Win some, lose some: enthalpy–entropy compensation in weak intermolecular interactions

Enthalpy–entropy compensation is a general feature of many chemical reactions and processes in biological systems, but its origin has remained obscure. A simple thermodynamic argument suggests that enthalpy–entropy compensation is a general property of weak intermolecular interactions, and that the two contributions to the free energy should nearly balance out for a hydrogen bond at 300 K.

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Enthalpy–entropy compensation has been discussed under several names (for example, isokinetic or isoequilibrium relationships) and from many points of view in countless papers over the years. The term refers essentially to the specific linear relationship found to exist between the change in enthalpy and the change in entropy in many biological processes, especially those occurring in aqueous solution and involving changes in hydrogen bonding [1–6]. For example, standard enthalpy and entropy changes in the unfolding of proteins are of the same sign and make approximately equal contributions (of opposite sign) to the free energy change, so that ΔG^o is close to zero [1]. The small ΔG^o means that the process is never far from equilibrium, even though the separate enthalpy and entropy terms may be substantial. Similar considerations apply to many other biological processes. Searle and Williams [7] have discussed the relevance of enthalpy–entropy compensation to the binding of agonists versus antagonists to a common receptor site. They suggest that binding of agonists is mainly enthalpy driven while that of antagonists is mostly entropy driven, as has indeed been shown experimentally to be the case for the A1 adenosine receptor [8]. Recently, the topic is attracting more attention in the contexts of supramolecular host–guest and biomolecular drug–receptor association reactions [7, 9–11]. Although enthalpy–entropy compensation has in the past been regarded as a 'ubiquitous property of water' [1], it appears to be a property of all weak intermolecular interactions, of which hydrogen bonding in aqueous solution is merely the one most frequently encountered in biochemical and supramolecular reactions. In this article, I use a simple statistical mechanical model to derive a semi-quantitative estimate for enthalpy–entropy compensation in the interaction of two molecules. This model suggests that the opposite enthalpic and entropic contributions to the free energy nearly balance out around physiological temperature for an enthalpic stabilization of $\approx$5 kcal mol^{-1}. This is approximately the energy of a hydrogen bond, which may help to explain why such compensation is so prevalent in biological systems.

The trade-off between enthalpic and entropic terms is basic to thermodynamics, as expressed in the two terms of the free energy expression: $G = H - TS$. As H becomes more negative (stronger bonding), S tends to decrease due to the tightening up of the system. As H becomes less negative (weaker bonding), S tends to increase as the system becomes increasingly disordered.

Some examples of enthalpy–entropy compensation may appear to be trivial: for instance, the relationship between the enthalpy and entropy changes that occur on melting a solid. Here the entropy change on fusion ΔS_f can be defined (and is often experimentally determined) as $\Delta H_f/T_f$, since the free energy change ΔG_f on melting must be zero. On a rather different plane, if the equilibrium constant for a particular type of association is required to lie within a given range, for reasons of practical or biochemical necessity, it follows that $\Delta H^o - T\Delta S^o$ must be approximately constant at the temperature of interest. For this to be true, any change in ΔH^o must be balanced by an equivalent change in $T\Delta S^o$, and indeed this is what is experimentally observed. Finally, the experimental demonstration of enthalpy–entropy compensation for a particular host–guest association reaction in different solvents [12] would seem to call for explanation.

In a recent paper Searle, Westwell and Williams [13] presented a curve derived from qualitative thermodynamic considerations, showing the general form of the exothermicity of an association reaction ($-\Delta H^o$) as a function of the entropic cost ($-298\Delta S^o$). They consider the association of two molecules A and B to yield a complex A–B. For very strong A–B association (e.g. a covalent bond between the partners), the change in standard free energy, ΔG^o, is clearly dominated by the enthalpic term, ΔH^o. The associated entropy change, ΔS^o, reaches a limit, which can be said to correspond to the loss of one mole of translational and rotational freedom per mole of A and B, at least in the gas phase. The entropy change for an association in solution is not so easy to quantify, but at any rate there will be a large decrease due to loss of independent motion of the two molecules. For weaker bonding this loss will be partially compensated by contributions from translational and rotational vibrations of the A and B components within the A–B complex. In the limit of zero bonding, these

Box 1. Contributions to the entropy of a liquid.

