Solvent Reorganization and Thermodynamic Enthalpy–Entropy Compensation

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Abstract: This paper develops a formalism for treating the solvent reorganization that accompanies all chemical reactions and physical processes in liquid solutions. In particular, cage environments are shown explicitly, and overall equations are separated into a nominal equation (which is essentially the conventional chemical equation) and an environmental (env) equation. The separation is useful because it follows from the Second Law that in dilute solution ΔG_{env} (same as $\Delta G°_{env}$) for solvent reorganization is generally zero, so that the nominal equation accounts for the observed standard free energy change $\Delta G°$ associated with the process. On the other hand, ΔH_{env} and ΔS_{env} can be substantial, especially when the solvation involves hydrogen bonding. And since $\Delta G_{env} = 0$, there is enthalpy–entropy compensation to the extent that $\Delta H_{env} = T\Delta S_{env}$. Conventional thermodynamic accounting requires that ΔH_{env} and ΔS_{env} are added to, and become part of, $\Delta H°$ and $\Delta S°$ for the overall process. Thus, when $\Delta H_{env} \gg \Delta G°$, the plot of $\Delta H°$ vs $\Delta S°$ is nearly a straight line, with a slope close to the experimental temperature T. Two examples approaching this situation are presented and discussed.

Introduction

The term "solvent reorganization" has long been used to denote the transfer of solvent molecules between the bulk of the solvent and the solvation shells of solutes. It is generally agreed that solvent reorganization and the *change* in solvent reorganization which may accompany reactions and spectral transitions have thermodynamic consequences, especially in hydrogen-bonding solvents.[1-3] One such consequence may be a propensity toward enthalpy–entropy compensation,[4] dramatic examples of which have recently been published.[5,6]

In this paper we shall propose a formalism for including solvent reorganization in chemical equations and develop the thermodynamic consequences. A key result is that under common conditions, solvent reorganization is indeed attended by enthalpy–entropy compensation.

Environmental Equations and Solvent Reorganization

Thermodynamics specifies compensation in terms of components, while chemical equations describe the behavior of molecular species, which may be defined as the macroscopic analogs of molecules. The thermodynamic equation for the solvation of gaseous X in a liquid solvent A is given in eq 1.

$$X(g) = X(\text{solute in solvent A}) \tag{1}$$
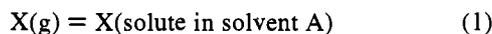
This equation tells us that the solute dissolves, but it gives no information about the concomitant changes in liquid environments. For simplicity let us suppose that the solution is dilute
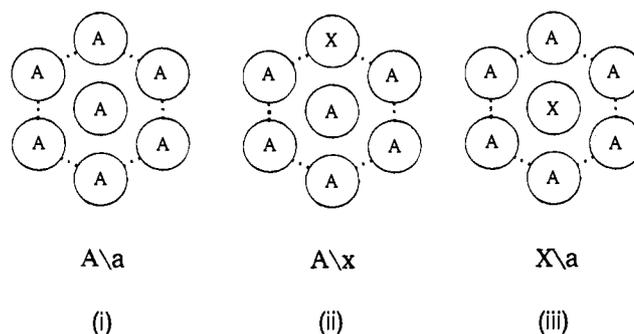
® Abstract published in *Advance ACS Abstracts*, May 1, 1995.
(1) Ritchie, C. D.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1972**, *94*, 4966–71; **1973**, *95*, 1882–89.
(2) Mirejovsky, D.; Arnett, E. M. *J. Am. Chem. Soc.* **1983**, *105*, 1112.
(3) Chervenak, M. C.; Toone, E. J. *J. Am. Chem. Soc.* **1994**, *116*, 10533.
(4) Lumry, R.; Rajender, S. *Biopolymers* **1970**, *9*, 1125–227.
(5) (a) Gilli, G.; Borea, P. A. *Application of Charge Density Research to Drug Design*; Jeffrey, J. A., Piniella, J. F., Eds.; Plenum Press: New York, 1991. (b) Gilli, P.; Ferretti, V.; Gilli, G.; Borea, P. A. *J. Phys. Chem.* **1994**, *98*, 1515–8.
(6) Danil de Namor, A. F.; Ritt, M.-C.; Schwing-Weill, M.-J.; Arnaud-Neu, F.; Lewis, D. F. V. *J. Chem. Soc., Faraday Trans.* **1991**, *87*, 3231–3239.

Figure 1. Solvent (A) and solute (X) molecules in their solvent cages. In (i) and (iii) the cages consist only of solvent molecules; in (ii) the cage of A has a solute molecule.

and that in solution there are only the three caged species, (i)–(iii) of Figure 1, for which we shall adopt the following notation: A\a denotes an A molecule which only has A neighbors in its solvent shell, while in A\x one of the neighbors is X and the rest are A's. Similarly X\a denotes an X molecule which has only A neighbors. The label (\a, \x) after the species symbol (A, X) identifies the environment. There is no molecular-complex formation. If A and X were forming a complex A·X which then has only A neighbors in its solvent shell, we would write (A·X)\a. The model further assumes that the liquid environment of a molecule is controlled by its immediate neighbors, and that A\a and A\x are distinguishable.

