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Freezing Points of Aqueous Alcohols

Free Energy of Interaction of the CHOH, CH_2, CONH and C=C Functional Groups in Dilute Aqueous Solutions

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The freezing temperatures of dilute aqueous solutions of methanol, ethanol, 2-propanol, butanol, t-butanol, cyclohexanol and ethylene glycol were measured over the concentration range 0.1 to 1 mol kg^{-1}. Osmotic coefficients at 0°C were calculated. The limiting pairwise interaction coefficients of the alcohols, plus a variety of polyhydroxy compounds and carbohydrates, were calculated at 25°C from the available data and then correlated using the additivity principle of Savage and Wood. This correlation approximates effective free energies of CH_2 and CHOH group interactions with themselves and with each other. Literature data were used to estimate interactions between CONH and C=C groups. The CONH–CONH interaction appears to be large, consistent with a strong stabilizing effect of these on native protein structures. The $CH_2 \ldots CH_2$ interaction also indicates attractive forces between these groups. The present model for the hydrophobic interaction is most appropriate for small molecular interactions whereas previous treatments are best for situations involving site binding.

The CHOH . . . CHOH and $CH_2 \ldots$ CONH interactions are small, while the CHOH . . . CH_2 free energy of interaction is positive, due either to volume exclusion or net repulsive forces.

The entropy change associated with the $CH_2 \ldots CH_2$ interaction is large and positive as expected and is not completely compensated by a corresponding enthalpy change. The entropy change associated with the CONH . . . CONH interaction indicates that few degrees of freedom are involved, which is consistent with the formation of a strong hydrogen bond.

The correlation can be used to estimate thermodynamic properties of dilute non-electrolyte solutions and can also predict the effect of solutes on the solubility of solids and gases.

This paper is part of a continuing study on the thermodynamics of aqueous solutions of non-electrolytes to determine the interactions of the various functional groups with each other. Analysis in terms of functional group interactions allows predictions to be made of the thermodynamic properties of a large number of compounds using few parameters. A previous paper [1] reported the enthalpies of interaction of compounds containing amide and hydroxyl functional groups. A simple group additivity principle was able to predict over 60 pairwise enthalpies of interaction using as parameters only the 6 interactions occurring between the CH_2, CHOH and CONH functional groups. These predictions can be extended to other compounds. Because the additivity principle neglects both steric hinderance and nearest neighbour effects, only a rough correlation is expected, but the signs and magnitudes of all six of the interactions were determined. The purpose of the present investigation was to see if the additivity principle would work for excess free energies.

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This paper reports the osmotic coefficients of a variety of aqueous alcohol solutions measured by a new freezing-temperature technique. New measurements of the freezing temperature of aqueous alcohols were necessary because, with few exceptions, previous results did not give accurate values for the pairwise interaction constants. The present results show that the additivity principle can be successfully applied to free energy data for a wide variety of compounds containing CHOH, CH_2, CONH and C=C groups.

EXPERIMENTAL

Potassium chloride (Baker Analysed Reagent) was used without further purification after drying at 400°C for two days. Absolute ethanol (U.S. Industries) was used without further purification. Fisher reagent grade cyclohexanol and Fisher certified grade t-butanol were zone melted for one week. Methanol, propan-2-ol, butanol and ethylene glycol were Fisher certified grade used without further purification. The alcohols were analysed for water content by Karl Fisher titration. Corrections were made for this water content, which was never more than 0.08 %. All solutions and ice were prepared from distilled deionized water.

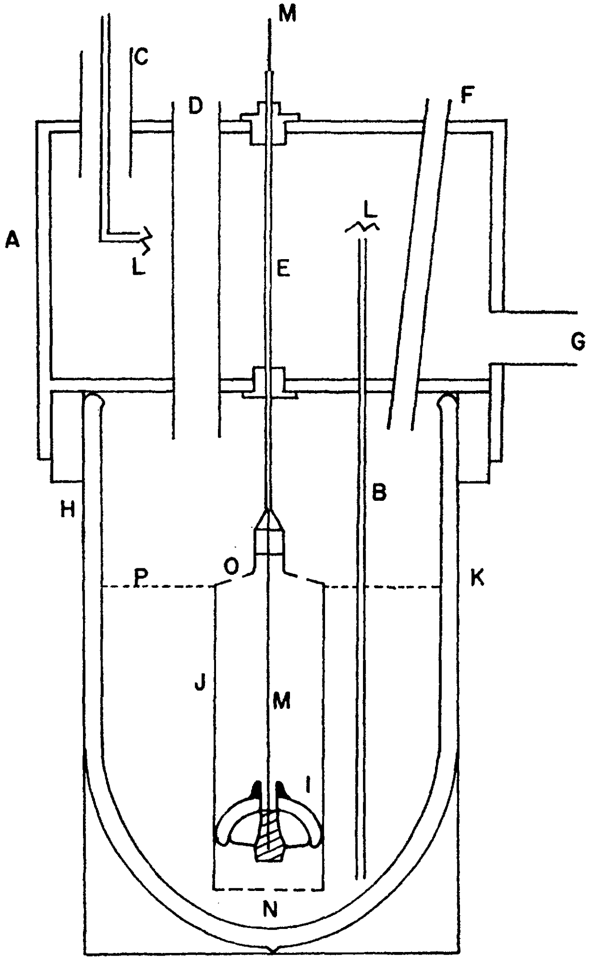

FIG. 1.—Diagram of the freezing point apparatus. Letters indicate features discussed in the text.

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Solutions were made up by weight and buoyancy corrections were applied. One dm^3 collapsible polyethylene bottles were used to minimize the vapour space above the solutions. A weighed amount of solute was injected into a known amount of water through a rubber septum fitted to the bottle cap. Solutions were removed by syringe through a Luer-Lok fitting without increasing the vapour space above the solution.

The main problem with previous freezing point measurements of alcohol solutions has been the difficulty in accurately determining the concentration of the actual solution for which a freezing point was measured. This is necessary because some ice melts when the solution and the ice are initially brought together. The present method, which eliminates the need for a concentration determination after the freezing point is measured, involves precooling the solution and the ice to the final freezing point temperature. Then, when the solution is brought into contact with the ice, only an insignificant amount of ice melts and the concentration is unchanged. This method has recently been used to obtain accurate freezing points for seawater.[2]

The freezing point vessel (shown schematically in fig. 1) consisted of a 300 cm^3 Dewar flask (K) fitted with a heavy copper cap (A) through which thermostat fluid circulated *via* large diameter ports (G and C). A plexiglass collar (H) sealed the cap to the Dewar with a cushion of G.E. silicon rubber. Two tubes passed through the cap to accommodate the thermistor thermometer (D) and needles for withdrawing solution (F). Stirring was accomplished with a lift pump similar to that described by Gibbard and Gossman.[3] It consisted of a 30 cm^3 plastic syringe (J) supported by a long, no. 15 gauge needle (E) which passed through the cap. Glass ball and socket joints (I) accomplished the necessary valve action for lifting fluid up and out through holes (O) in the syringe top on the upstroke and for refilling the syringe from the bottom on the downstroke. A motor driven, long, stiff wire passing through E effected the lifting action of the pump (at 60 strokes min^{-1}). Ice was excluded from the pump by a platinum wire screen (N). The solution and ice (at level P) occupied about 200 cm^3. A long coil (7.6 m, i.d. = 0.16 cm) of stainless steel tubing (L, L), mounted inside the cap (A) was used to bring the incoming solution to thermostat temperature. The entrance is through port C and the exit is through a long needle (B) extending to the bottom of the Dewar.

