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A Statistical Examination on the Compensation between the Enthalpies and Entropies Obtained from the Calorimetric Methods

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Abstract: The validity of the compensation between the enthalpies and entropies obtained from the calorimetric methods was statistically examined for the first time based on computer simulations. It turned out that the several claimed enthalpy-entropy compensations in literature based upon the calorimetric measurements were statistically correct. Interestingly, a linear relationship between the slopes and correlation coefficients of the $T\Delta S$-ΔH plots of different supramolecular systems was found, which indicated that the solvent reorganization was the physical origin of the compensation behavior.

Keywords: Calorimetry, enthalpy-entropy compensation, molecular recognition, solvent reorganization, statistics.

The widely observed enthalpy-entropy compensation in chemistry and biophysics is still in a state of great confusion, because the reported enthalpy-entropy correlations in literature were often found to be false[1-3]. This problem has promoted Exner[4]. Krug[5], Linert[6], and others to develop some statistical methods to examine the compensation between the enthalpies and entropies obtained from the indirect van't Hoff method. However, as pointed out by Connors in a recent review[7], it remains untouched whether or not the compensation was true between the enthalpies and entropies obtained from the direct calorimetric methods, which have been extensively documented recently especially in the field of molecular recognition[8-9].

In the present study, a statistical examination was performed for the first time on the compensation between the enthalpies and entropies obtained from calorimetric methods. Five typical supramolecular systems were addressed, *i.e.* cyclodextrins, crown ethers, glymes, cryptands, and antibiotics.

Methods

The experimental enthalpies and entropies were taken from ref 10-12. Reasonably, the relative error of the experimental enthalpy (ΔH_{exp}) was chosen as 15%. For simplicity, the possibility that the true enthalpy (ΔH_{true}) equaled to any number within the range ($\Delta H_{exp} \times (1-15\%)$, $\Delta H_{exp} \times (1+15\%)$) was supposed to be the same. Under this assumption, the true enthalpy of every host-guest complex was generated automatically by the computer. The same data-processing method was applied to the generation of

ΔS_{true} of every complex. After all the true enthalpies and entropies were generated, the standard linear regression was performed between the true enthalpies and entropies according to the equation $T\Delta S = B + A \times \Delta H$, from which the regression parameters, including the slope, intercept, and correlation coefficient, were obtained.

The above procedure was repeated 100,000 times by the computer. After the one million rounds, the average slope (A), intercept (B), and correlation coefficient (R) of the TΔS-ΔH plot were obtained. Their standard deviations, *i.e.* δA, δB, and δR, were also calculated.

Results and Discussion

Table 1 summarized the average slope (A), intercept (B), correlation coefficient (R), and their standard deviations δA, δB and δR of the TΔS-ΔH plots for the several typical host-guest systems. Since in every system the number of data points was sufficiently large (sometimes as many as near one thousand) and one million rounds of simulation were performed, the calculated regression parameters should be accurate enough.

Table 1 The average slope A, average intercept B, average correlation coefficient R, and their standard deviations δA, δB, and δR, of the TΔS-ΔH plots.

System	A	δA	B	δB	R	δR	Note
α-Cyclodextrin	0.815	0.015	8.10	0.25	0.897	0.005	a
	0.79	-	8	-	0.90	-	b
β-Cyclodextrin	0.772	0.013	10.86	0.18	0.855	0.005	a
	0.80	-	11	-	0.89	-	b
γ-Cyclodextrin	0.923	0.032	14.70	0.50	0.884	0.012	a
	0.97	-	15	-	0.93	-	b
Modified cyclodextrin	0.981	0.020	17.01	0.40	0.978	0.002	a
	0.99	-	17	-	0.99	-	b
Crown ether	0.740	0.017	2.26	0.09	0.854	0.007	a
	0.76	-	2.4	-	-	-	b
Glyme/podand	0.828	0.057	2.02	0.42	0.897	0.023	a
	0.86	-	2.3	-	-	-	b
Cryptand	0.495	0.025	3.93	0.18	0.694	0.020	a
	0.51	-	4.0	-	-	-	b
Antibiotic	0.936	0.067	5.46	0.34	0.897	0.019	a
	0.95	-	5.6	-	-	-	b

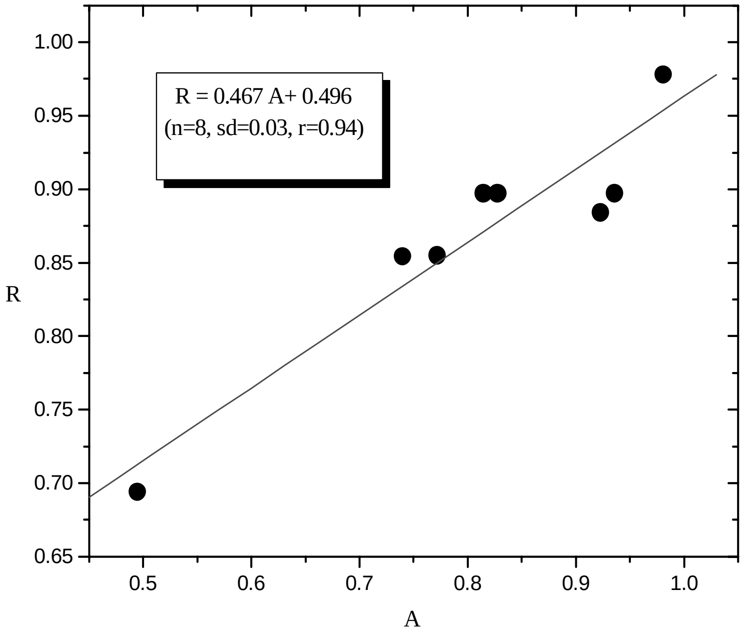
a: values from this study. b: values from the literature