The distinguishability imposed on species by virtue of their liquid environments has been examined by the authors.[7] In general there are two kinds of distinguishability: real (or observable), and ideal (or predicted by a primary theory such as wave mechanics). Ideal distinguishability exists for two liquid environments (such as A\a and A\x) when the difference between the potential energies of solvation of A in its electronic ground state, by \a vs \x, is at least of order 10 J/mol, a condition often met.[7] Owing to potential-energy noise caused by the Brownian motions of the molecules, real distinguishability

Chart 1. Composition Tree

| I.	Components	Solvent (1), n_1		Dilute solute (2), n_2
II.	Molecular Species	A, $n_A = n_1$		X, $n_X = n_2$
III.	Environmental Subspecies	A\a, $n_{A\backslash a}$	A\x, $n_{A\backslash x}$	X\a, $n_{X\backslash a}$

requires a much greater average difference in the potential energies of solvation, of order 1−3 kJ/mol, and is rare except in hydrogen-bonding solvents.[7c]

Within this more detailed framework we can now rewrite eq 1 in terms of molecular species as

$$X(g) + s_X \cdot A\backslash a \rightleftharpoons X\backslash a + s_X \cdot A\backslash x \qquad (2)$$
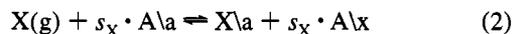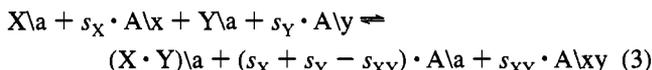
Each molecular species is here labeled by its liquid environment. The coefficient s_X denotes the mean number of A molecules in the solvent cage of an X molecule. Equation 2 shows why distinguishability is so important. If A\a and A\x were *not* distinguishable, these symbols would *not* correspond to different molecular species: the terms $s_X \cdot A\backslash x$ and $s_X \cdot A\backslash a$ on the two sides of eq 2 would cancel out, and (2) would reduce to (1).

Equations with environmentally labeled molecular species have another feature: They can be separated into two parts which will be called the **nominal** and **environmental** equation. For eq 2 these parts are shown in (2n) and (2e). The separation

$$X(g) \rightleftharpoons X\backslash a \qquad (2n)$$

$$s_X \cdot A\backslash a \rightleftharpoons s_X \cdot A\backslash x \qquad (2e)$$
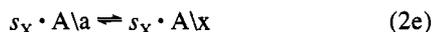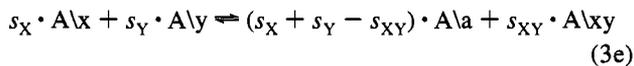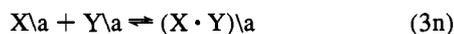
is useful because we shall show that the environmental part is subject to enthalpy−entropy compensation. If we are interested only in the change of free energy for the process we shall see that the nominal equation is all we need to consider because, at environmental equilibrium conditions, the change in free energy associated with (2e), ΔG_{env}, equals zero.

Equation 2 applies only to a single molecular species (X) in a solvent (A), but the ideas can be readily extended to an equilibrium involving several species. Consider, for example, the formation of a solvated complex (X·Y) from solvated X and solvated Y, eq 3. Here s_X, s_Y, and s_{XY} denote mean neighbor numbers for X, Y, and X·Y, respectively.

$$X\backslash a + s_X \cdot A\backslash x + Y\backslash a + s_Y \cdot A\backslash y \rightleftharpoons$$
$$(X \cdot Y)\backslash a + (s_X + s_Y - s_{XY}) \cdot A\backslash a + s_{XY} \cdot A\backslash xy \quad (3)$$

The nominal (or free energy) part of 3 is (3n), and the environmental part is (3e).

$$X\backslash a + Y\backslash a \rightleftharpoons (X \cdot Y)\backslash a \qquad (3n)$$

$$s_X \cdot A\backslash x + s_Y \cdot A\backslash y \rightleftharpoons (s_X + s_Y - s_{XY}) \cdot A\backslash a + s_{XY} \cdot A\backslash xy \qquad (3e)$$

The nominal part states that solvated X plus solvated Y forms solvated X·Y; the respective solvation numbers, i.e. mean neighbor numbers, do not enter into the equation. This information is given in the environmental part, which states that s_X moles of A in \x environments plus s_Y moles of A in \y

environments are transferred to $(s_X + s_Y - s_{XY})$ moles of A in \a environments plus s_{XY} moles of A adjacent to X·Y complexes.

Solvation and Thermodynamics

In this section we shall derive enthalpy−entropy compensation for environmental equations. Our examples for the molecular species involved in the nominal equations are simple and the mathematics correspondingly straightforward. Complicated nominal equations are often best handled by the powerful matrix methods recently described by Alberty in dealing with complex biochemical systems.[8]

For definiteness, we shall consider (as before) a dilute solute X in a solvent A, with the formation of the species A\a, A\x, and X\a. The **Composition Tree** (Chart 1) shows that composition can here be stated on three levels:

The first level is that of classical thermodynamics. The components are formal components—pure substances with known chemical formulas (those of A and X), and corresponding formula weights which may be adopted as units of macroscopic mass for the respective component. The formula-weight numbers, n_1 and n_2, on this level express the masses of the components in the system.

