

Entropy–enthalpy compensation and anticompensation: solvation and ligand binding

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Plots of ΔH° versus $T\Delta S^\circ$ are misleading and can suggest an apparent linear relationship (compensation) with a slope near to unity when ΔS° has been obtained from experimental ΔG° and ΔH° ; recently reported relationships with a slope of -1 in the fields of enzyme complexes and hydration processes are still more misleading and have arisen only by deliberately selecting the input data.

Linear dependences between enthalpy and entropy in a series of related reactions (isokinetic relationship) have been observed in various fields and have been the subject of many theoretical considerations.^{1,2} However, a regression or plot according to eqn. (1) presents non-trivial statistical problems. Neglecting these often leads to results^{2,3} which are totally at variance with the original experimental data.⁴

$$\delta\Delta H = \beta\delta\Delta S \quad (1)$$

In the notation used here, the symbol δ is the difference between a given reaction and the reaction used as reference and Δ is the difference between the products and reactants as usual. Both ΔH and ΔS may refer either to thermodynamics (ΔH° and ΔS°) or to kinetics (ΔH^\ddagger and ΔS^\ddagger). The slope β has dimension of temperature (isokinetic temperature). The problems and their solution depend on how ΔH and ΔS have been obtained.^{1,5} When the original experimental quantities are ΔH° (obtained for instance by calorimetry) and ΔG° (from equilibrium measurements),⁶ a plot according to eqn. (1) may yield a slope β near to the experimental temperature. One speaks about compensation^{2,4} since the contributions of ΔH° and of ΔS° to the resulting ΔG° are opposite. In a formal modification, eqn. (1a), the dimensionless slope (β/T) is near to unity.

$$\delta\Delta H = (\beta/T) T \delta\Delta S \quad (1a)$$

However, dependence with this slope means only that ΔG is nearly constant, a plot according to eqn. (1) or (1a) expresses in fact the dependence of ΔH on itself. A plot of ΔH vs. ΔG was recommended in these cases.⁷

In a recent communication,⁸ plots of $\delta\Delta H^\circ$ versus $T\delta\Delta S^\circ$ according to eqn. (1a) were reported for two series of reactions. In both, a regression line of a slope near to -1 was found. The conclusions were drawn⁸ that (a) there is a linear relation between enthalpy and entropy in both sets and (b) that a compensation of enthalpy and entropy^{2,4} is not a general feature since the present case is just an example of anti-compensation. The purpose of the present work is to prove that these conclusions are not right: (a) any plot of ΔH versus ΔS cannot be recommended when these two variables are *a priori* dependent by the procedure of their estimation and (b) the slope (β/T) equal to -1 is not a result of any natural law but has arisen by an arbitrary choice of data.

The first example, complex formation of various peptides with an enzyme, was thoroughly investigated^{9,10} by thermometric titration.¹¹ In this method, one obtains ΔG° and ΔH° simultaneously from a non-linear regression.¹² One can assume with a good approximation that their estimates are not intercorrelated, *i.e.* not statistically dependent from the procedure of their calculation.¹² Fig. 1(a) shows all data from one experimental study,⁹ concerning seven compounds at five

temperatures. No dependence is evident: ΔH° are more variable than ΔG° and depend rather more on temperature, still more strongly than on the reactant. In any case, it is evident that the choice of data into the correlation,⁸ eqn. (1a), was arbitrary. One has always withdrawn two data and plotted their difference. Four such pairs are shown by arrows in Fig. 1(a). Their position is suitable to obtain the slope $\beta/T = -1$ in eqn. (1a) but other points would yield different slopes. For instance, it would be sufficient to choose the same pair of compounds as in the uppermost example in Fig. 1(a) (points $\circ \rightarrow \Delta$) but at a different temperature (dashed arrow): instead of -1 a slope of $+0.61$ would be obtained in eqn. (1a).

The picture changes when one goes from the plot $\Delta H^\circ/\Delta G^\circ$ to the plot $\Delta H^\circ/T\Delta S^\circ$ [Fig. 1(b)]. Plots of this type may be misleading^{5,7} when ΔG° is almost constant, since they express mainly the dependence of ΔH° on itself. This is also the case in Fig. 1(b). The apparent correlation coefficient $R = 0.975$ expresses only this dependence. The slope $b = \beta/T$ is not significantly different from unity. In terms of eqn. (1), this means that the isokinetic temperature β is equal to the experimental temperature T . This was commonly assumed¹ as a proof that the isokinetic relationship is only apparent, although it is not a deciding proof in all cases.¹⁴ In the paper under criticism,⁸ the picture represented by Fig. 1(b) was not accepted as an (apparent or actual) dependence with unity slope but several particular pairs of points were taken off, yielding an opposite slope of -1 . As shown already in Fig. 1(a), selection of these points was arbitrary if not biased, and there is no physical reason for choosing just these points. The whole procedure⁸ of treating eqn. (1) is unique. The operator δ means commonly comparison with a reference object, reaction, or substrate but this reference is always common for all objects. Introducing this operator means shifting the origin of coordinates and has no effect on the statistics. In ref. 8, a particular

