

Enthalpy of interaction of some amides with ammonium methanoate in water at 25 °C

Interactions between ionic groups and peptide and hydrophobic groups

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The enthalpies of dilution at 25 °C of aqueous solutions containing ammonium methanoate and a series of amides: formamide, acetamide, *N*-methylformamide, *N*-methylacetamide, *N*-ethylformamide, *N*-methylpropionamide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and *N,N*-diethylformamide have been measured. The dilution experiments were performed on solutions equimolar in the salt and the amides. The enthalpies of dilution of solutions containing only ammonium methanoate were also obtained. The results on the dilutions of the binary solute solutions were analysed using an excess function approach and enthalpic heterotactic interaction coefficients were obtained representing interactions between the ammonium methanoate and the amides.

Consideration of these interaction coefficients using a group additivity approach shows that ammonium methanoate interacts more favourably, in a thermochemical sense, in water with tertiary amide (secondary peptide) groups than with secondary amide (primary peptide) groups, and that the interactions of ammonium methanoate with methylene groups in water are thermochemically repulsive. These results are qualitatively similar to those found for a range of salts interacting with groups present on peptides. Examination of the information currently available on salt–amide interactions in aqueous solutions, gives further support to the idea that these are fairly quantitative correlations between the propensity solutes in water have to interact with each other and their hydration energetics.

A principal objective of our work over the past several years has been to obtain experimental information on the energetics of the interactions which occur between species in aqueous media. Most of our investigations have been directed towards systems in which the solutes have been amino acids and peptides and derivatives of these, or have, as part of their molecular structures, groups which are also present in peptides and proteins.^{1–7} Even for relatively simple species it would seem that a great diversity of possible interactions can occur, both with the solvent and with other solute molecules. However, notwithstanding the fundamental complexity of systems containing polyfunctional molecules, if there is to be any progress made in predicting the behaviour of such systems, it is necessary to have some general rules⁸ which allow, at least, estimates of the energetics of the interactions, since it is the energetics which generally determine what are currently called molecular recognition processes. One of our objectives has been to obtain such rules which are applicable to relatively complicated molecules when they are present in aqueous systems. Analogous studies have been initiated on non-aqueous solvent^{9–19} and mixed-solvent systems^{7,9,20–24} but at the moment the information available is fairly fragmentary.

As part of our programme of work, we have presented⁵ the results of a study on the interactions occurring between some amides and the amino acids glycine and α -alanine. From this investigation, quantitative measures were obtained of the interactions between aliphatic hydrophobic groups and peptide groups with the zwitterionic head-group, which is present on α -amino acids. This head-group contains two ionic components (NH_3^+ and CO_2^-), which are adjacent, and it seems possible that the mutual perturbations occurring between these will modify, to a greater or lesser extent, their interactions with other groups or molecular species. The perturbations will be from two of types of source: the first will

arise from direct, largely Coulombic, interactions between the charged groups on the α -carbon, and the second will stem from hydration region disruptions about these groups. It has been previously shown^{1–3,25} that simple salts containing ions of relatively low charge density, where the ionic constituents are separate and distant, interact with organic solutes in an ion-additive way. In the present paper we give the results of a similar investigation to some of those which have been performed earlier, into the interactions which occur between the salt, ammonium methanoate (formate), and several amides. The reason we chose to study this particular salt was because of its structural similarity to the zwitterionic head-group on the α -amino acids (Fig. 1). However, the ionic components, unlike those on the amino acids, are distinct and separate.

Experimental

Apparatus and methods

The procedures and apparatus used have been described in several publications.^{4,26} The calorimetric experiments were performed using a total flow rate of solutions of $4.00 \times 10^{-3} \text{ cm}^3 \text{ s}^{-1}$.

Materials

The amides were initially dried over 4 Å molecular sieve for several days and then purified as follows: formamide (supplier FSA, initial purity >99%), *N*-methylformamide (NMF)

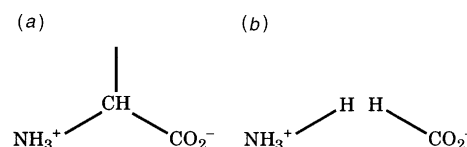


Fig. 1 Structural similarities between the head-group on (a) an α -amino acid and (b) ammonium methanoate