Atomic molecular theory enters at the second level, which is the usual level of chemical thermodynamics. The chemical formula is identified with the molecular formula, so that the solvent is said to consist of A molecules and the solute of X molecules. Composition is now expressed in terms of molecular species whose amounts are the mole numbers n_A and n_X, eq 4a.

$$n_A = n_1 \text{ and } n_X = n_2 \qquad (4a)$$

Although in this example the components and the molecular species are the same, this is not so in general. For example, in an aqueous salt solution, sodium chloride is a component while sodium and chloride ions are molecular species.

At the third level, an explicit composition model is introduced in which the environmental subspecies now appear. Composition is specified either in terms of the mole numbers $n_{A\backslash a}$, $n_{A\backslash x}$, and $n_{X\backslash a}$, or of n_A, n_X, and the previously defined mean neighbor number s_X, eq 4b.

$$n_{X\backslash a} = n_X; \quad n_{A\backslash x} = s_X n_X; \quad \text{and } n_{A\backslash a} = n_A - s_X n_X \quad (4b)$$

Similarly, the Gibbs free energy of the solution at constant T and P can be written at three levels, eqs 5a,b,c. G_1, G_2, etc. denote the partial free energies, or chemical potentials, of the respective components or molecular species. (We shall use the term "partial free energy" throughout.)

$$G = n_1 G_1 + n_2 G_2 \qquad (I)$$

$$G_1 = (\partial G / \partial n_1)_{n_2, eq}; \quad G_2 = (\partial G / \partial n_2)_{n_1, eq} \qquad (5a)$$

(7) (a) Grunwald, E.; Steel, C. *Pure Appl. Chem.* **1993**, *65*, 2543−9. (b) Grunwald, E.; Steel, C. *J. Phys. Chem.* **1993**, *97*, 13326−9. (c) Grunwald, E.; Steel, C. *J. Phys. Org. Chem.* **1994**, *7*, 734−42.

(8) Alberty, R. A. *Biophys. Chem.* **1992**, *42*, 117−31. Alberty, R. A. *J. Phys. Chem.* **1992**, *96*, 9614−21.

$$G = n_A G_A + n_X G_X \tag{II}$$

$$G_A = (\partial G/\partial n_A)_{n_X, eq}; \qquad G_X = (\partial G/\partial n_X)_{n_A, eq} \tag{5b}$$

$$G = n_{A\backslash a} G_{A\backslash a} + n_{A\backslash x} G_{A\backslash x} + n_{X\backslash a} G_{X\backslash a} \tag{III}$$

$$G_{A\backslash a} = (\partial G/\partial n_{A\backslash a})_{n_{A\backslash x}, n_{X\backslash a}}; \qquad G_{A\backslash x} = (\partial G/\partial n_{A\backslash x})_{n_{A\backslash a}, n_{X\backslash a}};$$
$$G_{X\backslash a} = (\partial G/\partial n_{X\backslash a})_{n_{A\backslash a}, n_{A\backslash x}} \tag{5c}$$

Superficially, these equations seem inconsistent. In (5a,b) G is a function of two composition variables ($n_1 = n_A$ and $n_2 = n_X$), while in (5c) it depends on three. However, in (5a,b) there is an implied constraint: the species and their environments must be at equilibrium. This we have emphasised by writing the subscript "eq". Equation 5c is more general and the variable mole numbers ($n_{A\backslash a}$, $n_{A\backslash x}$, $n_{X\backslash a}$) may depart from environmental equilibrium.

Equations 5a,b are mathematically analogous. The independent variables are equal ($n_1 = n_A$ and $n_2 = n_X$) and the constraint "eq" is the same. It follows that $G_1 = G_A$ and $G_2 = G_X$. We shall carry on using the notation for level II.

It will be convenient to transform the mole numbers in (5c) according to (4b). The result is (6). The definitions for the partial free energies (e.g. $G_{X\backslash a}$) remain the same.

$$G = n_A G_{A\backslash a} + s_X n_X (G_{A\backslash x} - G_{A\backslash a}) + n_X G_{X\backslash a} \tag{6}$$

To impose equilibrium on (6), we let n_A, n_X, T, P be constant and allow s_X to relax to equilibrium, so that G is at a minimum. The result for $\partial G/\partial s_X$, after simplification via the Gibbs–Duhem equation, is eq 7.

$$(\partial G/\partial s_X)_{n_A, n_X} = n_X(G_{A\backslash x} - G_{A\backslash a}) = 0 \tag{7}$$

Accordingly, at environmental equilibrium, $G_{A\backslash x} - G_{A\backslash a} = 0$. Since this difference represents the environmental process, A\a → A\x (e.g. solvent reorganization in (2e)), we have here a hint of enthalpy–entropy compensation:

$$\Delta G_{env} \equiv (G_{A\backslash x} - G_{A\backslash a}) = 0 \text{ at equilibrium;}$$
$$\text{hence } \Delta H_{env} = T \cdot \Delta S_{env} \tag{8}$$

We say "hint" because several logical pieces are still missing. First, it clearly would be fortuitous if the three quantities, ΔG_{env}, ΔH_{env}, and ΔS_{env}, vanished simultaneously at equilibrium. But in the Appendix we offer a formal proof that ΔS_{env}, and hence ΔH_{env}, normally are non-zero. Second, ΔH_{env} and ΔS_{env} must become part of the *standard* partial enthalpy $H°_X$ and entropy $S°_X$ of the solute species. Third, we shall suggest, for later proof, that enthalpy–entropy compensation in a chemical process such as (3) is exact only in the environmental part (3e).

