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Enthalpy–Entropy Compensation of Cyclodextrin Complexation with Different Classes of Substrates

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In this study, it was found that in the molecular recognition of cyclodextrins, the guest compounds fall clearly into different classes according to the behavior of enthalpy–entropy compensation. Good enthalpy–entropy compensation takes place when the substrates are hydrophobic, whereas poor or no enthalpy–entropy compensation occurs when the substrates are relatively hydrophilic. A thermodynamic theory is proposed to explain the behaviors, and it is suggested that solvent molecular reorganization constitutes the physical origin of the enthalpy–entropy compensation in cyclodextrin complexation.

Enthalpy–entropy compensation (EEC) is a phenomenon in which a change in enthalpy is offset by a corresponding change in entropy, resulting in a smaller net free-energy change.[1] Though it has been widely observed in many fields of chemistry and biophysics, the details and origin of the compensation remains poorly understood.[2]

Recently, EEC in the field of molecular recognition is causing considerable interest.[3] Among the many systems, the inclusion complexation of cyclodextrins (CD) is especially interesting because (1) the physical image of CD complexation is relatively clear and (2) the thermodynamic data of CD complexation are relatively easy to obtain.[4] Based on a systematic study, Inoue has suggested that the slope and intercept of an enthalpy–entropy (ΔH–$T\Delta S$) plot could be quantitative measures of the conformational change and the extent of desolvation upon complexation.[5,6]

However, some details remain to be studied concerning the EEC of CD complexation.[7] In 1989, Linert found that different groups of guest compounds exhibited different extents of EEC, which was explained as the result of different inclusion mechanisms.[8] Later, Gelb and Alper noticed that though CD complexes with large substrates showed good EEC, some small or ionic substrates significantly deviated from the compensation line.[9] Recently, Inoue also mentioned the EEC of CD complexation with different classes of substrates. It was found that compensation was evident when the individual classes of substrates were considered, but did not hold when the various classes of ligands were considered collectively.[10]

Herein, the EEC of CD complexation with different classes of substrates is systematically studied. The classification is based on the properties of the substrates; it turns out that substrates with different hydrophobicity exhibit different types of EEC. A thermodynamic theory is proposed to explain the observed behaviors.

Materials and Results

The thermodynamic data of CD complexation in aqueous solution at 298 K are taken from Ref. 6, which are divided into the following classes according to the properties of the substrates: (1) ionic organic substrates bearing one or more charges; (2) neutral organic substrates; (3) highly hydrophilic organic substrates, including amines, alcohols, and acids, bearing no more than six carbon atoms; (4) highly hydrophobic substrates including benzene, naphthalene, pyrene, anthracene, and insoluble esters; (5) ionic inorganic substrates. Only the classes with not less than 10 members are considered to ensure statistical meaning of the results. In fact, because more than half of the classes contain more than 50 members, it is expected that the influence of the experimental errors is reasonably small. An enthalpy–entropy regression was performed for each class; the results are compiled in Table 1. Notably, because most of the thermodynamic data in Ref. 6 were obtained from direct calorimetric measurements, it is not necessary to worry about any possible false compensation between the van't Hoff enthalpy and entropy.[11]

From Table 1, it can be seen that the classes with a regression correlation coefficient larger than 0.98 include class 4 (0.99), 8 (0.98), and 16 (0.98). They all correspond to CD complexation wigh highly hydrophobic organic substrates. The slopes of the ΔH–$T\Delta S$ plots in these classes are also near to unity (1.02, 0.95, and 0.98, respectively). Thus, the compensation in these cases is very good.

Those classes with a regression correlation coefficient larger than 0.90, but smaller than 0.98, include class 2 (0.94), 6 (0.90), 10 (0.96), 12 (0.97), 14 (0.93), and 15 (0.91). Except for class 15, they correspond to CD complexation with neutral organic compounds, most of which are fairly hydrophobic. The slopes of the ΔH–$T\Delta S$ plots in the classes are around unity (0.86 for class 2, 0.80 for class 6, 0.90 for class 10, 0.99 for class 12, and 0.91 for class 14). Thus, the compensation in these cases is fair.