The thermometer used to measure the temperature of the solution contains a Victory thermistor with a resistance of 5320 Ω at 0°C and a temperature coefficient of 4.7 %°C^{-1}. The resistance of the thermistor was measured in a 10 : 1 ratio arm, Wheatstone bridge and balanced against a 100,000 Ω decade resistance box, which had been calibrated against a NBS 100 Ω resistor. General Radio gold-plated copper binding posts and low thermal e.m.f. solder were used to make all connections. The ESI ratio arm resistors (temperature coefficient of 5 p.p.m.°C^{-1}) were soldered directly to these posts. A Fluke 845A high impedance voltmeter-null detector was used to balance the circuit. The thermistor was calibrated against a Pt resistance thermometer from −10 to 60°C. The resistances were least-squares fit to an equation of the form:

$$R = R_0 \exp(a/T + b/T^2 + c/T^3) \qquad (1)$$

with a standard temperature deviation of 9×10^{-4} K.

The freezing point apparatus was placed in a Haake Fk-10 thermoregulator bath containing an ethylene glycol+water mixture and this same fluid was pumped at a high rate through the cooling cap of the apparatus. The temperature of the bath, as determined by a mercury thermometer immersed in the bath, was stable to ±0.05 K.

To measure the freezing points, an ice-distilled water mixture was allowed to equilibrate for 30 min and its temperature was measured. The water was removed by a syringe with a needle that reached to the bottom of the Dewar. More than 95 % of the water was removed. ≈90 cm^3 of the solution (prechilled in ice) was injected *via* a 100 cm^3 syringe through the tubing in the cap at a rate of 20-30 cm^3 min^{-1}. Solution entering the Dewar was within 0.1 K of the thermostat temperature. The mixture was allowed to equilibrate for 5-10 min after which the temperature was measured and the thermostat readjusted to the temperature inside the Dewar (±0.03 K). The solution was then withdrawn and the process repeated several times. The first two cycles of this procedure brought the ice to

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within 1 % of the final equilibrium temperature and two additional cycles were then performed. In this way, the final solution entered the vessel at the final equilibrium temperature (±0.1 K) with a negligible amount of ice being melted.*

To test the apparatus, the freezing points of 0.1006, 0.4830 and 1.0303 mol kg^{-1} KCl solutions were measured and compared with the results of Scatchard and Prentiss.[4] The values of θ found in this research and those of Scatchard and Prentiss were 0.3463 against 0.3456 K, 1.601 against 1.600 K, and 3.348 against 3.354 K, respectively.

CALCULATIONS AND RESULTS

The calculations in this paper require equations for the thermodynamic properties of an aqueous solution of one or two non-electrolytes. We begin with solutions of a single solute, A (for alcohol). The excess free energy, G^E, in a solution containing W kg of solvent at 25°C can be written as a power series in molality:

$$G^E/W = \{AA\}_g m^2 + \{AAA\}_g m^3 + \{AAAA\}_g m^4 + \dots \quad (2)$$

where $\{AA\}_g$ is the pairwise free energy interaction of A with A, m is the molality, *etc.* Appropriate manipulation of this equation gives the activity (γ_A) and osmotic (ϕ) coefficients.[5]

$$RT \ln \gamma_A = 2\{AA\}_g m + 3\{AAA\}_g m^2 + 4\{AAAA\}_g m^3 + \dots \quad (3)$$

and

$$\phi = 1 + (m/RT)(\{AA\}_g + 2\{AAA\}_g m + 3\{AAAA\}_g m^2 + \dots). \quad (4)$$

The corresponding equations for excess enthalpy and heat capacity at 25°C are:

$$H^E/W = \{AA\}_h m^2 + \{AAA\}_h m^3 + \{AAAA\}_h m^4 + \dots \quad (5)$$

$$C_p^E/W = \{AA\}_c m^2 + \{AAA\}_c m^3 + \{AAAA\}_c m^4 + \dots \quad (6)$$

where $\{AA\}_h$ and $\{AA\}_c$ are the pairwise enthalpy (h) and heat capacity (c) interaction terms, respectively, *etc.* These equations are necessary to convert the alcohol freezing-point results into more useful thermodynamic quantities.

The molalities, m, and the freezing-point depressions, θ, of the aqueous alcohol solutions are given in table 1. Since θ is directly correlated to the solvent activity at the freezing temperature, small corrections are necessary to determine the solvent activity at the freezing temperature of the pure solvent, 0°C (T_f). The expression for the osmotic coefficient at 0°C is:[6]

$$\lambda m\phi = \{1 + (\bar{L}_1/\Delta H_f^\circ)\}\theta + \{(1/T_f) - \Delta C_f^\circ/(2\Delta H_f^\circ) + \bar{L}_1/(T_f \Delta H_f^\circ) - \bar{J}_1/(2\Delta H_f^\circ)\}\theta^2 + \dots \quad (7)$$

where λ is the molal freezing-point depression constant (1.860 K kg mol^{-1}), $\bar{L}_1$ and $\bar{J}_1$ are the relative partial molar enthalpy and heat capacity of the solvent at T_f, and ΔH_f° and ΔC_f° are the enthalpy and heat capacity of fusion of pure water at the freezing temperature, T_f (0°C). For solutions <1 mol kg^{-1}, the term in θ^2 is small. It is thus reasonable to neglect the $\bar{J}_1$ and $\bar{L}_1$ term in θ^2. One needs to determine $\bar{L}_1$ at T_f knowing its value at 298 K. In the notation of eqn (5)

$$\begin{aligned}\bar{L}_1^{(298)} &= -M_1 m^2 \frac{d(H^E/Wm)}{dm} \\ &= -M_1 m^2(\{AA\}_h + 2\{AAA\}_h m + \dots). \quad (8)\end{aligned}$$

---

* If the additions continue until there is no change in equilibrium temperature and if the incoming solution is T K warmer than the final temperature, the solution will be 1.3 T % more dilute because of the amount of ice melted in cooling the solution. The result is an osmotic coefficient which is now by 1.3 T %.