Environmental Enthalpy–Entropy Compensation

When we add dn_X moles of X to the solution, with equilibrium maintained at constant T and P, we not only produce dn_X moles of X\a but also change $s_X dn_X$ moles of A from A\a to A\x. If the solution is dilute so that s_X remains constant[9] (in spite of the increase in the moles of X), the partial free energy

$\partial G/\partial n_X$ (i.e. G_X) is therefore given by (9a).

$$G_X = G_{X\backslash a} + s_X(G_{A\backslash x} - G_{A\backslash a})$$
$$= G_{X\backslash a} \quad \text{(at equilibrium)} \tag{9a}$$

The partial enthalpy $\partial H/\partial n_X$ and entropy $\partial S/\partial n_X$ are given similarly by (9b,c).

$$H_X = H_{X\backslash a} + s_X(H_{A\backslash x} - H_{A\backslash a}) \tag{9b}$$

$$S_X = S_{X\backslash a} + s_X(S_{A\backslash x} - S_{A\backslash a}) \tag{9c}$$

Now ($H_{A\backslash x} - H_{A\backslash a}$) and ($S_{A\backslash x} - S_{A\backslash a}$) are properties of the solvent and so are virtually independent of m_X, the molality of X, in dilute solution. They therefore become part of the *standard* partial enthalpy and entropy of X. Thus we obtain, at equilibrium at constant T and P,

$$G°_X = G°_{X\backslash a} \tag{10a}$$

$$H°_X = H°_{X\backslash a} + s_X(H_{A\backslash x} - H_{A\backslash a}) \tag{10b}$$

$$S°_X = S°_{X\backslash a} + s_X(S_{A\backslash x} - S_{A\backslash a}) \tag{10c}$$

Equations 10 are our key equations. They tell us the following: (i) The addition of solute X to solvent A is attended by solvent reorganization according to eq 2e. (ii) This solvent reorganization has *no effect* on $G°_X$. (iii) The solvent reorganization contributes explicit terms $s_X(H_{A\backslash x} - H_{A\backslash a})$ and $s_X(S_{A\backslash x} - S_{A\backslash a})$ to the solute's standard partial enthalpy, $H°_X$, and entropy, $S°_X$. (iv) The solvent-reorganization terms are locked into exact enthalpy–entropy compensation, ($H_{A\backslash x} - H_{A\backslash a}$) = $T(S_{A\backslash x} - S_{A\backslash a})$, because ($G_{A\backslash x} - G_{A\backslash a}$) = 0, eq 8. (v) Since the result has been arrived at by general thermodynamic arguments, it is valid regardless of the microscopic nature of the solvent environments whose change generates the difference between $H_{A\backslash x}$ and $H_{A\backslash a}$ and between $S_{A\backslash x}$ and $S_{A\backslash a}$. Of course, the magnitude of the effect will depend on the nature of that change. Changes involving hydrogen bonds typically produce ten times greater effects than changes in dispersion interactions, as shown by the following numbers: In Pimentel and McClellan's review on hydrogen bonding,[10] the range in $\Delta H°$ for hydrogen-bond formation between phenols and alcohols and about 30 acceptors was found to be 30 kJ/mol while the standard deviation was 3 kJ/mol. By contrast, in a calculation by the present authors based on the regular-solution model,[7c] the range in ($H_{A\backslash x} - H_{A\backslash a}$) for benzene interacting with 12 different aprotic solutes was 400 J/mol and the standard deviation was 150 J/mol.

Enthalpy–Entropy Compensation in a Reaction

The above discussion is readily extended to equilibria in dilute solutions, since in a dilute solution each solute species is solvated as if the other solutes were absent. Thus, for X·Y complex formation according to eq 3, equations of the form of (10) may be written separately for each species. The standard enthalpy and entropy of reaction thus take the form of eqs 11.

(9) The molar shift term for H_2 and S_2 (and hence for H_X and S_X) vanishes when s_X is constant. See eq 6 in the following: Grunwald, E. *J. Am. Chem. Soc.* **1984**, *106*, 5414–6. Note that s_X is a progress variable analogous to α in that paper.

(10) Pimentel, G. C.; McClellan, A. L. *Annu. Rev. Phys. Chem.* **1971**, *22*, 347–85.