One should perhaps avoid talking about separate translational and rotational contributions to the entropy of a liquid (and, even more so, of a solution). Although these contributions can be calculated by standard statistical mechanical procedures for the ideal gas state (and in good approximation for real gases), they can be neither measured nor calculated for a liquid or a solution. For example, for water vapor the calculated translational and rotational entropies at 298 K and 1 atm pressure are 34.61 and 10.48 eu (1 eu = 1 cal mol^{-1} K^{-1} = 4.184 J mol^{-1} K^{-1}), totalling 45.09 eu. As the internal vibrational contributions are essentially zero (ν = 3652, 1592 and 3756 cm^{-1}), this value is to be compared with the calorimetric value calculated using the Third Law, 44.28 eu. Indeed, it was the small discrepancy between these two values that led to the realization that ice I, the normal crystalline form of ice, is not perfectly ordered at 0 K (for further details see [17]). Thus the translational and rotational components for water vapor can be calculated with confidence. For the liquid state, however, there is no way of separating the standard entropy (at 298 K) of 16.7 eu into translational and rotational components, even though the internal vibrational contribution is negligible at this temperature. At best, the entropy of a liquid can be regarded as an upper limit for the combined 'translational and rotational entropy' — what one might call the 'rigid-molecule entropy'. For solutions, estimates of the separate entropy contributions involve a change in standard state (from the pure substance, with unit activity, to a solution of, say, 1 M concentration, in which the activity is dependent on assumptions about ideality) and become even more perplexing.

vibrational degrees of freedom will become indistinguishable from the lost translational and rotational ones (see the discussion in Box 1).

How can we estimate the contributions of entropy and enthalpy to the free energy of association at varying bond strengths? Suppose that the interaction between the A and B components in the A–B complex is described by a potential energy function of the usual kind (Fig. 1). For a deep well, corresponding to a strong bond with large enthalpy change upon association, the vibrational energy levels of the system are widely spaced and the vibrational entropy is small; on the other hand, a shallow well corresponds to many closely-spaced vibrational levels and hence to a larger vibrational entropy.

These qualitative considerations do not help us much with the intermediate situation where enthalpic and entropic terms approach each other in magnitude. To go further, we have to introduce some numbers and make a few assumptions. The enthalpic contribution is straightforward, but to estimate the entropic contribution we need to first calculate the value of the vibrational frequency, ν, which depends in turn on the magnitude of the quadratic force constant, f. For any 'reasonable' function the quadratic force constant f of the equilibrium structure (the curvature of the function at the equilibrium position) is approximately proportional to the dissociation energy D_o. This proportionality is exact for the Morse potential, a mathematical representation of the potential energy curve in Figure 1:

$$V(r-r_o) = D_o\{e^{-2B(r-r_o)} - 2\,e^{-B(r-r_o)}\}, \qquad f = 2B^2D_o$$

(where V is the potential energy as a function of the interatomic distance r, r_o is the equilibrium distance and B is a constant), and for the inverse power potential:

$$V(r) = \frac{D_o}{l-m}\left[\left\{ m\left(\frac{r_o}{r}\right)^l - l\left(\frac{r_o}{r}\right)^m \right\}\right], \quad l>m, f = \frac{ml}{(r_o)^2}D_o$$

(where l and m are constants). For a harmonic oscillator, the frequency ν of the A–B stretching vibration is $\nu = (f/\mu)^{1/2}/2\pi$ where μ is the reduced mass of the system. In other words, for a given mass, the frequency ν increases as the square root of the force constant and hence as the square root of the dissociation energy D_o. Given ν, we can then use the standard statistical mechanical relationship [14]:

$$S_{vib} = R\left(\frac{x}{e^x-1} - \ln\left(e^x-1\right)\right)$$

where x = $h\nu/kT$ = 1.439 ν/T (ν in cm^{-1}, T in K; R is the gas constant), to estimate the corresponding contribution to the vibrational entropy at any temperature (in these

