A Group Additivity Approach to the Energetics of Pairwise Interactions of Peptides in Aqueous Solution

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Summary A group additivity method has been used to evaluate the free energies, enthalpies, and entropies of interaction of methylene and peptide groups in water at 298 K.

NONBONDING interactions between molecules in solution is an area of wide current interest,[1-3] not least because a multitude of biological phenomena rely on recognition between, and association of, paired molecular species. We have embarked on a study of the energetics of interactions between small peptides in aqueous solution, since these species embody some of the features which must dominate the behaviour of oligopeptides and of proteins in water.

What is wanted are methods of measurement that reflect interactions, associative or repulsive, between solute molecules in aqueous solution. The procedure we have adopted is based on the excess function concept. The excess specific Gibbs free energy,[4] G^{ex}, for a binary solute system containing species A and B can be written as in equation (1). In this expression, for example, g_{AB} represents

$$G^{ex} = g_{AA}m_A^2 + g_{BB}m_B^2 + 2g_{AB}m_Am_B + \text{higher order terms} \quad (1)$$

the free energy of pairwise interaction between species A and B, and m_A is the molality of species A. Similar ex-

pressions apply for other thermodynamic functions such as the excess enthalpy and the excess entropy The g_{AB} terms are derivable from isopiestic measurements, and the h_{AB} terms from microcalorimetric data

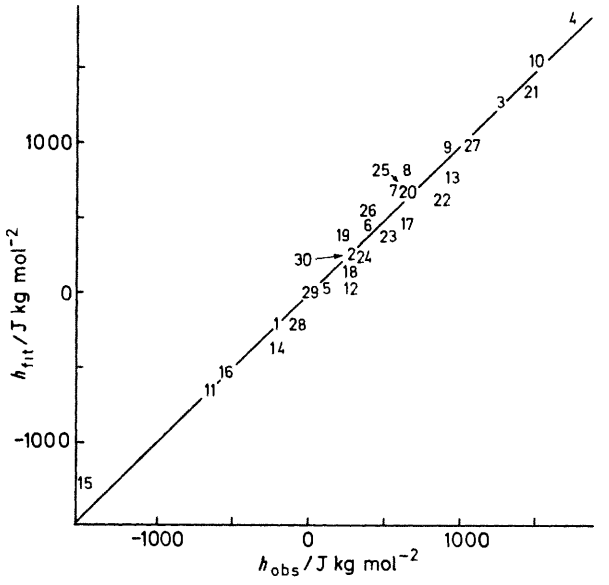

FIGURE 1 Experimental (h_{obs}) and fitted (h_{fit}) pairwise enthalpic coefficients Key 1, *N*-acetylglycinamide (G) + G,[7] 2, *N*-acetyl-L-alaninamide (A) + A,[7] 3, *N*-acetyl-L-valinamide (V) + V,[7] 4, *N*-acetyl-L-leucinamide (L) + L,[7] 5 G + A,[7] 6, G + V,[7] 7, G + L,[7] 8, A + V,[7] 9, A + L,[7] 10, L + V,[7] 11, *N*-acetylglycylglycinamide (G_2) + G_2, 12, *N*-acetyl-L-alanylglycinamide (AG) + AG, 13, *N*-acetyl-L-alanyl-L-alaninamide (A_2) + A_2, 14, G + G_2, 15, *N*-acetylglycylglycylglycinamide (G_3) + G_3, 16, G + G_3, 17, A + A_2, 18, *N*-methylformamide (NMF) + NMF,[8] 19, *N*-methylacetamide (NMA) + NMA,[8] 20, *N*-methylpropionamide (NMP) + NMP,[8] 21, *N*-butylacetamide (NBA) + NBA,[8] 22, NMF + NBA,[8] 23, NMF + NMP,[8] 24, NMF + NMA,[8] 25, NMA + NBA,[8] 26, NMA + NMP,[8] 27, NMP + NBA,[8] 28, formamide (F) + F,[9] 29, acetamide (A) + A,[9] 30, propionamide (P) + P[9]