$$\Delta H° = [H°_{X \cdot Y\backslash a} - H°_{X\backslash a} - H°_{Y\backslash a}] +$$

$$[s_X \cdot_Y(H_{A\backslash xy} - H_{A\backslash a}) - s_X(H_{A\backslash x} - H_{A\backslash a}) - s_Y(H_{A\backslash y} - H_{A\backslash a})]$$

$$= \Delta H°_{nom} + \Delta H°_{env}$$

$$= [\text{term 1}] + [\text{term 2}] \qquad (11a)$$

$$\Delta S° = [S°_{X \cdot Y\backslash a} - S°_{X\backslash a} - S°_{Y\backslash a}] +$$

$$[s_X \cdot_Y(S_{A\backslash xy} - S_{A\backslash a}) - s_X(S_{A\backslash x} - S_{A\backslash a}) - s_Y(S_{A\backslash y} - S_{A\backslash a})]$$

$$= \Delta S°_{nom} + \Delta S°_{env}$$

$$= [\text{term 3}] + [\text{term 4}] \qquad (11b)$$

Note that terms 1 and 3 go with the nominal eq 3n, while terms 2 and 4 represent the solvent reorganization, eq 3e. Owing to enthalpy−entropy compensation in solvent reorganization, $\Delta H°_{env} = T \cdot \Delta S°_{env}$, that is $\Delta G°_{env} = 0$, but there is no compensation requirement for terms 1 and 3. Indeed, $[\Delta H°_{nom} - T \cdot \Delta S°_{nom}]$, i.e. $\Delta G°_{nom}$, equals the standard free-energy change $\Delta G°_{react}$, which in general is *not* zero.

In the following examples we shall apply these concepts to data for a series of reactions, $X_i\backslash a + Y_j\backslash a \rightarrow (X_i \cdot Y_j)\backslash a$, yielding a series of free-energy changes $\Delta G°_{ij}$, with similar series for $\Delta H°$ and $\Delta S°$. Clearly, since $\Delta G°_{env,ij} = 0$,

$$\Delta G°_{ij} = \Delta G°_{nom,ij} \qquad (12a)$$

$$\Delta H°_{ij} = \Delta H°_{nom,ij} + \Delta H°_{env,ij} \qquad (12b)$$

$$\Delta S°_{ij} = \Delta S°_{nom,ij} + \Delta S°_{env,ij} \qquad (12c)$$

Accordingly, when both $\Delta G°_{ij}$ and $\Delta H°_{ij}$ are plotted against i and/or j or any index of i and/or j, the plot of $\Delta G°$ will be easier to interpret because solvent reorganization does not enter. Moreover, for a series $X_i + Y \rightarrow X_i \cdot Y$ the variability of $\Delta G°$ is probably smaller than that of $\Delta H°$, because the effects of a change in X on the nominal reaction and on solvent reorganization are separate phenomena. We shall find that the effect of solvent reorganization is accentuated in hydrogen-bonding solvents, and may become large in processes involving substantial transfers of water molecules, as in the folding/unfolding of proteins in contact with water, or in the closing/opening of channels in membrane proteins.

The *variation* in $\Delta H°$ can be written as $(\Delta H°_{ij} - \Delta H°_{00}) = \delta\Delta H°$ with similar definitions for $\delta\Delta G°$ and $\delta\Delta S°$.

Thus,

$$\delta\Delta H° = \delta\Delta H°_{nom} + \delta h \qquad (13a)$$

with $\delta h = \delta\Delta H°_{env} = (\Delta H°_{env,ij} - \Delta H°_{env,00})$ and

$$\delta\Delta S° = \delta\Delta S°_{nom} + \delta h/T \qquad (13b)$$

When $|\delta h| \gg |\delta\Delta H°_{nom}|$, environmental factors dominate in controlling the variations in $\Delta H°$ and $\Delta S°$ so that

$$\delta\Delta H°/\delta\Delta S° \approx T, \quad \text{with } |\delta\Delta G°| \ll |\delta\Delta H°| \qquad (14)$$

In this case the plot of $\Delta H°$ vs $\Delta S°$ should be linear with a slope equal to the temperature; this is the case of virtually complete compensation.

However, compensation does not *require* an explanation in terms of solvent reorganization since there are other mechanisms for enthalpy−entropy compensation. One such mechanism is solute-induced molar shifts—that is, shifts in equilibria among
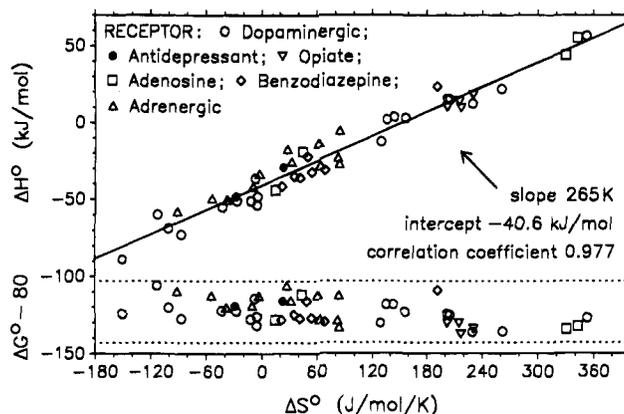

Figure 2. Plot of $\Delta H°$ and $\Delta G°$ vs $\Delta S°$ for the binding of drugs dissolved in water by receptor sites in a series of membrane proteins. Data from ref 5a.
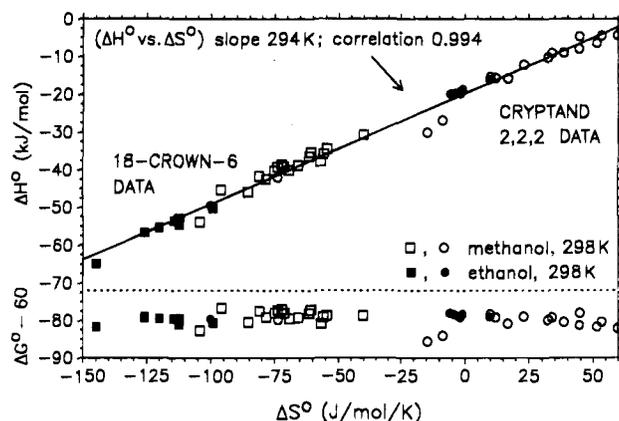

