Pure & Appl. Chem., Vol. 66, No. 3, pp. 429–434, 1994.
Printed in Great Britain.
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Interactions in solutions: The interplay between solute solvation and solute–solute interactions

Terence H. Lilley

Biothermodynamics Laboratory, Chemistry Department, The University of Sheffield, Sheffield S3 7HF, U.K.

Abstract

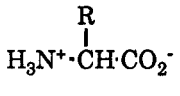
Some results are presented for the partial molar heat capacities and the enthalpies of hydration of amides in water; both can be represented using a group additivity approach. Results are also given for various enthalpic interaction coefficients of some amides in water. From the information given a general chemical principal is postulated namely that the more strongly solutes are solvated the less will be their propensity to interact with other solutes.

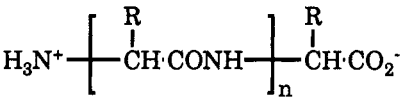
The thermodynamic properties of solutions containing amino acids, peptides and derivatives of these, have occupied our attention for some time and the results of our studies have been reported in an ongoing series of papers (ref.1) and in some other publications (refs. 2,3). The principal reasons we have for studying such systems are directed towards problems in protein chemistry and in particular the energetic problems controlling protein folding and assembly and the interaction of substrates with the active sites of enzymes. More generally, we also have interests in the interactions which occur in solution, between organic and inorganic solutes and how the chemical reactivity of molecules in solution depends on the solvent environment. In the present paper, a summary of some of our recent results, directed towards the hydration of solutes, will be given and this will be complemented by some information on the interactive behaviour of the same types of solutes. In the final section of the paper some correlations between solvation and interaction will be presented which illustrate what seems to be a general feature of chemical systems.

TYPES OF COMPOUNDS INVESTIGATED

Most, if not all, of the compounds with which we have been concerned fall into one of three main categories.

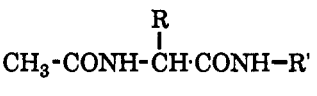
α-Amino acids and peptides

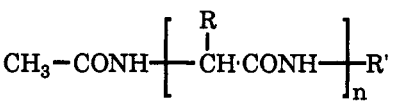




Compounds of these types are zwitterionic in nature and the disparate charges have a marked effect on solution properties.

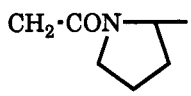
Terminally substituted amino acids and peptides

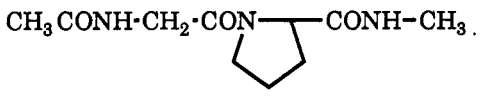




R' = -H, -CH_3

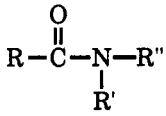
Our studies have also included investigations in which the imino acid, proline, is present *e.g.*





Compounds like these contain the secondary peptide (tertiary amide) group (-CON<) and the primary peptide (secondary amide) group (-CONH-).

Simple amides



R, R', R" = -H, aliphatic residue

The reason we chose to study compounds of this type was because they contain either the primary peptide or secondary peptide group.

It is worth stating here that the approach we have adopted in our studies on solvation and solute-solute interaction, has been to see if the properties of relatively simple species in solution can be represented in ways which are both concise and have clear physico-chemical bases. In other words, we have been searching for 'rules', established using simple, well-defined systems, which can be used to give guidance into the behaviour of more complex systems.

SOLVATION STUDIES

To illustrate the types of approach adopted, two examples will be given.

Partial molar heat capacities of amides and amino acid and peptide amides

A considerable body of information exists (ref. 4) on the standard state (infinite dilution) partial molar heat capacities of aliphatic amides in water and these have been supplemented (ref. 5) by some data on the *N*-acetyl amides of glycine (GLY), α-alanine (ALA), glycylglycine (GG), glycyl-L-α-alanine (GA), L-α-alanylglycine (AG) and L-α-alanyl-L-α-alanine (AA). All of the data were analysed assuming that the heat capacities are chemical group additive (ref.4) such that

$$C_p^\infty = n_{CH_3}C_{p,CH_3} + n_{CH_2}C_{p,CH_2} + n_{CH}C_{p,CH} + n_H C_{p,H} + n_{CONH}C_{p,CONH} \quad (1)$$

where n_i is the number of groups of type i on a solute molecule and $C_{p,i}$ is the group partial molar heat capacity. The quality of the fitting is shown in Table 1, using the following values obtained for the group contributions (all with units of J K^{-1} mol^{-1}): C_{p,CH_3} = 133; C_{p,CH_2} = 90; $C_{p,CH}$ = 65; $C_{p,H}$ = 45; $C_{p,CONH}$ = -13.