Peptides represented by the general formula CH_3CO-$(NHCHRCO)_nNH_2$, with n = 1–3 and R = H, Me, Pr^i, and Bu^i, were prepared[5] by conventional synthetic methods with optically pure species of (*S*) chirality throughout Analysis of the experimental microcalorimetric and isopiestic data derived at 298 K from solutions of these solutes in pure water led to the values of h_{AB} and g_{AB} shown (ordinate values in Figures 1 and 2 respectively) Qualitatively, as the hydrophobic character of the interacting pair of solutes increases so does the enthalpic coefficient The converse is evident for the free energy terms (Figure 2) However, in all cases reported here, these interactions are small compared to thermal energies

Under these circumstances, the data can be rationalised using a group additivity approach[6] For this purpose generally, molecules A and B are envisaged as being constructed from different combinations of functional groups † In particular, the simple peptides we have studied can be so defined in terms of just two groups, CONH and CH_2, by

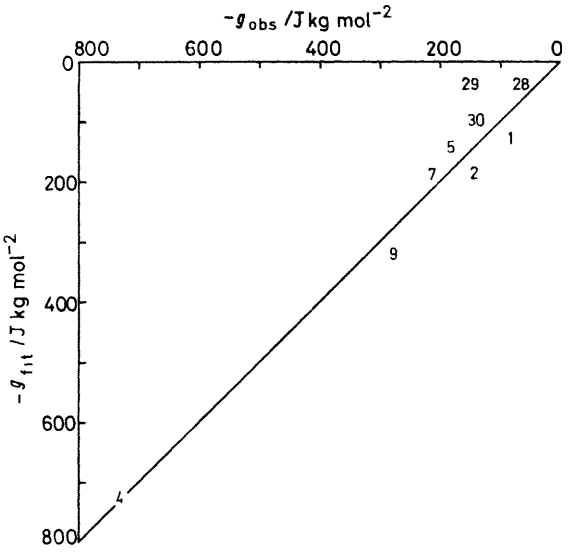

FIGURE 2 Experimental (g_{obs}) and fitted (g_{fit}) pairwise free energy coefficients The numbering system is the same as that in Figure 1 The data for points 28, 29 and 30 were obtained from reference 10

using the simplification that a methyl group is equivalent to 1 5 methylene groups and a methine group to half a methylene group This leads to the expression (2) for the free energy coefficient for interaction between molecules A and B, where *e g* $n^{(A)}_{CH_2}$ represents the number of methylene

$$g_{AB} = n^{(A)}_{CH_2} n^{(B)}_{CH_2} G_{CH_2-CH_2} + n^{(A)}_{pep} n^{(B)}_{pep} G_{pep-pep} + (n^{(A)}_{CH_2} n^{(B)}_{pep} + n^{(A)}_{pep} n^{(B)}_{CH_2}) G_{CH_2-pep} \quad (2)$$

groups in solute species A and $G_{pep-pep}$ is a term representing the free energy of interaction between two amide groups Analogous expressions can be written for the enthalpy terms

Non-linear regression methods were used to evaluate the group interaction parameters ($H_{pep-pep}$ *etc*) for the enthalpy data, and $G_{pep-pep}$ *etc* for the free energy data, to give the values shown in the Table With the data set available, we have obtained reliable values for these interaction terms, from which we have calculated values for the enthalpy or free energy data (abscissae of Figures 1 and 2 respectively) The excellent quality of fit is shown by the relationship between observed and calculated values (which would be perfect if all points lay on the lines of unit slope)

TABLE Group interaction coefficients at 298 K

	G	*H*	*TS*
Interacting groups	J kg mol^{-2}		
$CH_2 \cdot CH_2$	−29	+14	+43
$CH_2 \cdot \cdot CONH$	+28	+95	+67
$CONH \cdot \cdot \cdot CONH$	−49	−311	−262

† All possible pairwise intermolecular interactions between these groups are allowed Collectively, they sum to the interaction observed between the species A and B

In terms of the free energy parameters, it is clear that attractive contributions result from methylene–methylene and also from peptide–peptide group interactions, while there is a repulsive contribution from methylene–peptide interactions.

We acknowledge financial support from A.R.C. and S.R.C.

(*Received, 8th August* 1980; *Com.* 879.)

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