Table V, through

$$\Delta G_s°(\text{rare gas in water}) = -1.7331R + 9.3278 \qquad (6)$$

Using this equation to calculate the expected $\Delta G_s°$ values for n-alkanes leads to very similar $\Delta G_h°$ values as obtained by use of eq 5; see Table VII. The C_2 to C_8 $-CH_2-$ increment is now 0.541 kcal mol^{-1}. Values of $\Delta G_h°$ for a number of alkane and alkane-like solutes are in Table VII, there being a general increase in $\Delta G_h°$ with increasing solute size. The $\Delta G_h°$ values for cycloalkanes are smaller than those of the n-alkanes of the same carbon number, but the R_4M compounds all behave as alkane-like solutes.

It is now possible to analyze the C_2 to C_8 $-CH_2-$ increment for n-alkanes more completely than hitherto (see Scheme I). The overall increment for the hexane → water transfer (0.915 kcal mol^{-1}) can be split into a favorable gas → hexane transfer of 0.739 kcal mol^{-1} and an unfavorable gas → water transfer of 0.176 kcal mol^{-1}. The latter is made up of an unfavorable hydrophobic effect amounting to 0.541 kcal mol^{-1} together with a favorable normal solvent effect of 0.365 kcal mol^{-1}. This latter value is quite reasonable compared to values of 0.562 (methanol) and 0.739 (hexane). The actual hydrophobic effect is estimated to 0.541 kcal mol^{-1} for each $-CH_2-$ group, much larger than the overall effect in the gas → water transfer of 0.176 kcal mol^{-1}. According to the present analysis, not only is the presence of a hydrophobic effect demonstrated, but it is much larger than previous estimates suggested.

Prediction of Free Energies of Solution and Henry's Law Constants. The excellent correlation of $\Delta G_s°$ values through eq 2 and 3 suggests that these linear equations may provide a simple but reliable method for the prediction of unknown $\Delta G_s°$ values of the solutes listed in Tables I and IV. This amounts also to the prediction of Henry's law constants, which are related to $\Delta G_s°$ by the equation

$$\Delta G_s° = RT \ln K^H \qquad (7)$$

and which are of considerable industrial importance. Monfort et al.[43] have recently used both an empirical correlation and solubility parameter theory to estimate K^H values of small solutes in hydrocarbon solvents. The latter theory has also been used by Linford and Thornhill,[7] again with respect to small solutes but in a variety of nonpolar and moderately polar aprotic solvents. Good agreement with experiment was found in the above work, although restricted in scope both in terms of solute type and solvent type. A more ambitious scheme was devised by de Ligny et al.,[6] who estimated K^H (as log K^H) values of small solutes in a very wide range of solvents through the four-parameter equation

$$\log K^H = G_1S_1 + G_2S_2 \qquad (8)$$

The adjustable parameters G_1 and G_2 refer to the solute gas and S_1 and S_2 to the solvent. Equation 8 correlated 408 literature values of log K^H with a standard deviation of only 0.13 units.

Equations 2 and 3 compare very favorably with 8, and with fewer adjustable parameters enable $\Delta G_s°$ values to be corre-

Table VIII. Observed and Predicted Values of Log K^H at 298 K

solute	solvent	obsd[a]	calcd through eq 2	3	8
Ar	MeCN	3.24	3.21	3.27	
Rn	cyclohexane	1.06	1.17	1.19	1.24
Rn	acetone	1.72	1.65	1.68	1.46
Rn	ethanol	1.83	1.85	1.87	1.62
Rn	methanol	2.01	2.11	2.12	1.78
CH_4	$MeNO_2$		3.27	3.26	3.21

[a] See ref 43.

lated with standard deviation of only 0.09 kcal mol^{-1}, eq 2 for plots of all solutes in Table I or all solutes in Tables I and IV, and 0.08 kcal mol^{-1}, eq 3 for similar solutes. These deviations correspond to 0.07 and 0.06 units in log K^H and compare very well with those obtained by de Ligny.[6] The analysis of de Ligny covers more solvents than used in the present work, but it is clear that eq 2 and 3 could be applied to all the solvents used by de Ligny (39 nonaqueous solvents). Equations 2 and 3, however, do cover much larger solutes than have ever been dealt with in this way before. The actual predictions of eq 2, 3, and 8 are usually quite close, but obviously further new data are required to test the predictions. A number of values of $\Delta G_s°$ (or log K^H) that were not used to set up the equations are available[44] as tests, and in Table VIII are given the observed and calculated log K^H values. Bearing in mind that the experimental observations on Rn are all over 50 years old,[44] it does seem that eq 2 and 3 can be used to estimate $\Delta G_s°$ or log K^H values quite reliably.