TABLE 1. Experimental and fitted values of the partial molar heat capacities, at infinite dilution, of amides in water at 25°C. See text for the abbreviations used.

	C_p^∞ / J K^{-1} mol^{-1}			C_p^∞ / J K^{-1} mol^{-1}	
	expt.	fitted		expt.	fitted
Formamide	82	77	*N* - Butylacetamide	516	524
Acetamide	161	165	*N* - Methylpentamide	524	524
Propionamide	254	253	GLY	238	242
N - Methylformamide	164	165	ALA	346	350
N - Methylacetamide	258	253	GG	322	319
N - Ethylacetamide	343	343	GA	422	427
N - Methylpropionamide	334	343	AG	431	427
N - Propylacetamide	437	434	AA	538	535
N - Methylbutyramide	434	434			

It is apparent that the procedure adopted works rather well and is a simplifying feature which could be used to estimate heat capacities of, say, the denatured states of proteins in water.

The enthalpy of hydration of peptide groups

We now consider the evaluation of the enthalpy of hydration of peptide groups (ref. 3) *i.e.*

$$\text{-CONH- (gas)} \rightarrow \text{-CONH- (aq.)} \tag{2}$$

and

$$\text{-CON< (gas)} \rightarrow \text{-CON< (aq.)} \tag{3}$$

Experimental information is available (ref. 6) for the enthalpies of hydration ($\Delta_{hyd} H_m^{\infty}$) of several aliphatic amides, both secondary and tertiary. If it is assumed that the enthalpy of hydration of an amide is chemical group additive then for a secondary amide of structure, R~CONH-R', we can write

$$\Delta_{hyd} H_m^{\infty}(\text{secondary amide}) = \Delta_{hyd} H_m^{\infty}(\text{-CONH-}) + \Delta_{hyd} H_m^{\infty}(\text{R-}) + \Delta_{hyd} H_m^{\infty}(\text{-R'}) \tag{4}$$

or, more generally for secondary amides

$$\Delta_{hyd} H_m^{\infty}(\text{secondary amide}) = \Delta_{hyd} H_m^{\infty}(\text{-CONH-}) + \sum \Delta_{hyd} H_m^{\infty}(\text{R-}) \tag{5}$$

with an analogous expression for tertiary amides

$$\Delta_{hyd} H_m^{\infty}(\text{tertiary amide}) = \Delta_{hyd} H_m^{\infty}(\text{-CON<}) + \sum \Delta_{hyd} H_m^{\infty}(\text{R-}) \tag{6}$$

It is not possible, of course, to obtain a direct measure of the enthalpies of hydration of the aliphatic groups *per se* but these can be estimated by assuming that, as an example,

$$\Delta_{hyd} H_m^{\infty}(C_2H_5\text{-}) = \Delta_{hyd} H_m^{\infty}(C_2H_6) + \tfrac{1}{2}\Delta_{hyd} H_m^{\infty}(H_2) \tag{7}$$

Using this approximation the second terms on the r.h.s. of eqns. (5) and (6) can be evaluated and when combined with experimental enthalpies of hydration, the enthalpies of hydration of the -CONH- and -CON< groups can be obtained. From the information presented in Fig. 1 the values obtained are:

$$\Delta_{hyd} H_m^{\infty}(\text{-CONH-}) \approx -52 \text{ kJ mol}^{-1}; \quad \Delta_{hyd} H_m^{\infty}(\text{-CON<}) \approx -35 \text{ kJ mol}^{-1}.$$