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Here M_1 is the molecular weight of the solvent (kg). Assuming that the excess heat capacity is independent of temperature and using only the pairwise interaction terms, one can write for $\bar{L}_1^{(T_f)}$ at the temperature, T_f

$$-\bar{L}_1^{(T_f)}/(M_1 m^2) = \{AA\}_h^{(T_f)} = \{AA\}_h + \{AA\}_c(T_f - 298.15). \qquad (9)$$

The calculated osmotic coefficients at 0°C are listed in table 1. The values of $\{AA\}_h$ and $\{AA\}_c$ at 25°C which were used in the calculations are given in table 2. Because only the first terms in eqn (5) and (6) were used in the correction of the osmotic coefficient to 0°C the corrections at molalities above about 0.5 mol kg^{-1} are only approximate. The error should be $< \sim 0.1$ % at 1 mol kg^{-1}.

The osmotic coefficients at 0°C for each of the systems investigated were fitted to a polynomial similar to eqn (4)

$$\phi(0°\text{C}, m) = 1 + a_1 m + a_2 m^2 + a_3 m^3. \qquad (10)$$

The results are given in table 2. An appropriate number of terms were kept to obtain the best fit of the data. The standard deviation of the fit indicates that the precision of the measurement is ≈ 0.1 %.

Webb and Lindsley[7] have measured the freezing temperatures of some alcohol solutions by precooling the solution to 0°C and making corrections for the calculated amount of ice melted. Harkins and Wampler,[8] Scatchard and Prentiss,[9] and Knight[10] have all measured the freezing temperatures of some alcohol solutions at low molalities and have analysed the solution concentration by different means. The present results for the osmotic coefficient for butanol agree with those of Webb

TABLE 1.—FREEZING POINT DEPRESSIONS AND OSMOTIC COEFFICIENTS [a]

$\frac{m}{\text{mol kg}^{-1}}$	$\frac{\theta}{\text{K}}$	ϕ(0°C)	$\frac{m}{\text{mol kg}^{-1}}$	$\frac{\theta}{\text{K}}$	ϕ(0°C)
	methanol			ethanol	
0.3088	0.5742	1.0000	0.1641	0.3033	0.9938
0.3977	0.7355	0.9945	0.2647	0.4869	0.9893
0.6960	1.2882	0.9952	0.3371	0.6191	0.9876
0.7737	1.4292	0.9932	0.4367	0.7989	0.9838
0.8913	1.6439	0.9916	0.5888	1.0730	0.9799
0.8945	1.6535	0.9938	0.7214	1.3118	0.9778
1.2014	2.2123	0.9896	0.8263	1.5012	0.9770
1.2327	2.2753	0.9919	0.9908	1.7979	0.9757
1.5050	2.7697	0.9884	1.149	2.0837	0.9747
1.6530	3.0519	0.9912	1.582	2.8648	0.9731
1.6590	3.0585	0.9897			
	propan-2-ol			butanol	
0.2239	0.4097	0.9840	0.1026	0.1876	0.9831
0.3076	0.5615	0.9815	0.2572	0.4637	0.9694
0.3486	0.6348	0.9793	0.2809	0.5057	0.9680
0.4861	0.8847	0.9788	0.3715	0.6651	0.9625
0.6781	1.2251	0.9716	0.4164	0.7428	0.9590
0.7110	1.2863	0.9729	0.5100	0.9067	0.9557
0.8701	1.5719	0.9715	0.6231	1.1045	0.9527
0.9806	1.7722	0.9718	0.8145	1.4342	0.9459
1.190	2.1604	0.9764	0.9360	1.6360	0.9386
			1.209	2.097	0.9304

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Table 1.—*continued.*

$\frac{m}{\text{mol kg}^{-1}}$	$\frac{\theta}{\text{K}}$	ϕ(0°C)	$\frac{m}{\text{mol kg}^{-1}}$	$\frac{\theta}{\text{K}}$	ϕ(0°C)
	t-butanol			ethyleneglycol	
0.1066	0.1970	0.9934	0.08290	0.1549	1.0049
0.1417	0.2600	0.9866	0.2327	0.4338	1.0022
0.2716	0.4965	0.9829	0.2454	0.4592	1.0060
0.2753	0.5043	0.9851	0.4104	0.7697	1.0085
0.3638	0.6631	0.9801	0.6216	1.1725	1.0142
0.3967	0.7237	0.9811	0.7195	1.3592	1.0157
0.4501	0.8218	0.9818	0.8038	1.5227	1.0185
0.4767	0.8706	0.9821	0.9324	1.7727	1.0220
0.5462	0.9986	0.9832	0.9843	1.8734	1.0230
0.7569	1.3890	0.9867	1.3233	2.5381	1.0304
0.7690	1.4134	0.9884			
1.0228	1.9050	1.0014			
	cyclohexanol				
0.06843	0.12511	0.9830			
0.08773	0.1596	0.9778			
0.1231	0.2223	0.9708			
0.1907	0.3407	0.9607			
0.1956	0.3485	0.9580			
0.2174	0.3861	0.9550			
0.2935	0.5152	0.9440			
0.2953	0.5181	0.9435			
0.3728	0.6477	0.9345			

[a] The correction of the osmotic coefficient to 0°C is only approximate above 0.5 mol kg^{-1}.

and Lindsley and are 0.5 % higher than the results of Harkins and Wampler. Webb and Lindsley's values compared with ours are 1 % lower for methanol, 0.3 % lower for ethanol and 0.5 % lower for propan-2-ol. Scatchard and Prentiss's freezing point depressions for ethanol are in reasonable agreement with the present results, although their precision was not as high. Knight's values are larger than ours, but there is a large scatter in the points and ϕ does not seem to approach 1 at infinite dilution.

Table 2.—Values of coefficients in eqn (5), (6), (9) and (10)

	$\frac{\{\text{AA}\}_h{}^j}{\text{J kg mol}^{-2}}$	$\frac{\{\text{AA}\}_c{}^i}{\text{J kg mol}^{-2}\text{ K}^{-1}}$	$a_1{}^h$	$a_2{}^h$	$a_3{}^h$	σ^g
methanol	238 [a]	−4.1 [e]	−0.010 (3)[f]	0.0021 (20)		1.6×10^{-3}
ethanol	230 [a]	−0.6 [e]	−0.042 (3)	0.016 (2)		1.0×10^{-3}
propan-2-ol	326 [b]	3.3 [d]	−0.070 (6)	0.043 (7)		1.6×10^{-3}
ethyleneglycol	387 [c]	−5.5 [e]	0.023 (2)			1.5×10^{-3}
butanol	1170 [c]	15.6 [e]	−0.153 (17)	0.16 (4)	−0.068 (26)	1.9×10^{-3}
t-butanol	607 [c]	11.7 [e]	−0.093 (14)	0.13 (5)	−0.037 (32)	1.5×10^{-3}
cyclohexanol	1170 [d]	50 [d]	−0.257 (12)	0.22 (4)		9.4×10^{-4}

[a] E. Lange and H. G. Margraf, *Z. Elektrochem*, 1950, **54**, 73; [b] W. Dimmling and E. Lange, *Z. Elektrochem*, 1951, **55**, 322; [c] E. Lange and K. Moehring, *Z. Elektrochem*, 1953, **57**, 660; [d] estimated; [e] C. Jolicoeur and G. Lacroix, *Canad. J. Chem.*, 1976, **54**, 624; [f] the 95 % confidence level of the last digit is given in parentheses; *i.e.*, −0.010 (3) is −0.010 ± 0.003; [g] standard deviation of the fit; [h] coefficient in eqn (10) at 0°C; [i] coefficient in eqn (6) and (9) at 25°C; [j] coefficient in eqn (5) and (9) at 25°C.