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(Fluka, initial purity >99%), *N*-methylacetamide (NMA) (Aldrich, initial purity >99%), *N*-ethylformamide (NEF) (Fluka, initial purity >99%), *N*-methylpropionamide (NMP) (Fluka, initial purity >97%), *N,N*-dimethylacetamide (DMA) (GPR) and *N,N*-diethylformamide (DEF) (Fluka, initial purity >99%) were all purified by vacuum distillation from solid NaOH. Acetamide (Fluka, initial purity >99%) was recrystallized from ethanol–diethyl ether (1:8 v/v). *N,N*-dimethylformamide (Fluka, initial purity >99%) was used as supplied after storing under N₂. Following purification the amides were stored in a vacuum desiccator over P₂O₅ (the liquid amides over 4 Å molecular sieve). A more detailed description of the purification processes can be found in ref. 1, 3 and 4.

Ammonium methanoate (B.D.H. Ltd., initial purity >97%) was twice recrystallised from hot water and dried and stored in a desiccator over PO₅ for some days before use.

Results and data treatment

The analysis procedures used were based on the excess function concept^{27–29} which has been reviewed and discussed several times previously.^{8,30–34}

Enthalpy of dilution of ammonium methanoate

A literature search indicated that enthalpy of dilution data were not available for this salt and so some measurements were made in the molality range over which mixing information was to be obtained.

Experimental values for the molar enthalpies of dilution ($\Delta_{\text{dil}} H_m$), which are equivalent to the changes in the molar excess enthalpies ($H_{m,\text{MX}}^{\text{ex},\circ}$) for diluting solutions from an initial molality $m_{\text{MX},\text{in}}$ to a final molality $m_{\text{MX},\text{fin}}$, are deposited as Supplementary Data.† Since the dilutions were performed using a flow microcalorimeter, when analysing the data it was appropriate that the fittings should use the experimental powers (P). We chose to use Pitzer's³⁵ semi-empirical extension of the Debye–Hückel treatment of electrolytes as the basis of the analysis method on the dilution enthalpies.

The power is related to the flow rate (\dot{n}) of the number of moles of the salt and to the molar excess enthalpy change by

$$P = \dot{n}[H_{m,\text{MX}}^{\text{ex},\circ}(m_{\text{MX},\text{fin}}) - H_{m,\text{MX}}^{\text{ex},\circ}(m_{\text{MX},\text{in}})] \\ = \dot{n}\Delta H_{m,\text{MX}}^{\text{ex},\circ} \equiv \dot{n}\Delta_{\text{dil}} H_{m,\text{MX}} \quad (1)$$

The following equation derived from Pitzer's treatment³⁶ for the molar excess enthalpy of a uni-univalent electrolyte was used:

$$H_{m,\text{MX}}^{\text{ex},\circ}(m_{\text{MX}}) = (2A_{\text{DH}}/3.6)\ln(1 + 1.2m_{\text{MX}}^{1/2}) \\ - 2RT^2(B_{\text{MX}}^L m_{\text{MX}} + C_{\text{MX}}^L m_{\text{MX}}^2 + D_{\text{MX}}^L m_{\text{MX}}^3) \quad (2)$$

where A_{DH} is a calculable constant ($=2918 \text{ J mol}^{-1}$)³⁷ and B_{MX}^L , C_{MX}^L and D_{MX}^L are fitting coefficients. The form of B_{MX}^L is given by:

$$B_{\text{MX}}^L = \beta^0 + \beta^1\{[1 - (1 + 2m_{\text{MX}}^{1/2})\exp(-2m_{\text{MX}}^{1/2})]/2m_{\text{MX}}\} \quad (3)$$

where β^0 and β^1 are the constant-pressure temperature derivatives of the corresponding free energy function coefficients. We found it necessary to include the term in D_{MX}^L in the data analysis although such terms, which notionally represent concurrent specific interactions between four ionic species, are not usually used when fitting to data.