It is apparent that this group additivity approach works rather well and that we have a 'rule' which is applicable to the hydrational properties of polyfunctional molecules. The 'rule' is not exact and cannot be expected to be so since some deviations from perfect additivity must result from *e.g.* intramolecular solvation region interactions between peripheral groups. The values for the enthalpies of hydration are both negative indicating thermochemical attraction between both

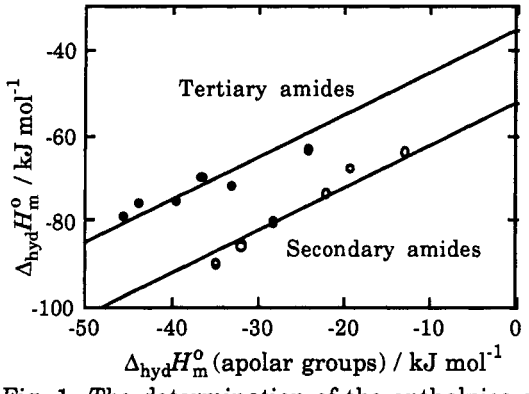


Fig. 1 The determination of the enthalpies of hydration of the -CONH- and the -CON< groups.

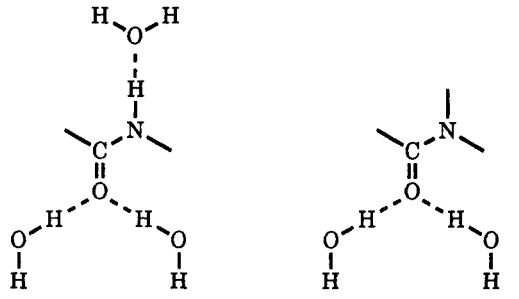


Fig. 2. Hydrogen bonding of primary and secondary peptide groups in water.

types of peptide group and water and, not surprisingly, the primary peptide group interacts more strongly with this solvent than does the secondary peptide group. It seems likely that the dominant interactions are of the hydrogen-bonding type as shown in Fig. 2 and that each of the hydrogen-bonds formed has associated with it a net enthalpy change of ~ -17 kJ mol^{-1}.

SOLUTE–SOLUTE INTERACTIONS

The most customary way of dealing with interactions between solvated solutes in a solvent is to use the excess function approach. In this *e.g.*, the excess enthalpy (H^{ex}) of a solvation containing 1 kg of solvent, is written as a polynomial expansion in the molarities of the solutes present *i.e.*

$$H^{ex} = \sum_x \sum_y h_{xy} m_x m_y + \sum_x \sum_y \sum_z h_{xyz} m_x m_y m_z \qquad (8)$$

where h_{xy}, h_{xyz} are enthalpic coefficients representing interactions between the subscripted solvated species. In relatively dilute solutions, the pairwise coefficients are dominant and it is only with these that we will be concerned. Details on how these are evaluated from experiment have been given elsewhere (ref. 8).

Interactions in aqueous solutions containing simple amides and terminally substituted amino acids and peptides

Homotactic and heterotactic interactions between amides. A large body of information exists (ref.1) on the pairwise enthalpic coefficients of species of this type and it has been rationalised using a group additivity approach first suggested by Schrier and Schrier (ref.9) and imaginatively extended by Savage and Wood (ref. 10). The free energetic coefficient for the interaction of two solute species A and B is given by

$$g_{AB} = \sum n_A^i n_B^j G_{ij} \qquad (9)$$

where *e.g.* n_A^i is the number of groups of type i on the solute A and G_{ij} is a free energetic coefficient representing the interaction of solvated group i with solvated group j. A summary of the results obtained is given in Table 2 and it is apparent from this that methylene-methylene, primary peptide-primary peptide, and second peptide-secondary peptide groups interact with each other in an attractive way but the interactions between methylene groups and both types of peptide group indicate repulsions between these solvated groups. The most striking result is that the interaction between secondary peptide groups is *more* attractive than that between primary peptide groups.

