The Honig–Flory–Huggins Combinatorial Entropy Correction—Is it Valid for Aqueous Solutions?

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A number of assumptions used in the derivation of the combinatorial entropy term of Honig–Flory–Huggins are shown not to be valid for the case of dilute solutions in water: these include (*a*) only combinatorial entropy need be considered, (*b*) the solution configuration is random, and (*c*) random distribution of molecular segments in the solution lattice. Accordingly, the combinatorial term as calculated by Honig–Flory–Huggins is not appropriate for aqueous solutions, and is particularly inappropriate for dilute solutions in water. It is suggested that the use of the Honig–Flory–Huggins combinatorial entropy term to 'correct' observed thermodynamic parameters for solvation of solutes in water be abandoned.

The dissection of the total Gibbs energy of hydration of molecules, or of the total Gibbs energy of transfer from water to non-polar solvents, into component parts is of considerable importance in many areas of chemistry. If the Gibbs energy of interaction can be obtained from the total Gibbs energy of hydration or of transfer, the solute–water interaction term will lead to a quantitative estimate of the hydrophobic effect. In this way, the hydrophobic effect of alkanes has been deduced, which in turn leads to the hydrophobic effect of alkyl side-chains in amino acid and other residues. Quite recently, it has been argued by Honig *et al.*[1] that the dissolution of a gaseous solute molecule in a solvent leads to an increase in the availability of volume for a solvent molecule, and hence to an increase in the entropy of the system. There will thus be a decrease in the Gibbs energy of the system given by $\Delta G(\text{Honig}) = -RT\ln\Delta S(\text{Honig})$, where we refer to the Gibbs energy and entropy due to the solvent expansion as ΔG(Honig) and ΔS(Honig) respectively. Since this entropy term of Honig can be equated to the Flory–Huggins combinatorial entropy, we shall refer to it as the latter. It follows from the argument of Honig *et al.*[1] that if the Gibbs energy term, corresponding to the combinatorial entropy, is not taken into account, incorrect values of the solute–water interaction term will be calculated, and will lead to incorrect values of the hydrophobic effect. Indeed, Honig *et al.*[1] have even argued that experimental Gibbs energies of hydration of solutes should be 'corrected' for the combinatorial entropy effect.

There are other severe consequences if Honig's argument is valid. Thus if a peptide, or other, side-chain in aqueous solution is transformed into another side-chain of different volume, by the computational alchemical method of McCammon,[2] there will be a combinatorial Gibbs energy term, ΔG(Honig), to take into account. This term is by no means negligible, being some 2.7 kcal mol^{-1} for the transformation of a propyl group into an octyl group in water at 298 K.† Furthermore, this combinatorial term is not limited to the case of non-polar side-chains; any alchemical transformation that involves a change in solute volume will necessitate the incorporation of a combinatorial term into the calculation. Indeed, calculation of ΔG° for any equilibrium in which there is a change in volume will require incorporation of such a term. Consider a simple equilibrium such as eqn. (1). The volume change, ΔV°, will be given by eqn.

$$\text{A(aq)} + \text{B(aq)} = \text{C(aq)} \qquad (1)$$

(2) where V(X) is the partial molar volume of species X. Now if B

$$\Delta V^\circ = V(\text{C}) - V(\text{A}) - V(\text{B}) \qquad (2)$$

is a molecule such as haemoglobin, with rather hydrophobic pockets or cavities[3] it might be possible to sequester non-polar solutes with but little change in volume, so that $V(\text{B}) = V(\text{C})$, and thus $\Delta V^\circ = -V(\text{A})$. Even in the case of sequestering a solute of only moderate size, such as toluene with a partial molar volume in water[4] of 98 cm^3 mol^{-1} at 298 K the combinatorial term will contribute no less than 2.6 kcal mol^{-1} in Gibbs energy. We give this example, not in any way to suggest that haemoglobin actually does sequester toluene with $\Delta V^\circ = -98$ cm^3 mol^{-1} in water, but just to illustrate the possible consequences of Honig's argument. The combinatorial term of Honig has already been used in the calculation of the solubility of hydrocarbons in water[5] and so consideration of Honig's argument is of some urgency.

Honig *et al.*[1] show that the contribution to the entropy of the system from changes in volume is given in eqn. (3) where n_2 and

$$-\Delta S/R = n_2\ln(n_2V_2/V) + n_1\ln(n_1V_1/V) \qquad (3)$$

n_1 are the amounts in moles of solute (2) and solvent (1), of molar volume V_2 and V_1, in a mixture of volume V. This is exactly the same equation derived by Flory[6] and by Huggins,[7] and known in polymer chemistry[8] as the Flory–Huggins equation for the combinatorial entropy. In order to obtain the corresponding entropy change for the case of an infinitely dilute solution of a solute in a solvent, eqn. (3) must be differentiated with respect to n_2 at constant n_1, P and T. Honig *et al.*[1] then obtain the expression given in eqn. (4) where $r = V_2/V_1$. The

$$-\Delta S = R(1 - r) = -\Delta S(\text{Honig}) \qquad (4)$$

corresponding expression for ΔG is given in eqn. (5).

$$\Delta G = RT(1 - r) = \Delta G(\text{Honig}) \qquad (5)$$

With slightly different assumptions in the differentiation of eqn. (3), Barton[8] obtains eqn. (6).

$$\Delta G = RT(1 - r) + RT\ln(r) = \Delta G(\text{Barton}) \qquad (6)$$

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† 1 cal = 4.184 J.