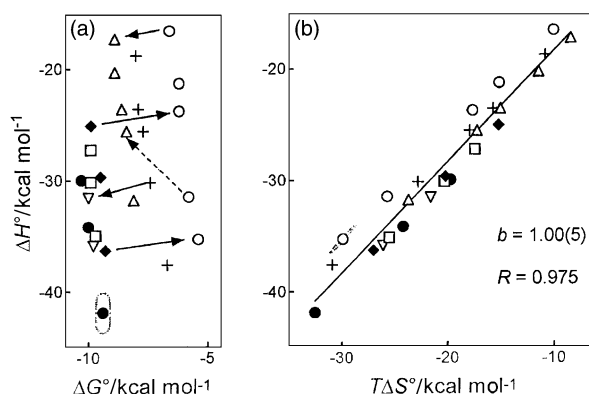


Fig. 1 (a) Experimental (ref. 9) enthalpy ΔH° versus Gibbs energy ΔG° of binding in a series of peptides with ribonuclease S: (\circ) peptide M13A, (Δ) M13ANB, (∇) M13V, (\square) M13I, (\blacklozenge) M13L, (\bullet) S15, ($+$) M13F. The arrows show the pairs of peptides selected in ref. 1; the broken arrow is an alternative possibility. (b) Plot of ΔH° versus $T\Delta S^\circ$ for the same set of data. The experimental uncertainty is shown as an ellipse corresponding to $\pm 3\sigma$ at one point in each graph.

reference object is chosen in each case: one does not deal with the objects but with the arbitrarily selected pairs of objects.

The conclusion for this set of data is that there is no relationship between experimental ΔG° and ΔH° . The values of ΔH° are strongly dependent on temperature and it seems that their experimental uncertainty was somewhat underestimated.⁹ When one chooses arbitrarily two compounds, one can observe various slopes, even the reported⁸ value of -1 .

The second case⁸ concerns hydration enthalpies ΔH°_h and Gibbs energies ΔG°_h of simple organic compounds and is different in character. The two quantities have been obtained from independent experiments. From some 160 compounds listed in a review,¹⁵ 33 pairs were selected,⁸ again rather arbitrarily: some compounds were even chosen several times. In all pairs the first compound is simpler, the second may be considered as its derivative or analogue. However, the relation is not always evident. In Fig. 2(a) only these selected⁸ compounds are shown. In the whole set, there is no stochastic dependence of ΔH°_h and ΔG°_h but relationships are evident when one divides the compounds into classes; most evident is a group of O- and N-derivatives with large negative values of both ΔH°_h and ΔG°_h . Pairs of compounds compared were selected intentionally to obtain an increase in the two quantities in a ratio approximately $\delta\Delta G^\circ_h/\delta\Delta H^\circ_h = 2$; two such pairs are shown in Fig. 2(a) by arrows. Some of these choices were quite artificial and certain alternatives seem more natural (broken arrows) which would not produce the desired result. For instance, one cannot understand why cyclohexane should be compared with toluene (arrow $\odot \rightarrow \square$) instead of with benzene (broken arrow $\odot \rightarrow \square$) or cyclopropane with but-1-yne (arrow $\odot \rightarrow \nabla$) and not with prop-1-ene (broken arrow $\odot \rightarrow \Delta$). When the plot is transformed into a plot $\Delta H^\circ_h/T\Delta S^\circ_h$ [Fig. 2(b)], the groups of compounds are represented by approximate linear relationships which can be considered as a dependence of ΔH°_h on itself (slope near to +1). Arbitrary pairs of near points can be selected in this graph, giving a slope -1 , similarly one can select pairs with any other slope.

The conclusion concerning the hydration process is that there is a stochastic, not a linear dependence between ΔH°_h and

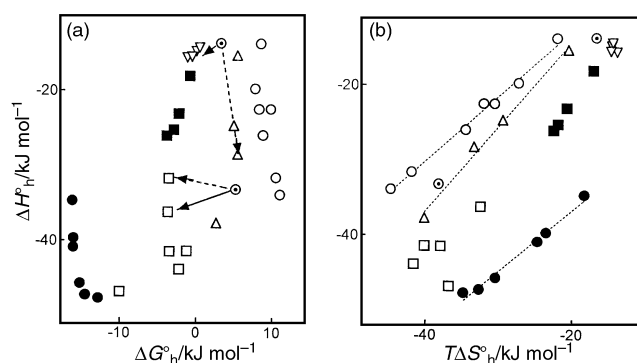


Fig. 2 (a) Experimental (ref. 15) hydration enthalpy ΔH°_h versus hydration Gibbs energy ΔG°_h : (○) alkanes, (⊙) cycloalkanes, (Δ) alkenes, (▽) alkynes, (□) aromatic hydrocarbons, (■) monohalogenomethanes, (●) oxygen and nitrogen derivatives. The arrows show some of the pairs selected in ref. 8, broken arrows indicate physically more justified choices. (b) The plot of ΔH°_h versus $T\Delta S^\circ_h$ for the same set of data. Dotted lines are regression lines for some subgroups.

ΔG°_h ; compounds can be divided into groups, in which greater negative values belong particularly to hydrophilic compounds. Values of ΔG°_h within each subset are nearly constant while ΔH°_h are more sensitive to small structural changes. For a given pair of compounds, any arbitrary slope can be found.

Examples analyzed here confirm the previous statement^{1,4,5} that the plots of ΔH° versus $T\Delta S^\circ$ are misleading and can suggest an apparent dependence without a physical meaning when ΔS° was obtained from ΔH° and ΔG° . Still more misleading may be comparing only pairs of reactions.⁸ Then even a slope of -1 can be obtained for selected pairs. Nevertheless, anti-compensation with a negative slope, not exactly -1 , exists and was detected in kinetics by exact statistical methods.¹⁴

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