Heterotactic interactions between amides and urea. When one addressed the interactions between amides and urea in water then the group additivity approach leads to the expressions:

$$h_{AU}(\text{secondary amide}) = H_{CONH\text{-urea}} + n_{CH_2}^{amide} H_{CH_2\text{-urea}} \qquad (10)$$

$$h_{AU}(\text{tertiary amide}) = H_{CON\text{-urea}} + n_{CH_2}^{amide} H_{CH_2\text{-urea}} \qquad (11)$$

The results obtained (ref.10) are shown in Fig. 3 and it is apparent that $H_{CON\text{-urea}} < H_{CONH\text{-urea}}$ *i.e.* the attraction between the tertiary peptide group and urea is greater than that between the primary peptide group and urea.

Heterotactic interactions between salts and amides. The same sort of approach can be used here but now, since each of the ions of the salt acts independently, we have for 1:1 electrolytes with cation M^+ and anion X^-:

$$h_{amide,\,salt}(\text{sec. amide}) = (H_{CONH\text{-}M^+} + H_{CONH\text{-}X^-}) + n_{CH_2}^{amide}(H_{CH_2\text{-}M^+} + H_{CH_2\text{-}X^-}) \qquad (12)$$

$$h_{amide,\,salt}(\text{tert. amide}) = (H_{CON\text{-}M^+} + H_{CON\text{-}X^-}) + n_{CH_2}^{amide}(H_{CH_2\text{-}M^+} + H_{CH_2\text{-}X^-}) \qquad (13)$$

A summary of the results obtained for some alkali metal halides interacting with amides is shown in Fig. 4 and the general picture which results is that the smaller ions, with a greater surface charge density, interact less well with both secondary and tertiary peptide groups than do the larger ions.

TABLE 2. Free energetic coefficients for the interaction of some chemical groups in water at 25°C. The methylene group is taken as being the basic apolar residue (ref.1).

Groups		G_{ij} / J kg mol^{-2}
i	j	
CH_2	CH_2	-20
-CONH-	-CONH-	-50
-CON<	-CON<	-62
-CONH-	CH_2	22
-CON<	CH_2	37

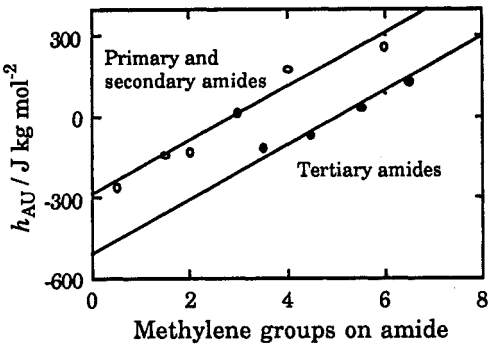


Fig. 3. Heterotactic enthalpic coefficients for the interaction of amides and urea in water as a function of the number of methylene groups on the amide.

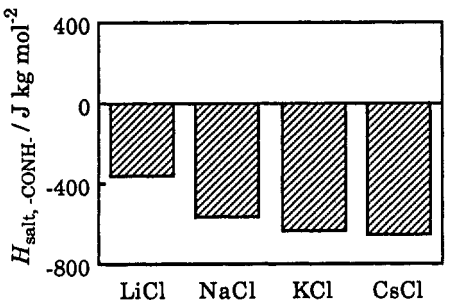


Fig. 4. Enthalpic group coefficients for the interaction of alkali metal halides with the primary peptide group in water at 25°C (J.Fernandez, T.H. Lilley and H. Linsdell, unpublished work).

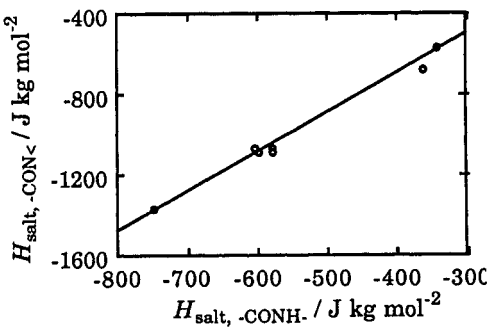


Fig. 5. Correlation between the enthalpic group interaction coefficients of alkali metal halides interacting with the primary peptide group and the secondary peptide group. The slope of the line is approximately two.