The regression correlation coefficients in the remaining

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Table 1. Slopes and Correlation Coefficients of the ΔH–$T\Delta S$ Plots for the Cyclodextrin Complexation with Different Classes of Substrates in Aqueous Solution at 298 K[a)]

Class	Cyclodextrins	Substrate	Size of the class	Slope	Correlation coefficient
1	α	Ionic	173	0.76	0.88
2	α	Neutral	293	0.86	0.94
3	α	Highly hydrophilic	92	0.72	0.87
4	α	Highly hydrophobic	10	1.02	0.99
5	β	Ionic	150	0.65	0.78
6	β	Neutral	281	0.80	0.90
7	β	Highly hydrophilic	23	0.82	0.88
8	β	Highly hydrophobic	24	0.95	0.98
9	γ	Ionic	27	0.77	0.89
10	γ	Neutral	13	0.90	0.96
11	Modified	Charged	50	0.82	0.93
12	Modified	Neutral	87	0.99	0.97
13	All	Ionic	400	0.78	0.87
14	All	Neutral	674	0.91	0.93
15	All	Highly hydrophilic	115	0.80	0.91
16	All	Highly hydrophobic	38	0.98	0.98
17	All	Ionic Inorganic	12	0.35	0.56

a) The data were taken from Ref. 6.

classes are low. The slopes of the ΔH–$T\Delta S$ plots are also far from unity. Thus, poor or no EEC occurs in these classes, which correspond to CD complexation with relatively hydrophilic compounds. Notably, class 17 includes all of the ionic inorganic substrates. In this case, the correlation coefficient is 0.56, and the slope of the ΔH–$T\Delta S$ plot is only 0.35.

In short, fair-to-good EEC takes place in CD complexation with hydrophobic substrates, whereas poor-or-no EEC occurs in CD complexation with relatively hydrophilic substrates.

Discussion

1. Theory of Enthalpy–Entropy Compensation. EEC has been in a state of confusion for many years due to the lack of a good explanation. Although many theories have been proposed, few of them have been widely accepted.[12] Recently, Grunwald proposed a theory of EEC in which solvent reorganization is suggested to be the physical origin of compensation.[13] In our previous work, this theory was successfully modified to describe protein unfolding.[14]

Herein, a theoretical model based on the concept of solvent reorganization is strictly developed for the EEC in CD complexation. Because CD complexation usually takes place in water, the following theoretical model will focus on water molecule reorganization. However, it should be mentioned that this theoretical model does not rely on any specific property of water and, therefore, could be easily modified and applied to any other solvent system.

Considering that there are certain amounts of CD and substrate in a dilute aqueous solution, there are seven distinguishable species in equilibrium:[15] i.e. X/w, Y/w, XY/w, W/x, W/y, W/xy, and W/w. The capital letters stand for the water molecules (W), cyclodextrin (X), substrate (Y), and their complex (XY). The lower-case letters immediately following describe the environmental constraint sensed by the species. For example, W/w describes a water molecule in bulk aqueous solution, and is hence surrounded solely by water, whereas W/x describes the water molecules in the hydration shell of a CD molecule, and hence contacting that molecule.

The enthalpy of the solution can be written as

$$\begin{aligned} H = {} & n_{X/w}h_{X/w} + n_{Y/w}h_{Y/w} + n_{XY/w}h_{XY/w} + n_{W/w}h_{W/w} \\ & + n_{W/x}h_{W/x} + n_{W/y}h_{\mathrm{W}/y} + n_{W/xy}h_{W/xy}, \end{aligned} \tag{1}$$

where h represents the partial molar enthalpy, and n the quantities of the species.

