

Entropy–Enthalpy Compensation in Solvation and Ligand Binding Revisited

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The phenomenon of entropy–enthalpy compensation, an empirical observation that in many chemical processes the change in enthalpy is partially compensated by a corresponding change in entropy, resulting in a smaller net free energy change, has been widely documented.^{1–7}

In this paper, we address the role of entropy–enthalpy compensation in the study of relative free energies of solvation and relative free energies of binding and address some issues regarding this subject in the literature.

Relative free energy in this context measures the change in free energy caused by replacing one molecule with another during thermodynamic cycles involving either solvation or ligand binding. In this process, the microscopic interactions between the molecules are effectively transformed producing a measurable change of thermodynamic properties. Such transformations, when carried out on a computer by free energy perturbation simulations, have been dubbed “computational alchemy”.^{8–12}

The enthalpy change measures a change in the strength of the interactions between molecules while the entropy change measures a change in the order of the system. It is more difficult, however, to interpret free energy changes. Invariably, in fact, the analysis of free energy changes must involve the analysis of the relative importance of the corresponding enthalpy and entropy changes.^{5,6,13–15}

The phenomenon of entropy–enthalpy compensation agrees with our intuition that a stronger interaction between molecules will also result in a reduction of the configurational freedom of the system and thus a reduction of the entropy. Correspondingly, weaker molecular interactions will produce a looser molecular association and an increase of the entropy.

The physical basis for entropy–enthalpy compensation is so intuitively obvious that this phenomenon is sometimes considered to be a thermodynamic requirement. In particular, the process of designing molecules that optimize properties, such as solubility or free energy of ligand binding, is often impeded by the fact that changes directed to strengthen the association of the solute with the solvent, or the ligand to the host, are accompanied by a compensating reduction of the entropy, resulting in a small change in free energy (that sometimes is not even in the expected direc-

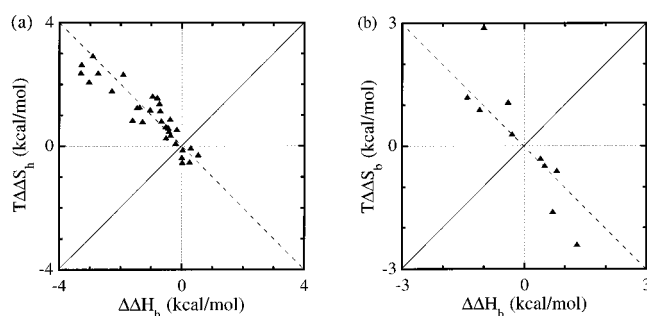


Figure 1. (a) Experimental relative entropy of hydration ($T\Delta\Delta S_h$) versus relative enthalpy of hydration ($\Delta\Delta H_h$) for a series of entropy–enthalpy noncompensating solute pairs and (b) experimental relative entropy of binding ($T\Delta\Delta S_b$) versus relative enthalpy of binding ($\Delta\Delta H_b$) for a series of entropy–enthalpy noncompensating ligand pairs. The full lines bisecting the upper right and lower left quadrants correspond to perfect entropy–enthalpy compensation, and the dashed lines bisecting the upper left and lower right quadrants correspond to perfect entropy–enthalpy reinforcement. See Tables 1 and 2 for a list of pairs and corresponding relative thermodynamic data.

tion).^{16,17} As we note in this letter, however, there are many exceptions to entropy–enthalpy compensation that can be exploited.

As an example of non-compensating behavior, in Figure 1a and Table 1 we show the differences of the experimental entropies of hydration $T\Delta\Delta S_h$ versus the corresponding differences in enthalpies of hydration $\Delta\Delta H_h$ for a series of solute pairs characterized by only the replacement of deletion/addition of at most one heavy atom.¹⁸ In Figure 1b and Table 2, we show a similar entropy–enthalpy reinforcing behavior for the relative entropies and enthalpies of binding of related peptide pairs to a host.^{17,19}