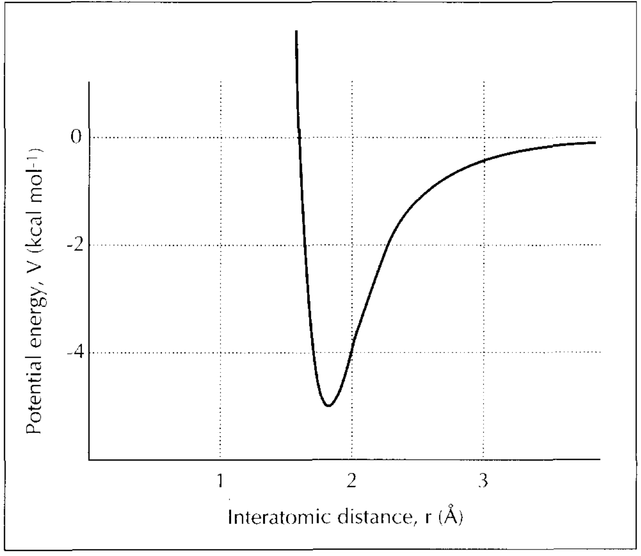

Fig. 1. The energy of a hydrogen bond depends on the interatomic distance. The curve shows a typical potential energy curve for a O–H···O hydrogen bond; vertical scale, energy in kcal mol^{-1}; horizontal scale, H···O distance in Å. As the interatomic distance decreases, the bond becomes stronger, but as the atoms approach each other too closely, repulsion forces take over.

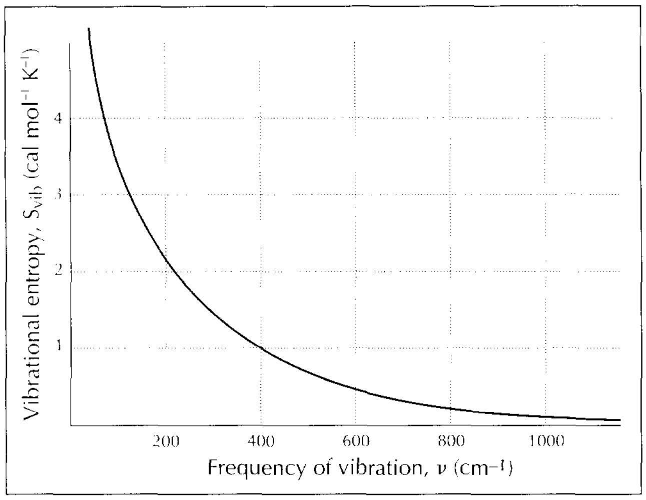

Fig. 2. As the frequency ν increases, the vibrational entropy S_{vib} decreases. The curve shows the relationship between ν and S_{vib} at 300 K. Both ν and S_{vib} are dependent on the strength of the bond; for strong bonds, ν is high and S_{vib} is small.

energy units, 1 kcal mol^{-1} ≈ 350 cm^{-1}). Incidentally, this relationship between vibrational frequency and thermodynamics (or rather a closely connected one involving the heat capacity) was first derived by Einstein in his treatment of a quantized vibration [15].

A plot of S_{vib} as a function of ν at T = 300 K is shown in Figure 2. At the frequencies typical of stretching and bending vibrations of covalent bonds (ν >1000 cm^{-1}) the entropy is negligibly small, whereas for lower frequencies the vibrational entropy increases rapidly. What can we expect for the entropy associated with a typical non-covalent intermolecular interaction, for example a hydrogen bond?

As a specific example we take a water molecule (A) bonded to a very large molecule (B) by a hydrogen bond with dissociation energy $D_o = -\Delta H^o = 5$ kcal mol^{-1}. The Morse potential with B = 2 Å^{-1}, a typical value, gives $f \approx 40$ kcal mol^{-1} Å^{-1}; the inverse power potential with m = 6, l = 12, $r_o = 2.8$ Å, gives $f \approx 45$ kcal mol^{-1} Å^{-1}. Within the approximations of the model, the two estimates are equal, and we adopt the lower value. Taking the reduced mass μ of the water molecule as its actual mass, 18 g/(6.023 x 10^{23}), we obtain $\nu \approx 160$ cm^{-1}. The above formula for S_{vib} then gives the value 2.5 cal mol^{-1} K^{-1} for the entropic contribution of the A–B stretching vibration at 300 K.