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Problems with loss of the volatile solute and the melting of ice will cause the measured osmotic coefficient to be lower than the actual osmotic coefficient. Since our osmotic coefficients are in general larger than the other measured values and approach unity at infinite dilution for each system, we believe we have overcome these problems.

TABLE 3.—VALUES OF $\{AB\}_g$ AT 25°C

solute A–solute B	$\{AB\}_g$ [a] calc. J kg mol^{-2}	$\{AB\}_g$ [a] expt. J kg mol^{-2}	ref.
(1) single solutes (A = B)			
methanol	−25	−52	this work
ethanol	−94	−125	this work
propan-2-ol	−230	−198	this work
butanol	−435	−466	this work
cyclohexanol	−707	−684	this work
ethylene glycol	1	15	this work
glycerol	24	37	*b*
D-mannitol	65	8	*c*
D-glucose	−9	62	*d*
sucrose	188	174	*b*, *c*
raffinose	339	330	*e*
α-methylglucoside	162	195	*b*
urea	−186	−106	*f*, *g*
methylurea	−243	−135	*h*
ethylurea	−343	−271	*h*
propylurea	−502	−506	*h*
1,1-dimethylurea	−418	−257	*h*
1,3-dimethylurea	−418	−269	*h*
1,1-diethylurea	−835	−790	*h*
1,3-diethylurea	−835	−993	*h*
hexahydropyrimidinone-2	−418	−450	*h*, *i*
acetamide	−153	−190 (20) [k]	*j*
N-methylacetamide	−328	−400 (40)	*j*
N,*N*-dimethylacetamide	−623	−1200 (200) [o]	*j*
t-butanol	—	−272	this work
(2) mixtures			
sucrose+D-mannitol	51	91	*c*
methane+ethanol	−125	−150	*l*
ethane+ethanol	−198	−200	*l*
butane+urea	−18	−87	*m*
diketopiperazine+urea	−239	−92	*n*

[a] This is the free energy pairwise interaction coefficient. See eqn (2). The calculated value is from eqn (16) with the coefficients in tables 5 or 7; [b] G. Scatchard, W. J. Hamer and S. E. Wood, *J. Amer. Chem. Soc.*, 1938, **60,** 3061; [c] R. A. Robinson and R. H. Stokes, *J. Phys. Chem.*, 1961, **65,** 1954; [d] P. N. Henrion quoted by R. H. Stokes and R. A. Robinson, *J. Phys. Chem.*, 1966, **70,** 2126; [e] H. D. Ellerton, G. Reinfelds, D. E. Mulcahy and P. J. Dunlop, *J. Phys. Chem.*, 1964, **68,** 398; [f] R. H. Stokes, *Austral. J. Chem.*, 1967, **20,** 2087; [g] H. D. Ellerton and P. J. Dunlop, *J. Phys. Chem.*, 1966, **70,** 1831; [h] G. Barone, E. Rizzo and V. Volpe, *J. Chem. Eng. Data*, 1976, **21,** 59; [i] this is $\overline{CH_2—NH—CO—NH—CH_2—CH_2}$; [j] G. C. Kresheck, personal communication; [k] where the accuracy of the data is limited a rough estimate of its standard deviation is given in parenthesis; [l] M. Yaacobi and A. Ben-Naim, *J. Solution Chem.*, 1973, **2,** 425; [m] D. B. Wetlaufer, S. K. Malik, L. Stoller and R. L. Coffin, *J. Amer. Chem. Soc.*, 1964, **86,** 508; [n] S. J. Gill, J. Hutson, J. R. Clopton and M. Downing, *J. Phys. Chem.*, 1961, **65,** 1432; [o] not included in the least squares imited accuracy of this point.

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It is useful to have the free energy coefficients $\{AA\}_g$ at 25°C for comparison with other thermodynamic data. From eqn (2) and (5)

$$\left(\frac{\partial(\{AA\}_g/T)}{\partial(1/T)}\right)_{p,m} = \{AA\}_h^{(T)}. \qquad (11)$$

Noting by comparison of eqn (10) and (4) that $(\{AA\}_g/\boldsymbol{R}T)^{(T_f)} = a_1$ and again using eqn (9) to eliminate $\{AA\}_h^{(T)}$, one obtains after integration of eqn (11)

$$\frac{\{AA\}_g}{\boldsymbol{R}T} = a_1 + (1/\mathbf{R})[[\{AA\}_h - T\{AA\}_c][T^{-1} - T_f^{-1}] + \{AA\}_c \ln(T_f/T)] \qquad (12)$$

where $T_f = 273.15$ and $T = 298.15$ K. The calculated values of $\{AA\}_g$ at 25°C are given in table 3. The correction factor to a_1 is ≈ -0.01. Table 3 also contains selected values of the two-solute pairwise interaction coefficient, $\{AB\}_g$, taken from the literature. When osmotic coefficients were available from isopiestic measurements, $\{AB\}_g$ was obtained using the two-solute analogue of eqn (4). In several cases, the solubility of a gas, G, in water and in the presence of cosolute, (C), was measured. In this case, the pairwise interaction coefficient is calculated from an equation similar to eqn (3). The result is:

TABLE 4.—VALUES OF $\{AB\}_g$ AT 25°C FROM SOLUBILITY MEASUREMENTS OF ROSEMAN AND JENCKS [a]

solute	experimental		calculated	
	$\{AN\}_g$ [b] J kg mol^{-2}	$\{AU\}_g$ [c] J kg mol^{-2}	$\{AN\}_g$ J kg mol^{-2}	$\{AU\}_g$ J kg mol^{-2}
urea	−320	−500	−248	−451
methylurea	−697	−576	−739	−514
ethylurea		−660		−556
n-butylurea		−1098		−630
1,3-dimethylurea	−1075		−1229	
1,1-dimethylurea		−970 [e]		−577
tetramethylurea	−2100 [d]	−650	−2110	−704
formamide	−385	−306	−336	−329
N-methylformamide	−787		−827	
N,*N*-dimethylformamide	−1565	−550	−1318	−455
acetamide	−574	−424	−664	−371
N,*N*-dimethylacetamide	−1592		−1645	

[a] M. Roseman and W. P. Jencks, *J. Amer. Chem. Soc.*, 1975, **97**, 631; [b] this is the interaction coefficient for solute A with naphthalene (N) obtained from the solubility of naphthalene in aqueous solutions of A; [c] this is the interaction coefficient for solute A with uric acid, (U); [d] not used in the correlation since limiting slope is uncertain (±250); [e] not used in the correlation since limiting slope is uncertain (±400).