In Figures 1a and 1b the line bisecting the upper right and lower left quadrants corresponds to perfect compensation between entropy and enthalpy changes. The transformations that lie along this line are compensating to a high degree, and as a consequence, the corresponding free energy changes are small. The transformations shown, instead, lie on the line bisecting the upper left and lower right quadrants where enthalpy and entropy changes are similar in magnitude but opposite in sign; they add constructively to produce a free energy change approximately twice as large in magnitude. It has been argued^{13,20–22} that entropy–enthalpy compensation in some cases is an artifact of correlated errors in the measurements. Although the databases of relative thermodynamic quantities we constructed have been mostly compiled from data obtained from experimental techniques that do not suffer from such error correlation, only about 10% of the data showed clear noncompensating behavior. This shows that, even though compensating processes are more likely to be observed, the phenomenon of entropy–enthalpy compensation is not universal and thermodynamically necessary but is determined by a particular pattern of molecular interactions. The occurrence of entropy–enthalpy compensating phenomena in

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Table 1. Experimental Relative Free Energy of Hydration ($\Delta\Delta G_h$), Relative Entropy of Hydration ($T\Delta\Delta S_h$), and Relative Enthalpy of Hydration ($\Delta\Delta H_h$) at 25 °C for Entropy–Enthalpy Noncompensating Solute Pairs

solute pair ^a		$\Delta\Delta G_h^b$	$\Delta\Delta H_h^b$	$T\Delta\Delta S_h^b$
methane	→ ethene ^c	-0.73	-0.37	0.36
	→ fluoromethane ^c	-2.22	-1.04	1.18
ethane	→ fluoromethane ^c	-2.39	-0.81	1.58
	→ chloroethane ^c	-2.46	-1.61	0.85
	→ bromomethane ^c	-2.65	-1.38	1.27
	→ iodomethane ^c	-2.72	-1.47	1.25
ethene	→ fluoromethane ^c	-1.49	-0.67	0.82
ethyne	→ 1-propyne ^c	-0.29	-0.20	0.09
	→ cyclopropane ^c	0.76	0.26	-0.51
propane	→ 2-methylpropane ^c	0.36	0.00	0.36
	→ 2-methyl-1-propene ^c	-0.79	-0.52	0.27
	→ chloroethane ^c	-2.58	-0.96	1.63
	→ acetonitrile ^c	-5.84	-2.91	2.93
1-propene	→ butane ^c	0.81	0.54	-0.27
	→ 2-propanone ^c	-5.12	-3.03	2.09
	→ propanenitrile ^c	-5.11	-2.74	2.37
1-propyne	→ 1-butyne ^c	0.14	0.03	-0.12
	→ 1-buten-3-yne ^c	0.35	0.29	-0.05
cyclopropane	→ 1-propyne ^c	-1.05	-0.45	0.60
	→ 1-butyne ^c	-0.91	-0.43	0.48
	→ 1-buten-3-yne ^c	-0.71	-0.16	0.54
butane	→ propanenitrile ^c	-5.92	-3.28	2.65
2-methylpropane	→ 2-methyl-1-propene ^c	-1.15	-0.52	0.63
1,3-butadiene	→ THF ^c	-4.08	-2.29	1.79
	→ 2-butanone ^c	-4.25	-1.92	2.33
hexane	→ cyclohexane ^c	-1.26	-0.38	0.87
cyclohexane	→ methylbenzene ^c	-2.11	-0.73	1.38
heptane	→ 4-methyl-2-pentanone ^c	-5.68	-3.30	2.38
1,3-dimethylbenzene	→ (1-methylethyl)benzene ^c	0.54	0.01	-0.52
propylbenzene	→ naphthalene ^c	-1.86	-0.71	1.15
(1-methylethyl)-benzene	→ naphthalene ^c	-2.09	-1.29	0.80

^a The numerical values reported correspond to the changes of thermodynamic quantities in the direction indicated. ^b In kcal/mol. ^c From ref 18.

Table 2. Experimental Relative Free Energy of Binding ($\Delta\Delta G_b$), Relative Entropy of Binding ($T\Delta\Delta S_b$), and Relative Enthalpy of Binding ($\Delta\Delta H_b$) for Entropy–Enthalpy Noncompensating Ligand Pairs

ligand pair ^{a,b}	host	temp ^f	$\Delta\Delta G_b^c$	$\Delta\Delta H_b^c$	$T\Delta\Delta S_b^c$
M13ANB → M13A ^d	ribonuclease S	5	2.3	0.7	-1.6
M13L → M13A ^d		15	3.7	1.3	-2.4
M13F → M13V ^d		20	-2.6	-1.4	1.2
M13L → M13A ^d		25	3.9	-1.0	2.9
2 → 1 ^e	pp60 ^c -src SH2	25	-1.5	-0.4	1.1
3 → 2 ^e		25	0.7	0.4	-0.3
9 → 5 ^e		25	1.4	0.8	-0.6
12 → 5 ^e		25	-0.6	-0.3	0.3
10 → 7 ^e		25	1.0	0.5	-0.5
12 → 9 ^e	25	-2.0	-1.1	0.9	

