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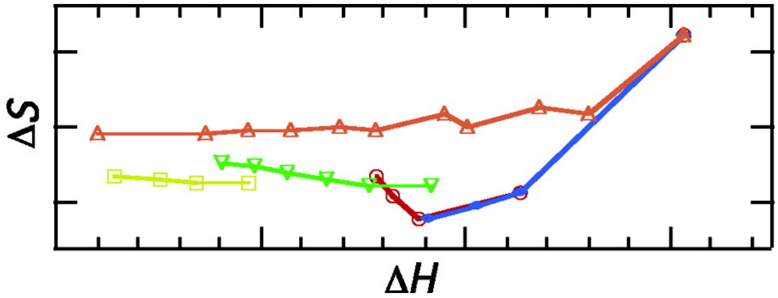

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Enthalpy−Entropy Compensation is Not a General Feature of Weak Association

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Abstract: Relationships between the enthalpy and entropy changes resulting from perturbations of a system have been discussed in the literature for some time. Both positive correlations (compensation) and negative correlations (anti-compensation) between ΔH and ΔS have been observed in various experimental contexts, including chemical reaction, physical association, solvation, and protein folding. Many examples have been demonstrated to be statistical artifacts, but some are genuine signatures of the perturbations in molecular characteristics. In particular, recent literature claims that compensation is a general feature of bimolecular associations arising from weak intermolecular interactions. We employ a statistical mechanical framework to predict the magnitude and direction of enthalpy−entropy correlation in bimolecular association. The theory links the macroscale thermodynamic correlation to the relationship between the intermolecular potential parameters. Using a harmonic approximation to the Lennard-Jones model and potential parameters taken from the literature, we show examples of both compensation and anti-compensation for gas-phase self-association among five homologous series. Furthermore, an aggregate presentation of data for 48 different chemical species shows no correlation in either direction, for the case of self-association in a dilute gas phase.

Introduction

Background. There are both energetic (enthalpic) and entropic contributions to the free energy difference upon a change in thermodynamic state,[1] as reflected in the statement $\Delta G = \Delta H - T\Delta S$. This equation represents a combined statement of the first and second laws of thermodynamics and is of course widely accepted. In many different classes of physicochemical processes,[2] researchers have observed a correlation between the enthalpic and entropic contributions to the free energy, as in the linear relationship

$$(\Delta H)_i = a(\Delta S)_i + b \tag{1}$$

where the subscript i denotes a perturbation variable and a,b are constants. The perturbation variable typically represents some aspect of molecular identity, such as the primary structure in a set of protein folding experiments[3] or the molecular structure in a series of chemical species undergoing the same process, such as reaction,[4] solvation,[5,6] adsorption,[7,8] or physical (weak) association.[9−12] The solvent used during such processes has also been considered as a perturbation variable.[13,14] Relationships like eq 1 are often referred to as extra-thermodynamic, due to their lack of basis in the laws of thermodynamics. Positive correlation between ΔH and ΔS is referred to as compensation (since this behavior tends to minimize changes in ΔG across the series), and negative correlation is referred to as anti-compensation.

Analyses[2,15] have shown that the apparent compensation seen in many data sets is a statistical artifact linked to experimental uncertainties in the measured quantities $(\Delta G)_i$ and $(\Delta H)_i$. Anti-compensation is also a subject of debate with respect to statistical significance.[16,17] Furthermore, for some choices of the perturbation variable i (e.g., temperature), compensation is a trivial consequence of thermodynamics.[15] However, when “false” cases are weeded out, many instances of valid extra-thermodynamic relationships remain, and they are apparently reflections of the molecular level changes in the system.

Molecular modeling can be helpful in understanding the origins of these relationships. Classical atomistic modeling[5,6,18]

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has focused mainly on solvation processes, yielding observations of (and explanations for) both compensation and anti-compensation. Compensation was observed when changing the solvent in an ab initio modeling study on the formation of van der Waals complexes.[13] A more abstract statistical mechanical density of states model by Sharp[15] yielded an elliptical entropy−energy diagram that admits the possibility of both compensation and anti-compensation.