Incorporation of eqn. (2) and (3) into the expression for the molar enthalpy of dilution gives

$$\Delta_{\text{dil}} H_{m,\text{MX}} = (2A_{\text{DH}}/3.6)\ln\left(\frac{1 + 1.2m_{\text{MX},\text{fin}}^{1/2}}{1 + 1.2m_{\text{MX},\text{in}}^{1/2}}\right) \\ - 2RT^2\beta^0(m_{\text{MX},\text{fin}} - m_{\text{MX},\text{in}}) \\ + RT^2\beta^1\{[1 + 2m_{\text{MX},\text{fin}}^{1/2})\exp(-2m_{\text{MX},\text{fin}}^{1/2}) \\ - (1 + 2m_{\text{MX},\text{in}}^{1/2})\exp(-2m_{\text{MX},\text{in}}^{1/2})] \\ - RT^2C_{\text{MX}}^L(m_{\text{MX},\text{fin}}^2 - m_{\text{MX},\text{in}}^2) \\ - RT^2D_{\text{MX}}^L(m_{\text{MX},\text{fin}}^3 - m_{\text{MX},\text{in}}^3) \quad (4)$$

In view of the fact that the first term on the right-hand side of this equation is calculable, we fitted to the experimental data by using eqn. (1) and (4) combined in the form

$$P - \dot{n}(2A_{\text{DH}}/3.6)\ln\left(\frac{1 + 1.2m_{\text{MX},\text{fin}}^{1/2}}{1 + 1.2m_{\text{MX},\text{in}}^{1/2}}\right) \\ = B_1[\dot{n}(m_{\text{MX},\text{fin}} - m_{\text{MX},\text{in}})] \\ + B_2[\dot{n}(F_{\text{MX},\text{fin}} - F_{\text{MX},\text{in}})] + B_3[\dot{n}(m_{\text{MX},\text{fin}}^2 - m_{\text{MX},\text{in}}^2)] \\ + B_4[\dot{n}(m_{\text{MX},\text{fin}}^3 - m_{\text{MX},\text{in}}^3)] \quad (5)$$

and where the terms in F_{MX} are of the form

$$F_{\text{MX}} = \left\{ \frac{[1 - (1 + 2m_{\text{MX}}^{1/2})\exp(-2m_{\text{MX}}^{1/2})]}{2} \right\} \quad (6)$$

The values obtained from the dilutions of ammonium methanoate solutions, from the least-squares routine used, were: $B_1 = 200(40) \text{ J kg mol}^{-2}$; $B_2 = -1319(97) \text{ J mol}^{-1}$; $B_3 = -84(19) \text{ J kg}^2 \text{ mol}^{-3}$; $B_4 = 12(4) \text{ J kg}^3 \text{ mol}^{-4}$. These coefficients are of the same magnitude as those found for other 1:1 electrolytes.³⁶

Enthalpy of dilution of mixtures of amides and ammonium methanoate

In all of the experiments which were performed, the solutions were equimolar in amide and ammonium methanoate within <0.1%. The data analyses were carried out using the total solute molality, m ($=m_{\text{MX}} + m_{\text{A}}$, where m_{A} is the amide molality). The experimental enthalpies of dilution are deposited as supplementary data.†

When binary solute solutions, such as those used here, are diluted, there are three contributions to the observed enthalpy change arising from the dilution process. These are: (i) from the dilution of the non-electrolyte, (ii) from the dilution of the electrolyte, and (iii) a contribution stemming from interaction between the ions of the electrolyte and the non-electrolyte. It is this last which we wish to evaluate. In terms of the gross molar enthalpy of dilution we have

$$\Delta_{\text{dil}} H_m = [H_{m,\text{MX}}^{\text{ex},\circ}(m_{\text{fin}}/2) - H_{m,\text{MX}}^{\text{ex},\circ}(m_{\text{in}}/2)] \\ + [H_{m,\text{A}}^{\text{ex},\circ}(m_{\text{fin}}/2) - H_{m,\text{A}}^{\text{ex},\circ}(m_{\text{in}}/2)] + \Delta H^* \quad (7)$$

where the first two terms on the right-hand side are calculable from information on the dilution of the electrolyte and non-electrolyte, respectively, and the term ΔH^* reflects the heterotactic interaction between the hydrated ions and the hydrated amide. The contributions to the enthalpies of dilution of the amides were obtained from the literature^{4,5,19,38–40} and the contributions from the electrolyte were obtained from the present work.

† Supplementary material (SUP 57204, 5pp.) deposited with the British Library. Details are available from the editorial office.