$$(\mathbf{R}T/2m_C)\ln(\gamma_G/\gamma_G^\circ) = \{GC\}_g + \{GG\}_g(m_G - m_G^\circ)/m_C \qquad (13)$$

where γ_G and γ_G° are the activity coefficients in solutions and in pure water. Since the molality of the gas, m_G, is small, we can neglect the second term in eqn (13). If S and S° are the concentrations (mol dm^{-3}) of G, then, since $\gamma^\circ m^\circ = \gamma m$, eqn (13) becomes (after correction for the molarity scale)

$$\{GC\}_g = \lim_{m_C \to 0} [(\boldsymbol{R}T/2m_C)\ln(S^\circ/S) - \phi_{V,C}\, m_C d^\circ] \qquad (14)$$

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where m_C and $\phi_{V,C}$ are the molality and apparent molar volume of cosolute and d° is the density of water. Roseman and Jencks[11] measured the solubilities of naphthalene and uric acid in water and in the presence of a wide variety of cosolutes. Eqn (13) also applies to these systems. Since the solubilities of naphthalene and uric acid are small, we can again neglect the second term in eqn (13). The limiting value in eqn (14) has been used wherever a variety of cosolute concentrations were measured. In some cases only a 1 mol dm^{-3} cosolute concentration was available and in these cases the value at 1 mol dm^{-3} was assumed to be equal to the limiting value. A comparison with systems where the concentration dependence was measured shows that errors of 20-30 % are frequent. In several cases the results varied so rapidly with concentration that the extrapolation could not be performed with any confidence and the data were not used. The results of these calculations are given in table 4.

ADDITIVITY PRINCIPLE

The additivity principle of Savage and Wood[1] assumes that every functional group on molecule A interacts with every functional group on molecule B and that each of these interactions has a characteristic effect on the enthalpy that is independent of the positions of the functional groups in the two molecules.* The total pairwise interaction is then the sum of all of the various interactions that are present. The resulting equation is:

$$\{AB\}_h = \sum_{i,j} n_i^A n_j^B H_{ij} \tag{15}$$

where n_i^A and n_j^B are the number of type i groups on molecule A and type j groups on molecule B, respectively, H_{ij} is the enthalpy of an i-j interaction, and $\{AB\}_h$ is the coefficient in the excess enthalpy of the solution reflecting pairwise interactions of A and B [see eqn (5)]. In adapting eqn (15) to deviations of free energy from ideality, it is necessary to choose the concentration scale on which to define an ideal solution. Choosing the mole fraction concentration scale gives:

$$\{AB\}_g = -(M_1RT/2)+\sum_{i,j} n_i^A n_j^B G_{ij} \tag{16}$$

where M_1 is the molecular weight of the solvent (in kg). This equation is derived from the osmotic coefficient of a mole fraction ideal solution:[13]

$$\phi = 1-M_1\,m/2+\ldots = 1-0.009\,m+\ldots. \tag{17}$$

The corresponding equation for the interaction coefficient in the excess entropy is

$$\{AB\}_s = +0.009R+\sum_{i,j} n_i^A n_i^B S_{ij} \tag{18}$$

where

$$G_{ij} = H_{ij}-TS_{ij}. \tag{19}$$

Although eqn (15), (16) and (18) are empirical, it is possible to give them a rough interpretation. The integral which must be evaluated in obtaining the second virial coefficient in the McMillan–Mayer standard state contains a factor, $[\exp(-W/kT)-1]$, where W is the potential of average force. Eqn (16) implies (1) that W can be written as a sum of separate group interactions and (2) that this sum must be small enough compared with kT to allow the above factor to expand into a linear sum of interaction terms. (1) means that the interaction between each pair

---

* See ref. (1) for a discussion of other additivity principles. Other models for non-electrolyte mixtures have been reported by W. Schröer,[12a] Palmer,[12b] and Fredenslund, Jones and Prausnitz.[12c]

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TABLE 5.—INTERACTION PARAMETERS FROM ALCOHOLS, CARBOHYDRATES AND POLYHYDROXY COMPOUNDS

	G_{ij}/J kg mol^{-2}	
$i \backslash j$	CH_2	CHOH
CH_2	−33.9(3.7) [a]	
CHOH	16.5(5.1)	−2.1(1.2)

[a] The standard deviation of fit, σ = 37 J kg mol^{-2}. The values in parentheses are the estimated 95 % confidence limits.

of groups must not depend on the presence of neighbouring groups on either molecule so that all steric effects are to be ignored and that the effects of solvation must be made up of additive contributions. Also, the sum of all of the group interactions must be small compared with kT so the group interactions must either be all small or contain cancelling contributions. The large repulsive part of the potential function, which leads to the volume exclusion effect, is least likely to satisfy this condition.

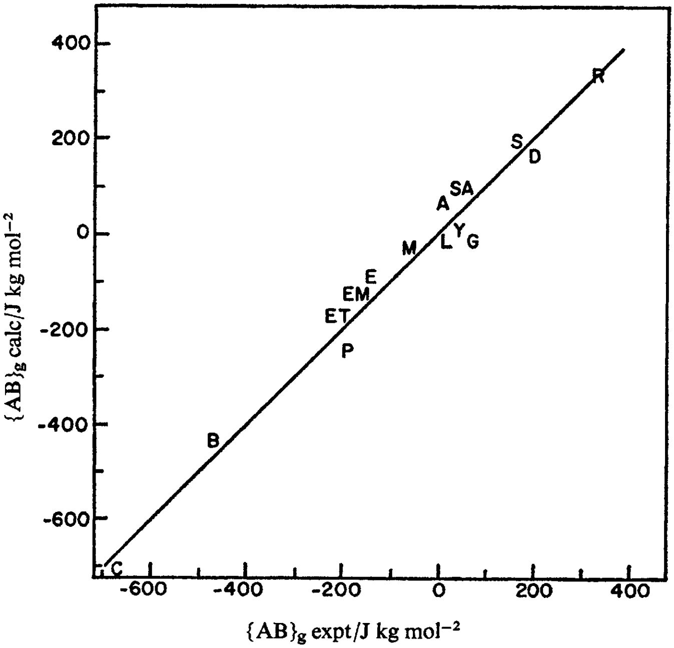

FIG. 2.—Calculated against experimental pairwise interaction coefficients. Calculated values from eqn (16) with G_{ij} from table 5. Tabulated values are given in table 3. The compounds are labelled as follows: A, mannitol; B, n-butanol; C, cyclohexanol; D, α-methylglucoside; E, ethanol; G, glucose; L, ethylene glycol; M, methanol; P, propan-2-ol; R, raffinose; S, sucrose; T, ethane; and Y, glycerol. The interaction of a molecule with itself is indicated by one letter and the interaction of two different molecules A and B is indicated by the symbol AB.