Figure 3. Guest−host binding of a series of amino acids by 18-crown-6 ether or cryptand-222 in methanol or ethanol. Data from ref 6.

solvent species when the pure solvent consists of two or more molecular species.[11,12] Examples considered by Grunwald and co-workers are shifts in the equilibrium between environmental isomers of water when nonpolar solutes are present[11,12] and shifts in hydrogen-bonded linkage equilibria in alcohol solvents when hydrogen-bonding solutes are present.[13] When such shifts occur, they contribute compensating additive terms ("lyodelphic" terms) to the standard enthalpy and entropy of the *solute*, and thus add to the overall compensation phenomenon.

Compensation may also be associated with the nominal parts of eqs 13. For example, when X and Y react to form the complex X · Y, the stronger the interaction the more rigid the complex.[10] This implies that as $\Delta H°_{nom}$ becomes more negative so does $\Delta S°_{nom}$, again leading to compensation, but now the compensation is incomplete. Typically, $\delta\Delta H°_{nom}/\delta\Delta S°_{nom} > T$, so that $\delta\Delta G°_{nom}$ is not negligible compared to $\delta\Delta H°_{nom}$ and has the same sign as the latter. These mechanisms can be quite significant and perhaps both, but certainly the latter, contribute to the changes plotted in Figures 2 and 3. However, there is no precedent in which the magnitude of incomplete nominal compensation or of molar-shift compensation approaches even half of the compensation seen in Figures 2 and 3. In first approximation, we shall therefore discuss the figures in terms of solvent reorganization only.

(11) Grunwald, E. *J. Am. Chem. Soc.* **1986**, *108*, 5726−31.

(12) Grunwald, E.; Comeford, L. *Environmental Influences and Recognition in Enzyme Chemistry*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers: New York, 1988; Chapter 3.

(13) Grunwald, E.; Pan, K.-C.; Effio, A. *J. Phys. Chem.* **1976**, *80*, 2937−40.
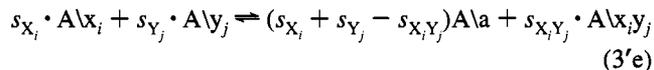
Examples[5,6]

Figures 2 and 3 are examples in which the variability of $\Delta H°$ is much greater than that of $\Delta G°$, showing that the compensated part of $\Delta H°$ dominates the uncompensated part: In a manner of speaking, the compensated tail wags the nominal dog. Both plots of $\Delta H°$ vs $\Delta S°$ show strong linear correlations, with slopes close to the experimental temperatures (T).

Binding by Membrane Proteins. Figure 2 represents the binding of a series of drugs dissolved in water by receptor sites in membrane proteins.[5] It is believed that the binding triggers conformational changes that are similar to, or tantamount to, the opening or closing of membrane channels.[5a] The attendant transfer of water molecules is not known quantitatively, but experiments suggest numbers which can be as high as about 60 water molecules.[14,15]

Let us look at the plot for $\Delta G°$ first. Measurements of useful accuracy are feasible in a range of about 40 kJ/mol, indicated by the dashed lines. The data points cover this entire range, so that $\Delta G°$ is as variable as can be, and the standard deviation of $\Delta G°$ is 8.4 kJ/mol. However, the range of $\Delta H°$, 150 kJ/mol, is nearly four times greater than the range of $\Delta G°$, and the standard deviation of $\Delta H°$ is 33 kJ/mol. The compensated contribution to $\Delta G°$ thus dwarfs the uncompensated contribution, so that the plot of $\Delta H°$ vs $\Delta S°$ is virtually a compensation plot, with a slope of 265 K (compared with a mean experimental temperature of 290 K) and a correlation coefficient of 0.977. The range in $\Delta H°$ seems to be much too large to be explained in terms of binding-energy variation alone.

From eq 3 we see that the environmental equation for the nominal reaction $X_i\backslash a + Y_j\backslash a \rightarrow (X_i \cdot Y_j)\backslash a$ is,

$$s_{X_i} \cdot A\backslash x_i + s_{Y_j} \cdot A\backslash y_j \rightleftharpoons (s_{X_i} + s_{Y_j} - s_{X_iY_j})A\backslash a + s_{X_iY_j} \cdot A\backslash x_iy_j$$

$$(3'e)$$

and so $\delta\Delta H°_{env} = (\Delta H°_{env,ij} - \Delta H°_{env,00})$ is,

$$\delta\Delta H°_{env} = s_{X_iY_j}(H_{A\backslash x_iy_j} - H_{A\backslash a}) - s_{X_i}(H_{A\backslash x_i} - H_{A\backslash a}) - \\ s_{Y_j}(H_{A\backslash y_j} - H_{A\backslash a}) - s_{X_0Y_0}(H_{A\backslash x_0y_0} - H_{A\backslash a}) + \\ s_{X_0}(H_{A\backslash x_0} - H_{A\backslash a}) + s_{Y_0}(H_{A\backslash y_0} - H_{A\backslash a}) \quad (15)$$