This paper focuses on molecular association. Previous theory in that specific area mainly comprises a widely referenced paper by Dunitz[19] and complementary work by Searle, Westwell, and Williams.[20] Dunitz's approach was based on assumptions about the changes in translational, rotational, and vibrational degrees of freedom that occur during a weak binding event. Using a standard expression for harmonic vibrational entropy of the stretching mode, and order-of-magnitude estimates for the other contributions, he generated an enthalpy−entropy plot for prototype hydrogen bonding interactions. Dunitz's result predicted compensation behavior only, as ΔS monotonically increased with ΔH; however, the curve was not linear as in eq 1 but rather showed a flattening of ΔS at lower values of ΔH (stronger binding). Searle, Westwell, and Williams[20] developed a qualitatively similar curve based on arguments about (1) the correlation between vibrational entropy and the depth of the potential energy well and (2) the existence of a practical upper limit on the entropy loss during association. A collection of 233 experimental data points for association in nonpolar solvents provides strong support for the compensation trend,[11] although resolving the degree of curvature is difficult.

Present Work. In this paper, we revisit the classical (nonquantum) theory of weak bimolecular association. In the next section, we describe a statistical mechanical formulation of association recently presented by Luo and Sharp[21] that requires no assumptions about the characteristics of the degrees of freedom and no approximate partition functions. Using this theory, we develop an analytical result that admits both compensation and anti-compensation, and we show how the trend depends on the relationship between the well depth and force constant of the underlying potential function. In the Results section, we discuss the general implications of this finding, especially in the context of previous work in the literature. We then apply the analytical result to predict the enthalpy−entropy trends for weak self-association of molecules in the gas phase, based on potential parameters from the literature. We observe both compensation and anti-compensation for several homologous series and no correlation in a large set of data.

Theoretical Basis

We assume the classical limit in our theoretical development, which is acceptable for the physical (nonchemical bonding) forces of interest here. We employ a formalism for molecular association presented recently by Luo and Sharp[21] that is traced back to Bjerrum. The basic model consists of a molecule of species A (assumed fixed near the origin) associating with a molecule of species B to form the AB bound complex. The equilibrium association constant is given by

$$K_{\mathrm{AB}} = \frac{[\mathrm{AB}]}{[\mathrm{A}][\mathrm{B}]} = \frac{1}{8\pi^2}\int H(\mathbf{r},\Omega)e^{-\beta\omega(\mathbf{r},\Omega)}\mathrm{d}\mathbf{r}\mathrm{d}\Omega \qquad (2)$$

where $\mathbf{r}$ and Ω are the position and orientation of B, $\beta = 1/k_{\mathrm{B}}T$ with k_{B} being the Boltzmann constant and T the temperature, ω is the potential of mean force between B and A, and $H(\mathbf{r},\Omega)$ is a bonding function that is 1 when the AB complex exists, and 0 otherwise. The molecular geometry of the bound state, $H(\mathbf{r},\Omega) = 1$, may be specified using heuristic energy criteria or information about a particular experimental detection technique. The free energy change associated with binding is given by

$$-\beta(\Delta G_{\mathrm{AB}}) = \ln(K_{\mathrm{AB}}/V_{\mathrm{ref}}) \qquad (3)$$

where V_{ref} is the volume that determines the reference concentration $1/V_{\mathrm{ref}}$ of species B.

In the simplest case, we ignore the solvent and any internal structure of species A and B (we discuss below the possible incorporation of these features). The potential of mean force then simplifies to $\omega(\mathbf{r},\Omega) = u(r)$, where $u(r)$ is the potential energy between A and B that depends only upon the scalar distance r between the centers of mass. For the convenience of obtaining an analytical result, we further assume that the binding potential between A and B is harmonic, with $u(r) = u_{\min} + (\kappa/2)r^2$. Note that we have assumed that molecule A is fixed such that the potential energy minimum for the AB complex is located at the origin, $r = 0$. Following Luo and Sharp,[21] we approximate the integral in eq 2 by one in which $H(\mathbf{r},\Omega) = 1$ over all of space since the Boltzmann factor, $\exp[-\beta u(\mathbf{r},\Omega)]$, will vanish for high energy (unbound) configurations anyway. Within these approximations we have

$$-\beta(\Delta G_{\mathrm{AB}}) = \ln\left[e^{-\beta u_{\min}}(2\pi)^{3/2}\frac{(\beta\kappa)^{-3/2}}{V_{\mathrm{ref}}}\right] \qquad (4)$$