As a first test of eqn (16), the data on alcohols and polyhydroxy compounds in table 3 were fitted by least squares to eqn (16) using two types of groups: CH_2 and CHOH.* In doing this, the contribution of H was assigned as 0.5 CH_2 and all

* The choice of groups is arbitrary. Any other choice (such as CH_2 and OH) would give exactly the same correlation with the new G_{ij} being linear combinations of the old G_{ij}.

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oxygens in the carbohydrates were counted as equivalent to OH groups. The result of the correlation is given in table 5 and fig. 2. The calculated values of $\{AB\}_g$ are recorded in table 3. An F test showed that the overall correlation is significant at well beyond the 99 % confidence limits. Choosing an ideal solution as one which obeys Henry's Law on the molality scale eliminates the first term in eqn (16) and (18) and results in a correlation that is not quite as good (σ is ≈ 6 % higher).

The McMillan–Mayer standard state [10, 14] is another logical choice for defining ideality. On this basis, second virial coefficients were computed from the values in table 3, but the resulting correlation was not nearly as good, although still significant at the 99 % confidence limit. However, F was a factor of 4 lower. Attempts to fit just the attractive part of B_2 [10] gave a poorer correlation. This was unexpected since examination of the integral for the second virial coefficient shows that, although the volume exclusion contributions are not expected to follow eqn (15), the attractive parts of the integral should be approximated by an additivity principle like eqn (16) provided that the interactions are $<kT$. A reason for the poor fit to B_{att} may follow from the fact that the excluded volume terms are about as large as B_{att} but of opposite sign. Since estimates of the volume exclusion are not yet precise there are correspondingly large errors in estimating B_{att}. Our conclusion is that the Raoults Law scale gives the best correlation, but this should be checked when more data become available. We do not expect eqn (15), (16) and (18) to be very accurate and this is confirmed by fig. 2. Savage and Wood [1] have pointed out that both steric and nearest neighbour effects are completely neglected by the equations and such effects are not necessarily small. Nevertheless, the results allow us to assign the sign and magnitude of all three interactions with reasonable confidence.

TABLE 6.—INTERACTION PARAMETERS FROM AMIDES AND SUBSTITUTED UREAS

	G_{ij}/J kg mol^{-2}	
$i\backslash j$	CH_2	CONH
CH_2	−30.9(11.5) [a]	
CONH	−3.6(19.0)	−16.7(41.1)

[a] The values in parenthesis are estimated 95 % confidence limits and σ = standard deviation of fit = 76 J kg mol^{-2}.

Encouraged by the semi-quantitative success of eqn (16), we searched for data on other functional groups. The data in table 3 for amides and substituted ureas were correlated using eqn (16). To do this, it was again necessary to make some poor approximations. As before,[1] urea was counted as 1.5 CONH groups and for lack of sufficient data no distinction was made between amide groups with zero, one or two hydrogens on the nitrogen. Again, CH_3 was counted as 1.5 CH_2 and H was counted as 0.5 CH_2.[1] The resulting correlation (table 6) was again significant at well above the 99 % confidence limits, but the standard deviation of the fit was twice as large as that found for the alcohols and sugars. The two independent estimates of $G_{CH_2 \ldots CH_2}$ from table 5 and 6 are in satisfactory agreement; -33.9 ± 3.7 and -30.9 ± 11.5 J kg mol^{-2}.

The next step was to add in the results in table 4 which were derived from the solubility measurements of Roseman and Jencks.[11] Because the data were not always available as a function of concentration, the limiting values of $\{AB\}_g$ in table 4 are generally not as accurate as those in table 3. In addition, the solubility of naphthalene in aqueous n-butylurea did not fit the correlation and had to be ignored (see fig. 3 and table 4). For these data the new group C=C was introduced.

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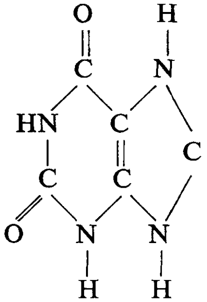
Counting the hydrogens in naphthalene as $\frac{1}{2}CH_2$ represents naphthalene as consisting of five C═C and four CH_2 groups. Similarly, uric acid, (I)



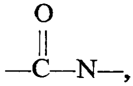
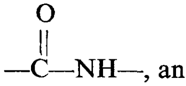
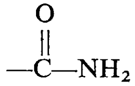
(I)

was assumed to consist of one C═C and 3.5 CONH. The results of the correlation are given in table 7. Comparing tables 5, 6 and 7 shows that all interactions common to the three tables agree within the estimated 95 % confidence limits.

Table 7.—Interaction parameters from amides, ureas and the solubility data of Roseman and Jencks [11]

	G_{ij}/J kg mol^{-2}	
$i\backslash j$	CH_2	CONH
CH_2	$-26.3(6.5)^a$	
CONH	0.6(9.7)	−72.8(21.9)
C═C	−44.3(9.5)	−30.7(18.8)

[a] Values in parentheses are the estimated 95 % confidence limits of G_{ij}. Standard deviation of the fit, σ = 100 J kg mol^{-2}.

As more data become available, the correlation should improve since it will be possible to eliminate some of the approximations used. For instance, we should have separate parameters for  $-\overset{\overset{\large O}{\|}}{C}-N-$,  $-\overset{\overset{\large O}{\|}}{C}-NH-$, and  $-\overset{\overset{\large O}{\|}}{C}-NH_2$ groups. It is also not obvious that counting CH_3 as 1.5 CH_2 is appropriate.*

The values $\{AB\}_g$ and $\{AB\}_h$ are the effects of A–B pair interactions on the excess free energy and enthalpy respectively in a solution containing 1 mol kg^{-1} of both A and B. Consider equations relating $\{AB\}_g$ and $\{AB\}_h$ to the usual free energies of association (ΔG_a) and association constants (K_a). The relation of G^E to the molal association constant for a model which assumes that only association contributes to non-ideality has been given by several authors [5, 15]

$$K_a = -\{AB\}_g/RT. \qquad (20)$$

Although positive values of $\{AB\}_g$ are allowed due to repulsive solute–solute forces, the corresponding, implied negative K_a values lack physical meaning as equilibrium constants. The free energy of association on the molal (ΔG_a^m) and mol fraction (ΔG_a^x) scales are given by:

$$\Delta G_a^m = -RT\ln K_a \qquad (21)$$

$$\Delta G_a^x = -RT\ln K_a - RT\ln 55.51. \qquad (22)$$

---

* There is some evidence that counting CH_3 as equal to CH_2 would be better. Hexahydropyrimidinone-2 would fit better with the other substituted ureas. Also, if the present correlation is applied to the gas phase second virial coefficients of hydrocarbons, the results are better with CH_3 counted as equal to CH_2.

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Similar relations previously derived[15, 16] give:

$$\{AB\}_h = K_a \Delta H_a \tag{23}$$

where ΔH_a is the enthalpy of association. This equation shows that the enthalpy term $\{AB\}_h$ depends on how many molecules are associated (through K_a) as well as on the enthalpy of association (through ΔH_a).