The s terms represent the numbers of solvent molecules associated with the various species, while the H terms are the solvent enthalpies in the different environments. If we say that the latter can vary over a range typically associated with hydrogen bonds (vide supra) and $s \approx 10$, then it is easy to generate values of about 100 kJ/mol for $\delta\Delta H°_{env}$. For example, for the series $X_i + Y \rightarrow X_i \cdot Y$

$$\delta\Delta H°_{env} = s_{X_iY}(H_{A\backslash x_iy} - H_{A\backslash a}) - s_{X_i}(H_{A\backslash x_i} - H_{A\backslash a}) - \\ s_{X_0Y}(H_{A\backslash x_0y} - H_{A\backslash a}) + s_{X_0}(H_{A\backslash x_0} - H_{A\backslash a}) \quad (16)$$

If $s_{X_iY} = s_{X_0Y} = s_{X_i} = s_{X_0} = s = 10$, then eq 16 becomes

$$\delta\Delta H°_{env} = s(H_{A\backslash x_iy} - H_{A\backslash x_0y}) - s(H_{A\backslash x_i} - H_{A\backslash x_0}) \quad (16')$$

And if $(H_{A\backslash x_iy} - H_{A\backslash x_0y}) = -(H_{A\backslash x_0} - H_{A\backslash x_i}) = 5$ kJ/mol then $\delta\Delta H°_{env} = 100$ kJ/mol. It is interesting to note that in examining the hemoglobin equilibrium, deoxygenated state (T) $\rightleftharpoons$ oxygenated state (R), Colombo et al.[15] found that about 60 extra water molecules were bound to the relaxed R state and that this contributed about 50 kJ/mol stability.

Binding of Amino Acids by 18-Crown-6 and Cryptand-2,2,2.

Figure 3 represents the binding of a series of zwitterion amino acids, $R \cdot CH(NH_3^+) \cdot CO_2^-$, with 18-crown-6 ether (I) or cryptand-222 (II), in methanol or ethanol. The amino acids are Gly, Ala, Arg, Asn, Asp, Cys, Glu, His, Ile, Leu, Met, Phe, Ser, Thr, Trp, Tyr, Val and thus cover a broad spectrum of R groups.

I   II
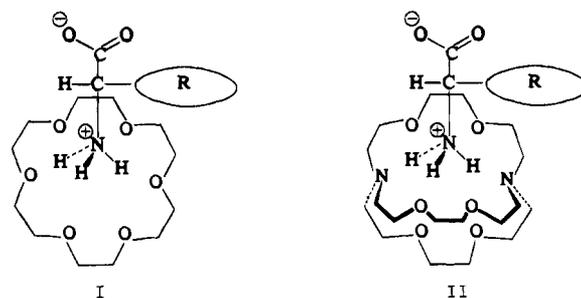
A key feature of Figure 3 is that $\Delta G°$ is nearly invariable, in spite of the variety of reactants and solvents. The standard deviation of $\Delta G°$ for all points is 1.8 kJ/mol, and the range is 9 kJ/mol. Accordingly, the plot of $\Delta H°$ vs $\Delta S°$ resembles a textbook example of compensation. The standard deviation of $\Delta H°$ is 17 kJ/mol, and the range is over 60 kJ/mol. The slope is 294 K (compared with an experimental temperature of 298 K), and the correlation coefficient is 0.994.

As to the position of the points along the line, there is a substantial separation of the points by host, with relatively little overlap and with $\Delta H°$ for binding by 18-crown-6 being more negative. Within the range for each host, the $\Delta H°$ points tend to be more negative in ethanol than methanol. The magnitudes of the ranges are (in kJ/mol) the following: for cryptand-222, 25 in MeOH and 35 in EtOH; for 18-crown-6, 20 in MeOH and 15 in EtOH.

In forming a molecular complex, the $-NH_3^+$ group of the amino acid invades the host cavity, probably more deeply in the case of 18-crown-6 which (judging by dipole moments of K^+ complexes) probably changes to the crown conformation.[16] The deeper invasion of the 18-crown-6 cavity (relative to cryptand-222) may explain the more negative values of $\Delta H°$ and $\Delta S°$. The accompanying solvent reorganization certainly involves alcohol molecules solvating the NH_3^+ group and one face of the host, and probably also some molecules solvating the CO_2^- group, whose solvation in the amino acid is strongly coupled to that of the NH_3^+ group, as evidenced for example by the marked participation of water molecules in proton transfer between these groups.[17] On the other hand, the substantial variability of $\Delta H°$ with the nature of the R group is unexpected. The data imply that the solvation shell of the R group is seriously perturbed by complex formation to the host, in a highly specific manner for which we know no analog. First, the R-group dependence of $\Delta H°$ for binding to 18-crown-6 shows no correlation with that for binding to cryptand-222. Second, the R-group dependence for either shows no correlation with that for pK_a (also called pK_2)[18] of the NH_3^+ group in water, nor does pK_a correlate with $\Delta G°$ for complex formation to either host in either solvent. It looks like solvent reorganization follows a logic of its own, grounded in the richness of eq 15, so that the substituent effect is distinct from that for nominal reactions.