Table 1 Coefficients of eqn. (8) for the dilution of equimolar solutions of ammonium methanoate and amides at 25 °C

| amide | h_2 /J kg mol ⁻² | h_3 /J kg ² mol ⁻³ | σ /J mol ⁻¹ |
|-----------|----------------------------------|---|----------------------------------|
| formamide | -143(5) | 20(2) | 1.7 |
| acetamide | 99(11) | -15(8) | 2.4 |
| NMF | 163(13) | -16(10) | 1.7 |
| NMA | 350(21) | -24(14) | 4.2 |
| NEF | 322(17) | -61(11) | 3.3 |
| NMP | 562(48) | -107(44) | 4.0 |
| DMF | 238(20) | -22(14) | 3.8 |
| DMA | 358(22) | -26(16) | 3.1 |
| DEF | 541(68) | -163(60) | 6.8 |

Numbers in parentheses are 95% confidence limits. σ is the standard deviation of the fit.

The polynomials, in the molalities of the amides and salt, of the form

$$\begin{aligned}
 P - (\dot{n}/2) \{ & [H_{m, MX}^{\text{ex}, \circ}(m_{\text{fin}}/2) - H_{m, MX}^{\text{ex}, \circ}(m_{\text{in}}/2)] \\
 & + [H_{m, A}^{\text{ex}, \circ}(m_{\text{fin}}/2) - H_{m, A}^{\text{ex}, \circ}(m_{\text{in}}/2)] \} \\
 = h_2 \left[\dot{n} \left(\frac{m_{\text{fin}} - m_{\text{in}}}{2} \right) \right] & + h_3 \left[\dot{n} \left(\frac{m_{\text{fin}}^2 - m_{\text{in}}^2}{4} \right) \right] \\
 + h_4 \left[\dot{n} \left(\frac{m_{\text{fin}}^3 - m_{\text{in}}^3}{8} \right) \right] & \quad (8)
 \end{aligned}$$

were fitted to the experimental powers. The coefficients in eqn. (8) represent various heterotactic interactions between the ions of the 1:1 salt (S) and the amide (A) and are, in terms of our usual^{1,8} terminology:

$$h_2 = h_{AS} = h_{AM} + h_{AX} \quad (9)$$

$$\begin{aligned}
 h_3 = 3(h_{AAS} + h_{ASS})/2 \\
 = 3(h_{AAM} + h_{AAX} + h_{AMM} + h_{AMX} + 2h_{AMX})/2 \quad (10)
 \end{aligned}$$

$$\begin{aligned}
 h_4 = 2h_{AAAS} + 3h_{AASS} + 2h_{ASSS} \\
 = 2(h_{AAAM} + h_{AAAX}) + 3(h_{AAMM} + 2h_{AAMX} + h_{AAXX}) \\
 + 2(h_{AMMM} + 3h_{AMMX} + 3h_{AMXX} + h_{AXXX}) \quad (11)
 \end{aligned}$$

where M and X denote the ions of the salt.

Table 1 gives the coefficients obtained on using eqn. (8) in a least-squares fitting routine.

Discussion

As in our earlier work,^{8,41} we will only consider those terms which represent pairwise interactions between the ions of the salt and the amides. The reason for this is that these higher-order terms are linked in a complicated way to component lower-order terms, as well as containing contributions from the many-body interaction themselves. Generally, where co-operative effects are absent, and in the concentration range studied here, the contributions from higher-order terms are small. The coefficients obtained for the present systems are given in Table 2. It should be reiterated and stressed that it is not possible to obtain, without using an extra-thermodynamic assumption, values of the coefficients for the interactions of single ions with amides.³

If group additivity for the interactions between solvated solutes, as first formulated by Schrier and Schrier,⁴² and extended by Savage and Wood,³⁸ applies for the interactions between the ions and the various amides then, using the earlier information on both electrolyte-containing and non-electrolyte-containing systems, we expect that the experimen-

Table 2 Enthalpic group coefficients for the interaction of some amides with various salts and urea

| solute | $H_{\text{CH}_2\text{-solute}}$ /J kg mol ⁻² | $H_{\text{Pep-solute}}$ /J kg mol ⁻² | $H_{\text{iPep-solute}}$ /J kg mol ⁻² |
|----------------------|--|--|---|
| LiCl ^a | 136 | -361 | -678 |
| NaCl ^a | 287 | -596 | -1084 |
| KCl ^a | 256 | -579 | -1064 |
| KF ^a | 255 | -341 | -570 |
| KBr ^a | 260 | -604 | -1239 |
| KI ^a | 288 | -748 | -1372 |
| GuHCl ^{a,b} | 119 | -666 | -924 |
| urea ^c | 101(17) | -296(59) | -517(94) |