Table 1 The Honig and Barton combinatorial contributions to the Gibbs energy of hydration of gaseous solutes in water, in kcal mol^{-1} at 298 K

Solute	V_2	r	ΔG(Honig)	ΔG(Barton)
Propane	81	4.5	2.1	1.2
Octane	164	9.1	4.8	3.5
Decane	196	10.9	5.9	4.5
Hexadecane	294	16.3	9.1	7.4
—	500	27.8	15.9	13.9

Table 2 Values of the enthalpy of solution of liquids in water, in kcal mol^{-1} at 298 K

Solute	ΔH°	Solute	ΔH°
Ethane	−2.4	Formamide	0.5
Propane	−1.8	*N*-Methylformamide	−1.8
Hexane	0.0	*N*,*N*-Dimethylformamide	−3.9
Heptane	0.6	*N*-Methylacetamide	0.9
Propanone	−2.4	*N*,*N*-Dimethylacetamide	−5.1
Propan-1-ol	−2.4	*N*-Ethylformamide	−2.3
Propylamine	−5.9	*N*-Ethylacetamide	−3.7

These expressions are general for the combinatorial entropic, and consequently Gibbs energy, effects due to differences in size of solute and solvent molecules. However, because of the small size of a water solvent molecule, the term $r = V_2/V_1$ becomes much larger when water is the solvent than with any other solvent. We give in Table 1, some calculated values of the combinatorial term for the solubility of various gaseous solutes in water, as the Gibbs energy contribution to the total Gibbs energy of hydration. In these calculations, V_2 is taken as the solute molar volume, although as pointed out,[1] the solute partial molar volume would be more correct. The volume of water is taken as 18 cm^3 mol^{-1}. We also give in Table 1, the contribution for a solute of molar volume 500 cm^3 mol^{-1}, to illustrate the effect for a molecule of the size of a small peptide.

As shown in Table 1, and also by the illustrations we gave in the introduction, the Honig combinatorial entropy term leads to very large Gibbs energy corrections when water is the solvent. The corrections as calculated by the method of Barton are smaller, but are still so large that some assessment of the combinatorial entropic effect is urgently required.

The Flory–Huggins derivation of the key eqn. (3) is based[9] on a lattice theory of mixing. It is assumed that (*i*) the pure solvent, the pure (polymeric) solute, and all intermediate compositions can be accommodated in the same lattice, (*ii*) only the combinatorial entropy need be considered, (*iii*) the solution configuration is random, and (*iv*) when a molecule ($i + 1$) is placed in the lattice, the segments of the i molecules previously added are distributed at random throughout the lattice.

These various assumptions, which are implicit in Honig's derivation and are spelt out in the Flory–Huggins derivation,[9] can now be considered. Assumption (*ii*) cannot be correct for any solvent, and is particularly wrong for water as a solvent. The entropy of mixing will include not only the combinatorial entropy, but also that due to the dissimilarity in free volume of the two components, and that due to structural effects. Thus, although the original Flory–Huggins theory correctly predicts phase separation in polymer solutions on cooling, it does not predict such separation on heating; this is usually attributed[10] to neglect of the free volume dissimilarity. Assumption (*iii*) is certainly not valid for aqueous mixtures, because the solution configuration will not be random. Numerous experimental[11,12] and theoretical[13,14] studies show specific hydration of solutes in water, which results in non-random configurations. Assumptions (*iv*) is particularly wrong for the case of the dilute solutions considered by Honig *et al.*[1] Segments of the i molecules previously added are not distributed at random through the lattice; in reality, they occur in sequences of consecutively occupied cells. Indeed, Flory[9] himself stated that the original Flory–Huggins theory was inappropriate, in general, for dilute polymer solutions.

We can conclude that the Honig–Flory–Huggins eqn. (3)–(6) are generally not valid in the dilute solution case for any solvent, they are not valid for aqueous mixtures, and they will certainly not be valid for dilute solutions in water solvent.

The Flory–Huggins combinatorial entropy term can be regarded[8] as a correction for the size effect to a reference mixture in which the enthalpy of mixing is zero, and the only entropy change on mixing is given by eqn. (3). Now mixtures with water, as we have pointed out, cannot simply be regarded as statistical, and generally do not give rise to a zero enthalpy term. In Table 2 are listed some values[15,16] for the enthalpy of solution of liquids in water at 298 K. In most cases, the enthalpy is not zero at all, especially for the important amide solutes.

Our conclusion is that the Honig–Flory–Huggins combinatorial entropy correction is not appropriate for systems, such as aqueous mixtures, in which structural features of the solvent can lead to non-random mixing. Whether or not some modified or damped-down version of the combinatorial entropy correction is appropriate, is another matter. As regards polymer mixtures, both Flory[17] and Patterson[18] have developed further theories but both of these theories are only semi-quantitative in the case of a non-polar polymer in a polar solvent.

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