Furthermore, we use the Gibbs−Helmholtz relationship to obtain the entropic and enthalpic components, as

$$\Delta H_{\mathrm{AB}} = u_{\min} + \frac{3}{2}k_{\mathrm{B}}T \qquad (5)$$

$$\frac{\Delta S_{\mathrm{AB}}}{k_{\mathrm{B}}} = \ln\left[e^{3/2}(2\pi)^{3/2}\frac{(\beta\kappa)^{-3/2}}{V_{\mathrm{ref}}}\right] \qquad (6)$$

Results and Discussion

General Implications. The molecular criteria for an extra-thermodynamic relationship between enthalpy and entropy of association may be obtained by examining eqs 5 and 6. If a change is made to the molecular pair (A,B) such that $u_{\min}$ and κ move in the *opposite* direction, the result will be compensation (i.e., ΔH_{AB} and ΔS_{AB} both decrease or both increase). On the other hand, if a change is made to the molecular pair (A,B) such that $u_{\min}$ and κ move in the *same* direction, the result will be anti-compensation (a decrease in ΔH_{AB} accompanied by an increase in ΔS_{AB}, or vice versa).

The main argument underlying the theoretical development of Searle, Westwell, and Williams[20] is that the former trend, and thus compensation, should be expected always. To our knowledge, there is no fundamental principle of weak interactions that dictates the relative dependence of well depth $u_{\min}$ and force constant κ. A recent detailed comparison of the various

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measures of *chemical bond* strength concluded that “contrary to general belief” bond stretching force constants are often not even qualitatively related to bond dissociation energies, except possibly for a “group of closely related molecules with similar bonds” for which the relationship should still be checked.[22] There is no reason to expect *physical bonds*, where a broad range of interaction mechanisms may occur, to exhibit stronger correlations between force constant and well depth. In the next section, we present results for weak gas-phase associations that exhibit both compensation and anti-compensation in homologous series and do not support any correlation in aggregate form.

The theoretical results presented by Dunitz[19] do not predict anti-compensation. While this may be due to an inherent limitation of the theory, we suspect that it is due to the way in which the potential parameters were varied to generate the enthalpy–entropy curve. Apparently, only the energy parameter (i.e., well depth) was varied while the size parameter (i.e., most probable bond length) was held fixed. In the next section, we present expressions for $u_{\min}$ and κ within the Lennard-Jones potential; combining those expressions with eqs 5 and 6 indicates that our model would predict only compensation under conditions where ϵ varies and σ is fixed. In real systems, both parameters would change as the species' identities were perturbed. In any case, the Bjerrum approach embodied in eq 2 is free of the assumptions employed by Dunitz.

Specific Calculations. As an example, consider self-association (A=B) of molecules in the gas-phase based on van der Waals interactions. We chose as model systems five molecular series for which high-quality interaction parameters[23,24] are available. The first two series represent typical alchemical changes. The first one is the complete set of chloromethanes, where methane (CH_4) is changed to carbon tetrachloride (CCl_4) by sequentially replacing the hydrogen atoms with chlorine. The second one is a series of halomethanes, where methane is modified to chloro-, bromo-, and iodomethane. The last three series are *n*-alkanes (C1–C10 and C13), brominated *n*-alkanes (bromoethane through bromoheptane), and primary alkanols (1-hexanol through 1-nonanol). In these three series, the perturbation variable is obviously the carbon number in the alkyl backbone. The Lennard-Jones (LJ) potential was chosen as the basis for the calculations. Of course, representing these complex molecules with a single LJ site is not very sophisticated in light of modern molecular modeling capabilities, but the effective interaction parameters were obtained by fitting to an equation-of-state and thus are in some sense optimized to capture the thermodynamic behavior; they should predict at least qualitative trends. Further study using detailed atomistic simulation would be of great interest. The harmonic approximation applied to the minimum of the LJ attractive well yields values of $u_{\min} = -\epsilon$ and $\kappa = (72 \times 2^{-1/3})(\epsilon/\sigma^2)$. The volume V_{ref} was chosen to be 37 220 Å^3/molecule (22.414 L/mol) based on an ideal gas at standard temperature (273.15 K) and pressure (1 atm).