^a Ref. 44. The uncertainty of these coefficients can be estimated to be within ± 50 (95% confidence limit). ^b Guanidinium chloride. ^c Ref. 4.

tal pairwise interaction coefficients will be expressible by

$$h_{A\text{-NH}_4^+} + h_{A\text{-HCO}_2^-} = n_{\text{CH}_2}^A H_{\text{CH}_2\text{-salt}} + H_{\text{Pep-salt}} \quad (12)$$

and

$$h_{A\text{-NH}_4^+} + h_{A\text{-HCO}_2^-} = n_{\text{CH}_2}^A H_{\text{CH}_2\text{-salt}} + H_{\text{iPep-salt}} \quad (13)$$

where H_{ij} is the enthalpic coefficient for the interaction of group i with species or group j . Eqn. (12) is expected, given our earlier findings, to be applicable to primary and secondary amide-containing systems and eqn. (13) to tertiary amide systems. As usual when using the Savage and Wood additivity of groups (SWAG) approach, we represent hydrophobic groups using the equivalent methylene groups concept which was introduced by Friedman,⁴³ in which it is assumed that a methyl group is equivalent to 1.5 methylene groups and a methyne group is equivalent to 0.5 methylene groups. Fig. 2 shows the data plotted according to eqn. (12) and (13) and it is apparent from this that rather good linear fits are obtained and the resulting coefficients representing the interaction of the ions with the three types of defined groups are:

$$H_{\text{CH}_2\text{-salt}} = (H_{\text{CH}_2\text{-NH}_4^+} + H_{\text{CH}_2\text{-HCO}_2^-}) = 184(24) \text{ J kg mol}^{-2} \quad (14)$$

$$H_{\text{Pep-salt}} = (H_{\text{CH}_2\text{-MH}_4^+} + H_{\text{CH}_2\text{-HCO}_2^-}) = -205(64) \text{ J kg mol}^{-2} \quad (15)$$

$$H_{\text{iPep-salt}} = (H_{\text{CH}_2\text{-NH}_4^+} + H_{\text{CH}_2\text{-HCO}_2^-}) = -451(118) \text{ J kg mol}^{-2} \quad (16)$$

where the parenthetical terms are 95% confidence limits.

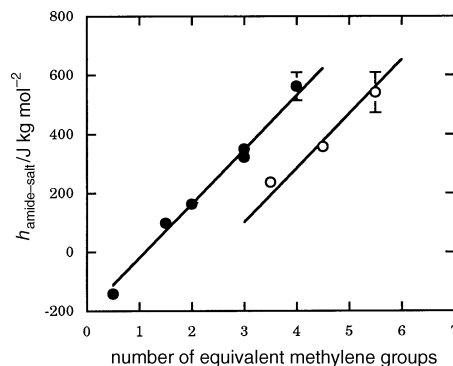


Fig. 2 Pairwise enthalpic coefficient for the heterotactic amide-ammonium methanoate interaction as a function of the number of equivalent methylene groups on the amide. (●) Primary and secondary amides, (○) tertiary amides. The error bars for most of the systems studied lie within the symbols.

It is evident from these that the methylene group-salt interaction is thermochemically repulsive, *i.e.* endothermic, whereas both peptide group-salt interactions are thermochemically attractive, *i.e.* exothermic. We will discuss these in more detail a little later. However, before doing this, it is worth pointing out that it is possible to extend the SWAG idea to correlate the results found here with those found from the earlier amino acid study.⁵

If we make what are fairly drastic assumptions, *viz.* that the hydrogens on the nitrogen of the ammonium ion and on the carbon of the methanoate ion are equivalent to hydrogens on carbon atoms, then the above coefficients can be written as

$$H_{\text{CH}_2\text{-salt}} = (H_{\text{CH}_2\text{-NH}_3^+} + H_{\text{CH}_2\text{-CO}_2^-}) + H_{\text{CH}_2\text{-CH}_2} \\ = H_{\text{CH}_2\text{-}\pm} + H_{\text{CH}_2\text{-CH}_2} \quad (17)$$

$$H_{\text{Pep-salt}} = (H_{\text{Pep-NH}_3^+} + H_{\text{Pep-CO}_2^-}) + H_{\text{Pep-CH}_2} \\ = H_{\text{Pep-}\pm} + H_{\text{Pep-CH}_2} \quad (18)$$