The only nonaqueous solvent, examined in this work, for which the ρ and σy values for eq 2 and 3 are not good enough to allow reliable estimations is ethylene glycol. At the moment it is not clear whether this is just due to larger random errors than usual, or whether there are also anomalous effects in the solution of alkanes in ethylene glycol.

It should be noted that the discussion and conclusions reached in the present work are all in terms of free energy. Using this function, it is shown that the solution of hydrocarbons, but not rare gases, is anomalous in water. Whether or not the solution of hydrocarbons and rare gases in water is anomalous in terms of the enthalpy function or the entropy function cannot be decided on the basis of free-energy data; a separate analysis in terms of enthalpy and entropy is required.

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(33) The solutes cyclopentane, cyclohexane, benzene, CF_4, and CCl_4 were found by Cramer not to fit into the usual pattern of $\Delta G_s°$ values in 1-octanol. However, the solutes cyclopentane and cyclohexane (Table IV) are well correlated by eq 2, and literature data indicates that the solutes benzene, CF_4, CCl_4, and SF_6 also conform to eq 2 with an average deviation of about 0.2 kcal mol^{-1} in $\Delta G_s°$ over four to seven nonaqueous solvents.
(34) Both the ρ value and σy for the alkanes in ethylene glycol indicate significantly lower correlations of $\Delta G_s°$ by eq 2 or 3 than for all the other nonaqueous solvents. It is just possible that there is some anomalous effect on solution of alkanes in ethylene glycol, but more data will be needed to test this point.
(35) Just as eq 2 well correlates $\Delta G_s°$ values for cyclopentane, cyclohexane, benzene, CF_4, CCl_4, and SF_6, so does eq 3. The *R* values for cyclopentane, cyclohexane, and isobutane are in Table V.
(36) G. Nemethy and H. A. Scheraga, *J. Chem. Phys.*, **36**, 3401 (1962).
(37) S. J. Gill and I. Wadso, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 2955 (1976).
(38) It may seem as though the standard state for octane of pure liquid octane is quite similar to the standard state for hexane of pure liquid hexane. The standard state of the pure liquid solute is, however, equivalent to a standard state of the gaseous solute at its saturated vapor pressure. This corresponds to octane gas at 0.0185 atm pressure and to hexane gas at 0.199 atm pressure, so that the two standard states are indeed appreciably different. Thus the standard state of pure liquid alkanes results in a different standard state for each alkane. If for gaseous alkanes the standard state of a gas at 1 atm pressure is used, yet another standard state is invoked.
(39) Calculated $-CH_2-$ increments are nearly always different for the C_1 to C_8 *n*-alkanes compared with C_2 to C_8 *n*-alkanes because plots of free energy against carbon number usually yield good lines excluding the point for C_1. In the present paper, all $-CH_2-$ increments are calculated from results of the C_2 to C_8 *n*-alkanes.
(40) R. Wolfenden and C. A. Lewis, *J. Theor. Biol.*, **59**, 231 (1976).
(41) The various $-CH_2-$ increments were all calculated from the slope of plots of free energy against carbon number. Note that it is not correct simply to average all the individual $-CH_2-$ increments; this corresponds to no more than taking the first and last members of the series.
(42) Almost identical results are obtained if any other nonaqueous solvent is used in eq 5.
(43) J. P. Montfort and J. R. Varela H., *Chem. Eng. J.*, **12**, 1 (1976); J. P. Montfort, J.-P. Montfort, J.-R. Varela-Ham, and J.-L. Perez-Meseguer, *J. Chim. Phys. Phys.-Chim. Biol.*, **74**, 409 (1977).
(44) F.-t. Chiang, Ph.D. Thesis, University of Minnesota, 1967, has collected literature data on the solubility of Rn and has determined the solubility of Ar in acetonitrile.