In addition to the stretching vibration, there are two other translational vibrations and three rotational ones to be considered. Their entropy contributions are more difficult to estimate but should not be too different from the one we have. We take them to be equal and arrive at the estimate of about 15 cal mol^{-1} K^{-1} ($6S_{vib}$, as there are six vibrational components) for the total vibrational entropy of a water molecule bonded to its large but otherwise indefinite partner. This estimate is certainly very rough, but it is of the right order of magnitude. The entropy associated with each immobilized water molecule in a hydrated crystal is approximately constant at about 10 cal mol^{-1} K^{-1} [16], and the standard entropy of liquid water is 16.7 cal mol^{-1} K^{-1}.

Our model system thus gives an estimated contribution, $6TS_{vib}$, of about 4.5 kcal mol^{-1} to the free energy at 300 K. Since the enthalpic stabilization was assumed to be 5 kcal mol^{-1}, the entropic contribution just about balances out the enthalpic term at this temperature. The general relationship between $6TS_{vib}$ at 300 K and the dissociation energy D_o is shown in Figure 3.

There is no question that the above derivation can be criticized on several counts: the Morse function (or any other applicable one) is far from harmonic and hence the assumptions made in estimating the frequency ν from the quadratic force constant f and in estimating S_{vib} from the frequency ν are unjustified; so is the assumption that the six vibrational degrees of freedom all contribute the same amount to the total vibrational entropy. Nevertheless, the model portrays in a semi-quantitative way essential features of enthalpy–entropy compensation. In particular, it shows that this is not a special feature of aqueous solutions, but is an almost unavoidable characteristic of weak interactions in

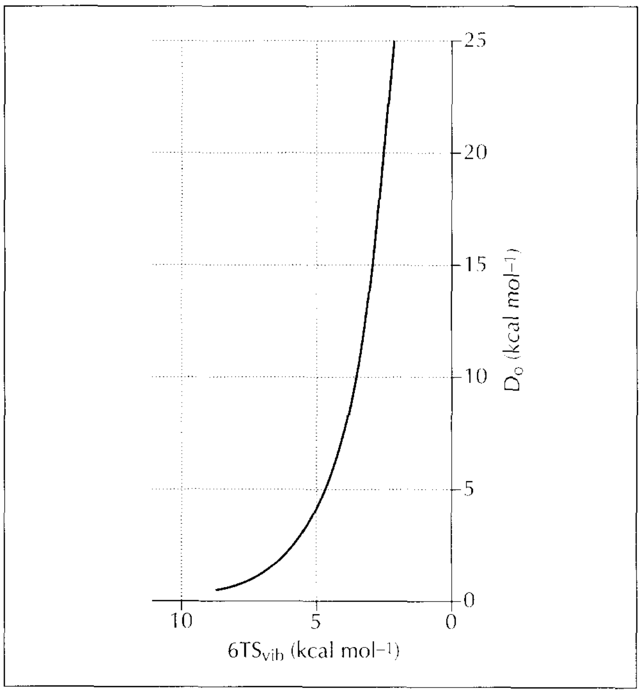

Fig. 3. The enthalpy–entropy compensation curve at T = 300 K for a simple association process, A + B $\rightleftharpoons$ A–B. The value of $6TS_{vib}$, the entropic contribution to the free energy, estimated from our simple model, is plotted against the dissociation enthalpy $D_o = -\Delta H^o$, both expressed in kcal mol^{-1}. For strong covalent bonds, enthalpy predominates, while for very weak associations, entropy predominates. For the intermediate case where $D_o \approx 5$ kcal mol^{-1}, the typical energy of a hydrogen bond, the value of D_o is nearly equal and opposite to the entropic term. The curve is qualitatively similar to that shown in Figure 2 of [13].

general. Since enthalpy–entropy compensation is almost complete for associations involving water at around 300 K, it is hardly surprising that it is ubiquitous in the chemistry of living systems.

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