$$H_{\text{iPep-salt}} = (H_{\text{iPep-NH}_3^+} + H_{\text{iPep-CO}_2^-}) + H_{\text{iPep-CH}_2} \\ = H_{\text{iPep-}\pm} + H_{\text{iPep-CH}_2} \quad (19)$$

where, as before,⁵ the zwitterionic head-group on α -amino acids (NH_3^+ , CO_2^-) is represented by ' \pm '. Consequently eqn. (12) and (13) become

$$h_{\text{A-NH}_4^+} + h_{\text{A-HCO}_2^-} = n_{\text{CH}_2}^{\text{A}}(H_{\text{CH}_2\text{-}\pm} + H_{\text{CH}_2\text{-CH}_2}) \\ + H_{\text{Pep-}\pm} + H_{\text{Pep-CH}_2} \quad (20)$$

and

$$h_{\text{A-NH}_4^+} + h_{\text{A-HCO}_2^-} = n_{\text{CH}_2}^{\text{A}}(H_{\text{CH}_2\text{-}\pm} + H_{\text{CH}_2\text{-CH}_2}) \\ + H_{\text{iPep-}\pm} + H_{\text{iPep-CH}_2} \quad (21)$$

Assuming that the coefficients obtained earlier⁵ are transferable, then the coefficients for ammonium methanoate interacting with species containing the three types of group considered are calculable. Fig. 3 compares the results obtained from the present study with those calculated using the earlier coefficients and, given the uncertainties in the several coefficients used and what seem to be rather gross assumptions, the agreement is impressive. This indicates that when charged carboxylate and amino groups interact with hydrophobic groups and with peptide groups, the energetics are not significantly perturbed by the proximity of the ionic groups to each other. This seems rather surprising but is, at least, approximately

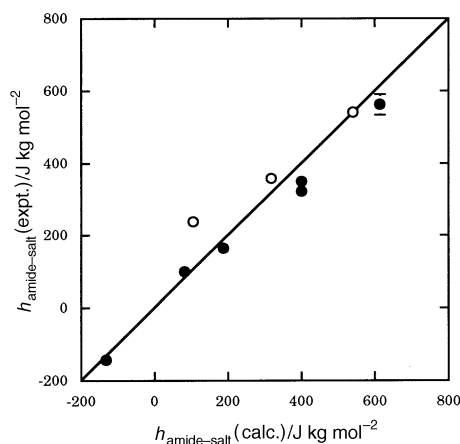


Fig. 3 Correlation between the heterotactic pairwise enthalpic coefficient for ammonium methanoate interacting with amides obtained in this study and these calculated using earlier group coefficients [see eqn. (20) and (21)]. (●) Primary and secondary amides, (○) tertiary amides. The error bars for most of the systems lie within the symbols.

true and, in the least, is a fortuitous simplifying feature of the energetics of these particular interacting species.

Comparisons between salts

As was mentioned above, ammonium methanoate interacts with hydrophobic and peptide groups in both qualitatively and quantitatively different ways. Broadly similar trends in the results for the group interaction coefficients were found for the same groups interacting with some salts (see Table 2) and with urea. The data base of group coefficients is rather limited but it can be extended by using the results obtained from other studies^{1,3,25,44} from which the heterotactic pairwise enthalpic coefficients were obtained for several salts interacting with the amides formamide (F), NMA and DMF. Making the assumption that group additivity applies, then for each salt we can write expressions analogous to those of eqn. (12) and (13). Consequently we obtain:

$$H_{\text{CH}_2\text{-salt}} = 0.4(h_{\text{NMA-salt}} - h_{\text{F-salt}}) \quad (22)$$

$$H_{\text{Pep-salt}} = 1.2h_{\text{F-salt}} - 0.2h_{\text{NMA-salt}} \quad (23)$$

$$H_{\text{iPep-salt}} = h_{\text{DMF-salt}} - 1.4(h_{\text{NMA-salt}} - h_{\text{F-salt}}) \quad (24)$$

The group interaction coefficients obtained using these expressions are included in Table 2 and given the limited information available there is probably greater uncertainty in these than in the corresponding values for other systems.

It is apparent from the information given in this table that, all the salts studied interact with the methylene group in a qualitatively similar way: for each of the systems which have been investigated there is a thermochemically repulsive net interaction with hydrophobic groups. This is not unexpected given the disparate nature of the salts and apolar groups.