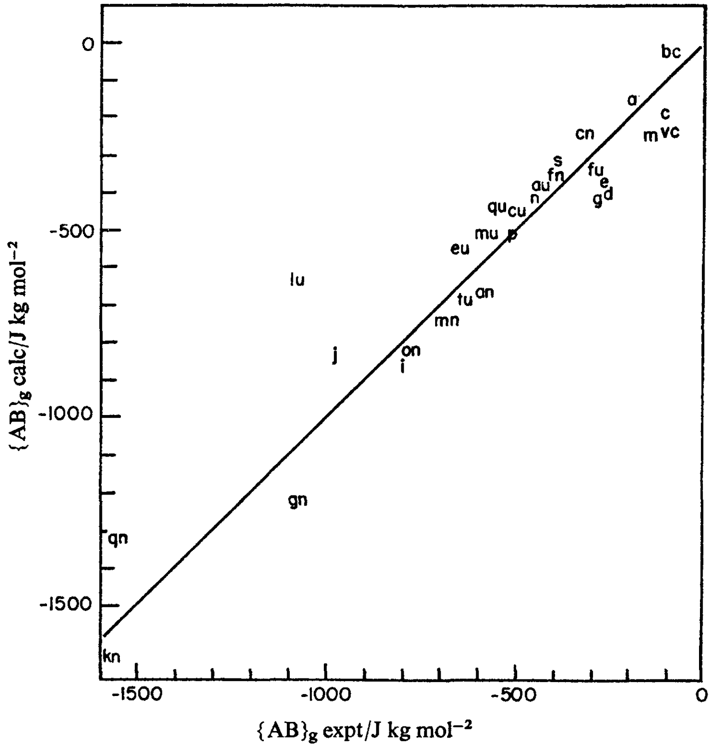

FIG. 3.—Calculated against experimental pairwise interaction coefficients. Calculated values are from eqn (16) with the coefficients from table 7. The compounds are labelled as follows: a, acetamide; b, butane; c, urea; d, 1,1-dimethylurea; e, ethylurea; f, formamide; g, 1,3-dimethylurea; h, hexahydropyrimidinone-2; i, 1,1-diethylurea; j, 1,3-dimethylurea; k, *N*,*N*-dimethylacetamide; l, n-butylurea; m, methylurea; n, naphthalene; o, *N*-methylformamide; p, propylurea; r, *N*,*N*-dimethylformamide; s, *N*-methylacetamide; t, tetramethylurea; u, uric acid; v, diketopiperazine. The interaction of two different molecules a and b is indicated by the symbol ab.

AMIDE-AMIDE INTERACTIONS

There has been controversy as to whether or not amide–amide interactions can appreciably affect the stability of protein structures.[15-23] The present results show that a single CONH . . . CONH interaction has a larger effect than a single $CH_2 \ldots CH_2$ interaction and thus can have appreciable effects on protein structure. We can estimate the contribution to K_a and ΔH_a for the CONH . . . CONH interaction using eqn (20) and (23), together with G_{ij} from table 7 and H_{ij} from ref. (1). Thus,

$$K_a = -G_{\mathrm{CONH}\cdots\mathrm{CONH}}/RT = 72.8/RT = 0.03 \text{ kg mol}^{-1} \tag{24}$$

and

$$\Delta H_a = H_{\mathrm{CONH}\cdots\mathrm{CONH}}/K_a = -251/0.03 = -8.5 \text{ kJ mol}^{-1}. \tag{25}$$

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These values are listed in table 8, together with experimental K_a and ΔH_a values found by various workers for a variety of amides. The rough agreement between the experimental values and our estimate of the CONH . . . CONH contribution confirms the view that this interaction is predominant. However, the results for *N*-methylacetamide (NMA) present an apparent anomaly. Klotz and Franzen,[19] using infrared techniques, found little association and no evidence for hydrogen bonding between amide groups except at high concentrations, whereas Kresheck [22] obtained significant association for NMA from osmotic coefficient data. Table 8 lists the contributions to K_a and ΔH_a of the various interactions in NMA as calculated from eqn (20) and (23). According to these results, only 20 % of the association between NMA molecules is due to amide–amide group interactions and the overall sign of the ΔH_a is reversed from that expected if this interaction were predominant. Thus, it is possible to have significant association in this system with little direct hydrogen bond formation between amide groups.

TABLE 8.—ASSOCIATION CONSTANTS, K_a, AND ENTHALPY OF ASSOCIATION, ΔH_a, FOR VARIOUS AMIDES

	K_a[a]	ΔH_a[b]				contribution to:		net value for:	
amide	kg mol^{-1}	kJ mol^{-1}	method[c]	ref.	*N*-methyl acetamide[e] interaction	K_a	ΔH_a	K_a	ΔH_a
urea	0.041	−8	os, *H*	16	$CH_2 \ldots CH_2$	0.095	2.9	0.132	2.9
	0.053	−7		18	$CH_2 \ldots CONH$	−0.001	1.9		
N-methyl-acetamide	0.005	(0)	i.r.	19	CONH . . . CONH	0.029	−1.9		
				21	ideal term	0.009	0		
N-methyl-acetamide	0.16[d]		os	22					
δ-valerolactam	0.015	−23	i.r.	20					
urea + diketo-piperazine	0.096	−14	s	17[b]					
diketopiperazine	0.06	−16	*H*	17[a]					
CONH—CONH	0.03	−8.5		present estimates; see text					

[a] Association constant on the molal scale; [b] enthalpy of association; [c] i.r. is infrared spectrophotometry, os is osmotic coefficient, *H* is enthalpy of dilution, and *s* is solubility; [d] K_a was calculated from the osmotic coefficient measured by Kresheck;[21] [e] these results for NMA were calculated from eqn (20) and (23) using data from table 7 and ref. (1).

As Kresheck has pointed out, the amide–amide interactions would probably not be detected by infrared spectroscopy if they were due to dipole–dipole forces.[23] This argument also applies to solvent separated pairs. Here one amide group polarizes a water molecule by hydrogen bonding which in turn allows the other end of the water molecule to form a stronger hydrogen bond with a second amide group. This could be the reason that Klotz and Franzen found very weak association in aqueous *N*-methylacetamide and no association in urea. It also explains why Finer, Franks and Tait [24] found no evidence for association when they studied n.m.r. relaxation and chemical shifts in aqueous urea solutions. Frank and Franks [25] explained the properties of aqueous urea solutions by assuming that urea shifted the water hydrogen bonding equilibria and this explanation is also compatible with the present results. Using the limited data available, there do not seem to be any striking differences between amide groups with and without hydrogens on the nitrogen, as would be expected if strong hydrogen bonds were present. However, the entropy effect to be discussed below is more compatible with hydrogen bonding.