From **Table 1**, it could be seen that the average values of the regression parameters obtained in the present study were similar to those reported in the literature[10-12]. It indicated that the experimental errors did not significantly affect the validity of enthalpy-entropy compensation. The fair-to-excellent correlation coefficients, which were obtained from a statistical method, convincingly confirmed that the compensation was a fact rather than an artifact in molecular recognition. This conclusion was important; for it was the first time that the validity of the compensation between the enthalpies and entropies from calorimetric measurements was verified statistically. Also, the observation of the compensation in substantially different host-guest systems indicated that the compensation was not a coincidence but a real extra-thermodynamic relationship, which hence should have its own physical origin.

However, from **Table 1** it could be seen that the standard deviations of the regression parameters were nontrivial. Sometimes, *e.g.* in the glyme/podand and antibiotic systems, the deviations in the slopes were so great that the ranges of these regression parameters actually overlapped with each other. Thus, to be cautious was advisable in comparing the parameters of different compensation plots.

Interestingly, it could be seen from **Table 1** that the higher the slope, the higher the correlation coefficient of the TΔS-ΔH plot. This trend could also be revealed by the plot of A *vs.* R, which was basically a straight line. (See **Figure 1**)

Figure 1 The plot of the average slope A *vs.* the average correlation coefficient R of the TΔS-Δ*H* plots of several host-guest systems.



The reason for the above correlation might be the different extents of solvent reorganization and different magnitudes of solvent-solute interaction in different host-guest complexation processes. As demonstrated in recent studies[13-14], the solvent reorganization involved in the molecular recognition was a compensating process, whose enthalpy and entropy exactly offset each other. However, the solvent-solute interaction for the host as well as the guest molecules was not a compensating one, and a larger solvent-solute interaction usually led to a worse overall enthalpy-entropy compensation. Herein, it was obvious that the extent of solvent reorganization should be in the order of crown ethers ≈ cryptand < cyclodextrins ≈ glyme < antibiotics, because the size of the host molecules increased in the same order. However, the solvent-solute interaction should favor crown ether and cryptand rather than cyclodextrins and antibiotics, because in the former systems the guest compounds were usually charged species. Thus, the extent and significance of the compensation, individually reflected by the slope and the correlation coefficient of the TΔS-ΔH plot, increased in the order of crown ethers ≈ cryptand < cyclodextrins ≈ glyme < antibiotics.

Conclusions

The compensation between the enthalpies and entropies obtained from the calorimetric measurements was for the first time examined based on a statistical method. Two pieces of valuable information could be generated from the study, *i.e*.

1. The compensation between the enthalpies and entropies obtained from calorimetric methods was statistically correct for the several reported cases in the field of molecular recognition. Thus, it seemed that it should be more important to investigate the physical origin of the compensation effect than to debate whether or not the compensation was true.
2. There was a monotonic relationship between the slopes and correlation coefficients of the TΔS-ΔH plots of different host-guest systems. It indicated that solvent reorganization was the physical origin of the above observed compensation effects.

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References

1. R. Lumry, S. Rajender, *Biopolymers,* **1970**, *9,* 1125.
2. J. D. Dunitz, *Chem. Biol.,* **1995**, *2,* 709.
3. A. Cooper, *Curr. Opin. Chem. Biol.,* **1999**, *3,* 557.
4. O. Exner, *Prog. Phys. Org. Chem.,* **1973**, *10,* 411.
5. R. R. Krug, W. G. Hunter, R. A. Grieger, *J. Phys. Chem.,* **1976**, *80,* 2335.
6. W. Linert, R. F. Jameson, *Chem. Soc. Rev.,* **1989**, *18,* 477.
7. K. A. Connors, *Chem. Rev.,* **1997**, *97,* 1325.
8. For examples, see: (a) C. Z. Wang, Z. A. Zhu, W. J. Ruan, Y. Liu, S.-K. Yan, R. T. Chen, *Chem. J. Chin. Univ.,* **1999**, *20,* 1509. (b) Q. X. Guo, X. Q. Zheng, X. Q. Ruan, S. H. Luo, Y. C. Liu, *J. Inclu. Phenom.,* **1996**, *26,* 175. (c) Y. Liu, H. Wang, Z. H. Zhang, B. Z. Tian, S. Huang, *J. Inclu. Phenom.,* **1999**, *34,* 187.
9. For a review, see: Y. Inoue, T. Wada, *Adv. Supramol. Chem.,* **1997**, *4,* 55.
10. Y. Inoue, T. Hakushi, *J Chem Soc Perkin 2,* **1985**, 935.
11. Y. Inoue, Y. Liu, L. H. Tong, B. J. Shen, D. S. Jin, *J. Am. Chem. Soc.,* **1993**, *115,* 10637.
12. M. V. Rekharsky, Y. Inoue, *Chem. Rev.,* **1998**, *98,* 1875.
13. (a) E. Grunwald, C. Steel, *J. Am. Chem. Soc.,* **1995**, *117,* 5687. (b) E. Grunwald, *Thermodynamics of molecular species,* John Wiley & Sons, New York, **1997**, pp120-136.
14. (a) L. Liu, C. Yang, Q. X. Guo, *Chin. Sci. Bull.,* **2000**, *45,* 1476. (b) L. Liu, C. Yang, Q. X. Guo, *Biophys. Chem,* **2000**, *84,* 239.

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