^a The numerical values reported correspond to the changes of thermodynamic quantities in the direction indicated. ^b Nomenclature of ligand peptides as in original references. ^c In kcal/mol. ^d From ref 19. ^e From ref 17. ^f Temperature in degrees centigrade.

biological systems, for instance, has been related to the properties of weak molecular interactions, particularly hydrogen bonding, near physiological temperature.⁷

The experimental measurements shown in Figure 1 seem, at first glance, to contradict the conclusions of a recent theoretical study by Qian and Hopfield.²³ They derived equations that show that the processes of varying temperature or volume of a system are entropy–enthalpy compensating. They also demonstrated that the changes of the entropy and the enthalpy of solvation in going from a constant pressure solvation process to a constant volume solvation process are entropy–enthalpy compensating. The values of the excess entropy and enthalpy of solvation, in fact, depend on the insertion conditions while the value of the excess free energy of solvation is independent of the insertion conditions.

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More interestingly, Qian and Hopfield derived equations for the infinitesimal changes of the entropy and enthalpy of solvation by varying the strength of the interaction potential and noticed that, in summing these two contributions to obtain the free energy change, a term related to the fluctuations of the potential energy is canceled and thus does not contribute to the free energy change. Other derivations of compensating terms have appeared in the literature.^{24–27} The process of varying molecular interactions, however, is intrinsically unlike performing a variation of temperature, volume, or insertion conditions. The factorization of the enthalpy and entropy in ways which identify a “compensating” contribution does not imply that the process is entropy–enthalpy compensating in the fundamental sense that the total enthalpy change and the total entropy change must make opposing contributions to the free energy change. Determination of whether the chemical transformations are entropy–enthalpy compensating in this sense requires an analysis of the magnitudes and signs of the terms which are common to the enthalpy and entropy relative to those which are not.

To provide a concrete statistical thermodynamics context for our analysis, we write the equations derived by Qian and Hopfield for the case of a particular variation of potential parameters, the partial charge dq_i on a solute site i (more generally, we can consider a thermodynamic transformation corresponding to a perturbation of any potential parameter):

$$dA = dq_i \bar{v}_i \quad (1)$$

$$dU = dq_i \left(\bar{v}_i - T \frac{\partial \bar{v}_i}{\partial T} \right) \quad (2)$$

$$-TdS = dq_i T \frac{\partial \bar{v}_i}{\partial T} \quad (3)$$

where dA , dU , and dS are, respectively, the changes of the Helmholtz free energy, internal energy, and entropy and \bar{v}_i is the average electrostatic potential (reaction field) at the site i . Even though the common term $T\partial\bar{v}_i/\partial T$ is canceled when summing eqs 2 and 3 to obtain eq 1, entropy–enthalpy compensation is not observed when \bar{v}_i and $T\partial\bar{v}_i/\partial T$ have the sign and $|\bar{v}_i| > |T\partial\bar{v}_i/\partial T|$.

The previous example stresses the fact that the occurrence of entropy–enthalpy compensation, although more likely (an increase in temperature will in general cause a decrease in the magnitude of the reaction field), is by no means required by thermodynamic laws. The compiled experimental data shown in Tables 1 and 2, for which, however, we still do not have a microscopic interpretation, clearly offer several examples of entropy–enthalpy reinforcing processes. We believe that the study of such non-compensating transformations can help to identify which aspects of the molecular interactions can be tuned to produce a change in which entropy and enthalpy reinforce each other to produce an even greater change in the free energy. In this regard, computer simulations can be helpful for developing a better understanding of the nature of the molecular interactions which control the magnitudes and signs of the non-compensating terms in the entropy and enthalpy relative to the compensating terms. Recent progress in the thermodynamic decomposition of hydration free energies by computer simulations has been reported by us.²⁸

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