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Discussion

Before closing, we shall compare thermodynamic mechanisms of enthalpy—entropy compensation, such as the present solvent-reorganization mechanism, with Leffler's classic isokinetic relationship.[19,20] We shall also comment on related statistical issues of data accuracy and covariance.[21,22]

Leffler found empirically that $\delta\Delta H^{\ddagger}$ in many reaction series varies linearly with $\delta\Delta S^{\ddagger}$. He fitted his data to the equation $\delta\Delta H^{\ddagger} = \beta \cdot \delta\Delta S^{\ddagger}$, where β is a parameter with the dimension of temperature. If one assumes that the fit is error-free over a temperature range including β, then there is exact enthalpy—entropy compensation at a single temperature $T = \beta$. In solvent reorganization, on the other hand, $\delta\Delta H^{\circ}_{env}$ is precisely equal to $T \cdot \delta\Delta S^{\circ}_{env}$ at *any* temperature, according to the Second Law. However, $\delta\Delta H^{\circ}_{env}$ is only part of the overall $\delta\Delta H^{\circ}$, and because the difference, $\delta\Delta H^{\circ}_{nom}$, does not have exact enthalpy—entropy compensation, the overall $\delta\Delta H^{\circ}$ is not exactly equal to $T \cdot \delta\Delta S^{\circ}$.

As for the statistical issues, when $\delta\Delta H^{\circ}$ ($\delta\Delta H^{\ddagger}$) and $\delta\Delta S^{\circ}$ ($\delta\Delta S^{\ddagger}$) are calculated from the temperature derivative of equilibrium or rate constants, the errors are correlated with a slope T, and it is possible for enthalpy—entropy compensation to be spurious. However, as this paper demonstrates, the fact that such a slope is T is not a proof that compensation must be due to correlated errors. The data in Figures 2 and 3 cover ranges that greatly exceed the experimental errors, and therefore are judged to be significant.

Appendix

To show that eq 8 implies genuine compensation, we must show that in general $(S_{A\backslash x} - S_{A\backslash a})$, in contrast to $(G_{A\backslash x} - G_{A\backslash a})$,

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does not vanish at equilibrium. The following proof will be based on the Second Law. To simplify the notation, we shall introduce the symbol $y \equiv \partial G/\partial s_X$.

When equating $S_{A\backslash x} - S_{A\backslash a}$ to $-[\partial(G_{A\backslash x} - G_{A\backslash a})/\partial T]$, we must be careful about the variables that remain inactive. If the closed system stays at equilibrium while the temperature is changing by ∂T, y stays constant at zero, and the partial derivative $-[\partial(G_{A\backslash x} - G_{A\backslash a})/\partial T]_{n_1,n_2,y=0}$ vanishes because eq 8 is true at all temperatures. *But this partial derivative is not equal to $S_{A\backslash x} - S_{A\backslash a}$!* At level III in Composition Tree (Chart 1), on which eqs 5c and 6b operate, the primary composition variables are $(n_{A\backslash a}, n_{A\backslash x}, n_{X\backslash a})$. Thus, to derive $(S_{A\backslash a}, S_{A\backslash x}, S_{X\backslash a})$, the temperature derivatives must be taken either with $(n_{A\backslash a}, n_{A\backslash x}, n_{X\backslash a})$ constant or with the transformed variables (n_1, n_2, s_X) constant. Choosing the latter, we obtain that at constant P,

$$S_{A\backslash x} - S_{A\backslash a} = -[\partial(G_{A\backslash x} - G_{A\backslash a})/\partial T]_{n_1,n_2,s_X}$$

The difference between this partial derivative and that with maintenance of equilibrium is that the independent variables now are P, T, n_1, n_2, s_X, rather than P, T, n_1, n_2, y.

To prove that $(S_{A\backslash x} - S_{A\backslash a})$ is nonzero, let P, n_1, n_2 be constant and transform the independent variables from T, s_X to T, y:

$$[\partial(G_{A\backslash x} - G_{A\backslash a})/\partial T]_y = [\partial(G_{A\backslash x} - G_{A\backslash a})/\partial T]_{s_X} +$$
$$[\partial(G_{A\backslash x} - G_{A\backslash a})/\partial s_X]_T (\partial s_X/\partial T)_y$$

When $y = 0$, the term on the left is zero because eq 8 applies at all temperatures. The first term on the right equals $-(S_{A\backslash x} - S_{A\backslash a})$, while differentiation of eq 7 at constant T, P, n_1, n_2 shows that $\partial(G_{A\backslash x} - G_{A\backslash a})/\partial s_X = (\partial^2 G/\partial s_X^2)/n_2$. The latter is the curvature of the plot of G/n_2 vs s_X and is a positive number, because $G(s_X)$ is at a minimum at equilibrium. At the same time, $(\partial s_X/\partial T)_y$ the temperature derivative of s_X at equilibrium, is a finite number which vanishes only in those rare cases in which s_X happens to be independent of T. Thus $S_{A\backslash x} - S_{A\backslash a}$ equals a positive number times a finite, usually nonzero, number.