HYDROPHOBIC INTERACTION

Comparison of the present results for the $CH_2 \ldots CH_2$ interaction with other quantitative estimates of the hydrophobic interaction is difficult because of the

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different models used. Nemethy and Scheraga [26] have estimated the free energy of interaction between two hydrophobic units when they come together with the expulsion of water. Similarly, Oakenfull and coworkers [27, 28] estimated the effect for each CH_2–CH_2 interaction assuming that long hydrocarbon chains line up along side each other. Both of these approximations are best applied where there is real site bonding between the two groups; *i.e.*, when only one configuration dominates the interaction. In contrast, the present correlation assumes there is no site binding and that every group on one molecule can interact with every group on the other molecule. These considerations imply that for any small model compound where the interactions are not large, the present correlation is the most appropriate. In addition, a site bonding model will not work when $\{AB\}_g$ is positive, since such a treatment would then imply a negative association constant, and the free energy of association could not be calculated. This situation occurs for all of the molecules in table 3 containing two or more CHOH groups, where volume exclusion effects apparently dominate the interactions.

On the other hand, the approximations of Scheraga or Oakenfull should be better able to estimate enzyme–substrate binding by hydrophobic interactions. These approximations may also be more suitable for micellization reactions and reactions where a hydrocarbon group is transferred from an aqueous environment to the interior of a protein.

In several cases, Scheraga and coworkers [29, 32] have calculated the effect of increasing chain length on the association constant for small molecules. Comparison with calculations using the present model give free energy and enthalpy effects within a factor of two of each other. For instance, for the carboxylic acid dimers, Schrier, Pottle and Scheraga [29] calculated the change in free energy of dimerization when the chain length is increased by adding two CH_2 groups, $\Delta G^{\circ}_{H\phi} = -2.7$ kJ. Neglecting COOH . . . CH_2 interactions, the present equations yield -5.2 kJ for the effect of the CH_2 groups. This is as good an agreement as can be expected, given the different assumptions and approximations of the two models.

OTHER INTERACTIONS

Tables 5-7 give quantitative estimates for many interactions for which there are no literature values. The net effect of the CH_2 interacting with the CHOH group is large and positive indicating predominantly repulsive forces between these two groups, *i.e.*, volume exclusion. This is not surprising since these groups have different interactions with the water. The net effect of a CHOH interaction with a CHOH group is small and negative, indicating that the attractive and repulsive forces present (when averaged using the appropriate statistical-mechanical procedure) nearly cancel. The competition between forming a strong hydrogen bond to an OH group or to a water molecule is presumably responsible for this cancellation.

The interaction of a CH_2 group with a CONH group is not large and of uncertain sign. Wetlaufer, *et al.*,[33] found that at 25°C 7 molar urea decreased the molar solubility of methane and ethane but increased the molar solubility of propane and butane. When corrected to the molal concentration scale, the pairwise interaction coefficient, $\{GU\}_g$, shows slight " salting in " for all of the hydrocarbons. This is evidence for a small and negative $G_{CH_2\text{–}CONH}$, although the urea concentration (7 mol dm^{-3} for all but the butane measurements) is so high that the effect may not be due to pairwise interactions alone.

The interaction of a CH_2 group with a C═C group is more negative than the CH_2–CH_2 interaction. This is another hydrophobic interaction and is attractive, as

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expected. The interaction of a C=C group with a CONH group is also attractive, due probably to the large dipole moment of the amide group interacting with the highly polarizable C=C group.

ENTHALPY AND ENTROPY EFFECTS

Savage and Wood [1] reported the values of H_{ij} listed in table 9. These have been used with the G_{ij} from the present work to calculate TS_{ij} values (table 9) from eqn (19). The entropy effect of the $CH_2 \ldots CH_2$ interaction is very large and positive as is characteristic of the hydrophobic interaction.[34] Savage and Wood [1] noticed that the enthalpy effect of a CH_2 group with a polar group (CHOH or CONH) produced as much enthalpy as a $CH_2 \ldots CH_2$ interaction. This occurs because the lower entropy of interaction is balanced by an increase in the free energy, possibly because the approach of a polar group breaks down the increased water structure around a CH_2 group but the effect is even larger when two CH_2 groups come together. This lower increase in entropy is accompanied by an increase in free energy because the polar group is repelled by the non-polar group. For aqueous solutions there are many examples where strong heat and entropy effects compensate each other at room temperature and produce very small free energies. This has become known as Lumry's Law.[35] The present results indicate that this is not characteristic of a single CH_2–CH_2 interaction at room temperature. Table 9 shows that for a CH_2–CH_2 interaction the entropy interaction is the most positive but that only 54 % of it is cancelled by the enthalpy effect. Thus for pure hydrocarbons in a one molal solution, we would expect the pairwise free energy effects to be about one-half of the entropy effects. A striking example of the compensation of enthalpy and entropy effects occurs with the larger tetra-alkylammonium halides.[36] In tetrabutylammonium bromide solutions, the large excess heat content at one molal is almost completely cancelled by a large entropy term. This is not generally characteristic of the hydrophobic effect in non-electrolytes and the charges on the groups have a considerable influence; *i.e.*, the expected strong attractive forces between the hydrocarbon groups are almost completely cancelled by the repulsive effect of the positive charges on the ions. Therefore, for these ions there is almost a complete cancellation of the heat and entropy effects.

TABLE 9.—FREE ENERGIES, ENTHALPIES AND ENTROPIES OF INTERACTION OF VARIOUS FUNCTIONAL GROUPS AT 25°C

$i\backslash j$		CH_2	CHOH	CONH
CH_2	G_{ij}	$-34(4)^a$		
	H_{ij}	$40(10)^b$		
	TS_{ij}	$74(11)^c$		
CHOH	G_{ij}	17(5)	$-2(1)$	
	H_{ij}	32(6)	$-4(3)$	
	TS_{ij}	15(8)	$-2(3)$	
CONH	G_{ij}	1(10)		$-73(22)$
	H_{ij}	41(32)	$-34(21)$	$-252(113)$
	TS_{ij}	40(33)		$-179(115)$

[a] Values in parentheses are estimated 95 % confidence limits. All values are in $J\ kg\ mol^{-2}$; [b] values of H_{ij} are from Savage and Wood;[1] [c] calculated from $TS_{ij} = H_{ij} - G_{ij}$, eqn (19).

The large decrease in entropy associated with the CONH ... CONH interaction

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indicates less freedom of motion when the two groups interact. A strong hydrogen bond would tend to reduce the entropy of the dimer, but this contradicts the evidence which indicates that there is no direct hydrogen bond (see above).

SUMMARY

The freezing temperatures of a variety of alcohols have been measured with a new apparatus which does not require determination of the concentration of the alcohol.

Pairwise interaction coefficients at 25°C were calculated from these results and correlated with the additivity principle of Savage and Wood. This led to a rough but useful correlation. Literature data for a variety of amides have also been tested.

The signs and magnitudes of the free energy of interaction of the CH_2, CHOH, C=C and CONH groups with each other have been determined, together with the enthalpy and entropy of interaction.

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