Figure 1 shows entropy–enthalpy plots for the five series described above. Methane is the point in the upper right of the plot, common to three of the series. The *n*-alkane series exhibits compensation (positive slope), which is stronger at low molecular weights and progressively weaker at high molecular weights; this qualitative behavior of the compensation curve was predicted previously.[19,20] The halomethane series exhibits strong compensation that is more nearly linear. On the other hand, the bromoalkanes exhibit significant anti-compensation, while the primary alkanols show mild anti-compensation. Perhaps the most interesting result is for the chloromethanes, where the curve changes slope in the middle of the series. These five data sets, chosen as a random sampling from the available literature on van der Waals fluids, indicate that both compensation and anti-compensation should be expected in problems of weak association. Furthermore, this rich variety of behavior was observed with the bare intermolecular potentials, without consideration of complex solvation effects.

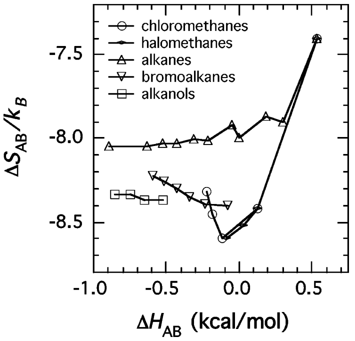

Figure 1. Relationship between entropy and enthalpy of self-association for five different molecular series.

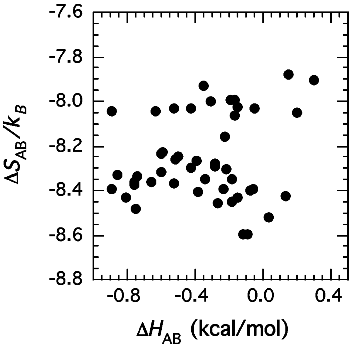

Figure 2. Relationship between entropy and enthalpy of self-association for 48 different chemical species.

Figure 2 shows a broader perspective, including all 48 species for which data are given in ref 24. The list spans substituted alkanes (as in Figure 1), alkenes, ketones, aromatics, and even ammonia (methane is not in this list—it appears in ref 23). The well depths $u_{\min}$ range from −0.5 to −1.7 kcal/mol, and the force constants κ range from 1.6 to 3.4 kcal/(mol Å^2). Clearly, no strong correlation in either direction is supported by the aggregate data; a linear fit yields a Pearson's *r* value of 0.0235.

The results of Figure 2 stand in contrast to similar plots for solution-phase association,[11] which span a much wider range of ΔH_{AB} (on the order of 20 kcal/mol) and appear quite linear (with a positive correlation). Barring any issues with statistical significance of the correlations, the following is a reasonable hypothesis that reconciles the different results: the compensation effect observed for solution-phase association is governed *not* by the details of the bare AB interaction potential curve, but rather by solvent effects. In fact, a recent molecular model for hydration in an alchemical series predicted dominance of the solute–water attractive energy over the other enthalpic contributions (although in this case, the result was anti-compensation).[6]

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Conclusions

Using the Bjerrum approach, we have developed a simple criterion for predicting the degree and direction of extra-thermodynamic effects in molecular association. The key point is how changes in the molecular system simultaneously affect the depth and curvature of the potential well. If molecular-level modifications increase the well depth (lower $u_{\min}$) and also increase the curvature (higher κ), the result will be compensation. Anti-compensation will be observed if the modifications simultaneously deepen the well and decrease the curvature. LJ molecular parameters from the literature were used as input to the model to create enthalpy−entropy plots for weak gas-phase associations. Examples of both compensation and anti-compensation were demonstrated across five homologous series, and an aggregate plot of 48 data points showed no significant correlation in either direction. These findings suggest that enthalpy−entropy compensation is not a general feature of association due to weak interactions. The Bjerrum framework described herein may be applied to more complex systems. Luo and Sharp[21] have already developed an expression for ΔG_{AB} of internally complex molecules in solvent within in the quasi-harmonic approximation, which could be used to extend the present work to more detailed molecular models in the solution phase (in conjunction with simulation). Extension to arbitrary (nonharmonic) shapes of the potential energy surface, via a direct application of eq 2, is possible, as well. Of course, the molecular-level rationale in this work can be mapped to related physical problems, such as protein folding, solvation, adsorption, and reaction.

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