This indicates that the smaller ions, because the are 'better' hydrated have a reduced tendency to interact with polar groups in water. In a complementary way, it is found that, for any given salt, it interacts less favourably with primary peptide groups than with secondary peptide groups (see Fig. 5) and this almost certainly arises because the secondary peptide groups are less well hydrated.

SOLUTE SOLVATION VERSUS SOLUTE-SOLUTE INTERACTIONS

It is from studies such as those referred to above that we are led to suggest a general chemical principle *viz.* that the better solvated species are the less will be their tendency to interact (or react) with other species. Two further illustrations will be presented which indicate that this principle has general applicability.

Enthalpies of solution and enthalpic interaction coefficients of *N*-methylformamide (NMF) in N,N-dimethylformamide (DMF) + water mixtures

In Fig. 6 are shown the combined results of two studies, one directed towards the enthalpies of solution of NMF in mixtures of DMF + water (ref.11) and the other concerned with pairwise homotactic interactions between NMF species in the same mixed solvents (T.E. Leslie and T.H. Lilley, unpublished work.).

It is apparent that an approximate mirror image exists between the two contrasting measures of molecular interactions and the results obtained indicate that the more exothermic is the interaction between the solute and the solvent, the more endothermic in the homotactic interaction between solvated solute species. It is striking that this relationship is seen and it

suggests that notwithstanding the nature of the solvent, or indeed whether a mixed solvent is used, that there is some underlying interplay occurring between solvation and interaction. We do not know at this point in time what the relationship is between the tendencies molecular species have for interaction and their solvation but one can only imagine that it will be complex, at least in a formal sense.

It is appropriate to mention here that, although most of the information presented here is of an enthalpic nature, perusal of the much more limited free energetic information also suggests that similar relationships exist. This is not too surprising given that linear free energy relationships are quite common.

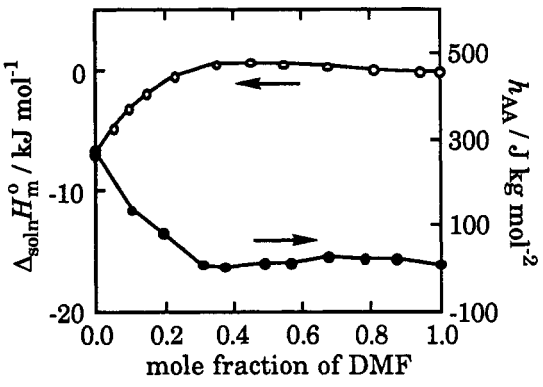


Fig. 6. Correlation between the enthalpies of solution of NMF and the enthalpic, homotactic interaction coefficients, in DMF + water mixtures.

Enthalpies of transfer of amides between water and 8 molar aqueous urea solutions and the corresponding changes in the homotactic interaction coefficients of the amides (ref. 12)

The correlation between these quantities is shown in Fig. 7 and although the line drawn has no special significance, the overall trend is quite apparent. The clear conclusion which can be drawn from this study is that as the solvation (as reflected in the change in the molar enthalpy of solution) becomes 'stronger', (*i.e.* more exothermic) there is a concomitant change such that the enthalpic, homotactic interaction coefficient becomes more positive (endothermic). In this particular example the solvation of the solutes in the urea solution almost certainly will be heterogeneous, in that about any groups on the molecules, the solvation region will be comprised of a mixture of water molecules and urea molecules.

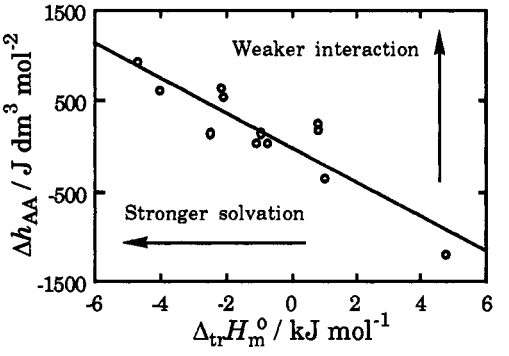


Fig. 7. Correlation between the enthalpies of transfer of amides from water to 8 molar urea solutions and the corresponding changes in the enthalpic homotactic interaction coefficients.

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