The primary peptide group and the secondary peptide group interact with salts in a thermochemically attractive way and again this is what might be expected on intuitive grounds, given the hydrophilic nature of both the ions and the groups involved. However, the most striking feature is that for each salt the interaction with the secondary peptide group is more attractive than the corresponding interaction with the primary peptide group. In other words, removal of hydrogen-bond-donation capacity reduces the interaction of peptide groups with ions. Superficially this is surprising, but is explicable if it is recognised and remembered that the experimental coefficients represent the compromise between the tendencies the solutes (or groups) involved have to interact with each other and their tendencies to interact with the solvent: this aspect has been commented on previously.⁴⁵⁻⁴⁷ Given the necessary interplay between solvation and solute-solute interaction we may say that, using the experimental information obtained: (a) The sodium ion interacts less well with primary peptide groups than with secondary peptide groups because the primary groups are more strongly hydrated than the secondary peptide groups. (b) The lithium ion interacts less well with the primary peptide group than does the potassium ion, because the hydration of the lithium ion is considerably more intense than the hydration of the potassium ion.

Similarly, if we consider the halide ion series then, each of the ions interacts less well with the primary peptide group than with the secondary peptide group. This also is a reflection of the weaker hydration of the latter group compared to the former. If we address the interaction of the halide ions with both types of peptide group, what we see is that as one descends the Periodic Table group, the net interaction becomes thermochemically more favourable. This can simply be rationalised in terms of the weaker hydration of the larger ions.

It is worth stressing that all these situations are the exact opposite of what would be expected if solvation was not con-

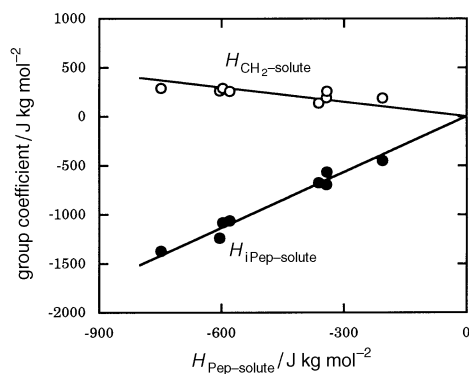


Fig. 4 Correlations between enthalpic group coefficients for the interactions of amides with salts and with urea. (○) Methylene group-solute coefficient and (●) secondary peptide (iPep)-solute coefficients vs. the corresponding primary peptide (Pep)-solute group coefficients.

sidered or if solvation was weak. Chemists seldom consider the moderating effect of solvation and most would accept without equivocation that the sodium ion would interact with primary peptide groups more strongly than with secondary peptide groups and that the lithium ion would interact more strongly with say primary peptide groups than would the sodium ion.

Another feature which is apparent, and again is surprising, from inspection of the currently available information, is that all the group coefficients which have been obtained on salts seem to correlate well with each other. This is illustrated in Fig. 4 where, for each salt, the primary peptide-salt coefficient is compared with the corresponding secondary peptide-salt and methylene group-salt coefficients. It is clear from this figure that, as the primary peptide group-salt interaction becomes more attractive, the corresponding secondary peptide group-salt interaction becomes even more attractive. Conversely, as the attractions between primary peptide groups and salts becomes more attractive, there is an increasing net repulsion between the salts and the hydrophobic group. We might have expected some qualitative correlations of this nature but the quantitative links are striking.

In conclusion, from the investigations that have been performed on the interactions occurring between polar solutes or salts and molecules containing some at least of the chemical features of peptides and proteins, we may say that there are some simplifying and (sometimes) unexpected features evident. First, a simple group additivity approach for the interaction between hydrated solutes works remarkably well not only for apolar (hydrophobic) and polar (peptide) groups but also for the zwitterionic head-group of amino acids. It is striking how closely the interactions of the zwitterionic group can be represented by the interactions of the salt, ammonium methanoate. Secondly, there are good correlations between the various group interaction coefficients for a wide range of solutes. This implies that if say, the primary peptide group-salt interaction coefficient is known for a particular salt, then it should be possible to make a good estimate of how the salt interacts with a molecule containing any number of primary and secondary peptide groups, and aliphatic groups. Finally, it is apparent from the information currently available as the result of several investigations that there is strong evidence for the presence of an interplay between solute-solvent and solute-solute interactions. This, in itself, is not unexpected, but what is remarkable is that these two distinct phenomena appear to be strongly and quantitatively correlated. If this is substantiated from further investigations it could lead to a new general chemical principle.

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