Considering the CD complexation undergoes a sequence of quasistatic process, on the basis of Gibbs–Duhem's equation and the fact that $dn_{W/x} + dn_{W/y} + dn_{W/xy} + dn_{W/w} = dn_W = 0$, we have[14]

$$\begin{aligned} \Delta H = \int dH = {} & \int (h_{X/w}dn_{X/w} + h_{Y/w}dn_{Y/w} + h_{XY/w}dn_{XY/w}) \\ & + [(h_{W/x} - h_{W/w})dn_{W/x} + (h_{W/y} - h_{W/w})dn_{W/y} \\ & + (h_{W/xy} - h_{W/w})dn_{W/xy}], \end{aligned} \tag{2}$$

Similarly, the entropy and free energy changes in the complexation are

$$\begin{aligned} \Delta S = \int dS = {} & \int (s_{X/w}dn_{X/w} + s_{Y/w}dn_{Y/w} + s_{XY/w}dn_{XY/w}) \\ & + [(s_{W/x} - s_{W/w})dn_{W/x} + (s_{W/y} - s_{W/w})dn_{W/y} \\ & + (s_{W/xy} - s_{W/w})dn_{W/xy},], \end{aligned} \tag{3}$$

$$\begin{aligned} \Delta G = \int dG = {} & \int (\mu_{X/w}dn_{X/w} + \mu_{Y/w}dn_{Y/w} + \mu_{XY/w}dn_{XY/w}) \\ & + [(\mu_{W/x} - \mu_{W/w})dn_{W/x} + (\mu_{W/y} - \mu_{W/w})dn_{W/y} \\ & + (\mu_{W/xy} - \mu_{W/w})dn_{W/xy}], \end{aligned} \tag{4}$$

where s and μ represent the partial molar entropy and chemical potential, respectively.

Interestingly, because the solution remains in a thermodynamic equilibrium during every quasistatic process, the following chemical potentials are always equal:

$$\mu_{W/w} = \mu_{W/x} = \mu_{W/y} = \mu_{W/xy}. \tag{5}$$

Therefore, the last three terms in the free-energy change actually disappear, i.e.

$$\Delta G = \int (\mu_{X/w} dn_{X/w} + \mu_{Y/w} dn_{Y/w} + \mu_{XY/w} dn_{XY/w}).$$

This means that the corresponding three terms in the enthalpy and entropy changes compensate each other, i.e.

$$\begin{aligned}&\int [(h_{W/x} - h_{W/w}) dn_{W/x} + (h_{W/y} - h_{W/w}) dn_{W/y} \\ &\qquad\qquad + (h_{W/xy} - h_{W/w}) dn_{W/xy}] \\ &= T \int [(s_{W/x} - s_{W/w}) dn_{W/x} + (s_{W/y} - s_{W/w}) dn_{W/y} \\ &\qquad\qquad + (s_{W/xy} - s_{W/w}) dn_{W/xy}].\end{aligned}$$

2. Knowledge from the Theory. On the basis of the above model, the enthalpy and entropy changes of CD complexation can be divided into two portions: the non-compensated one and the compensated one.

The non-compensated portion ($\int (h_{X/w} dn_{X/w} + h_{Y/w} dn_{Y/w} + h_{XY/w} dn_{XY/w})$) is related to the reactants (X and Y) and product (XY), themselves. In the portion, the values of $h_{X/w}$, $h_{Y/w}$, and $h_{XY/w}$ are determined by the interactions between the host and guest and their interactions with the environment. On the other hand, the compensated portion ($\int (h_{W/x} - h_{W/w}) dn_{W/x} + (h_{W/y} - h_{W/x}) dn_{W/y} + (h_{W/xy} - h_{W/w}) dn_{W/xy}$) is related to the reorganization of the water molecules (W/w, W/x, W/y, and W/xy) in the complexation. As the species with different chemical environments generally have different partial molar enthalpies (i.e. $h_{W/w} \neq h_{W/x} \neq h_{W/y} \neq h_{W/xy}$), this portion is usually nonzero. Nevertheless, the compensated portion disappears in ΔG because $\mu_{W/w} = \mu_{W/x} = \mu_{W/y} = \mu_{W/xy}$.

For simplicity, the above results can be expressed mathematically as $\Delta H = a + b$, $T\Delta S = c + b$, and $\Delta G = a - c$, in which a and c are the non-compensated portions, and b the compensated one. The variations of ΔH and ΔS among a series of reactions have the relationship: $\delta \Delta H = \delta(T\Delta S) + (\delta a - \delta c)$.

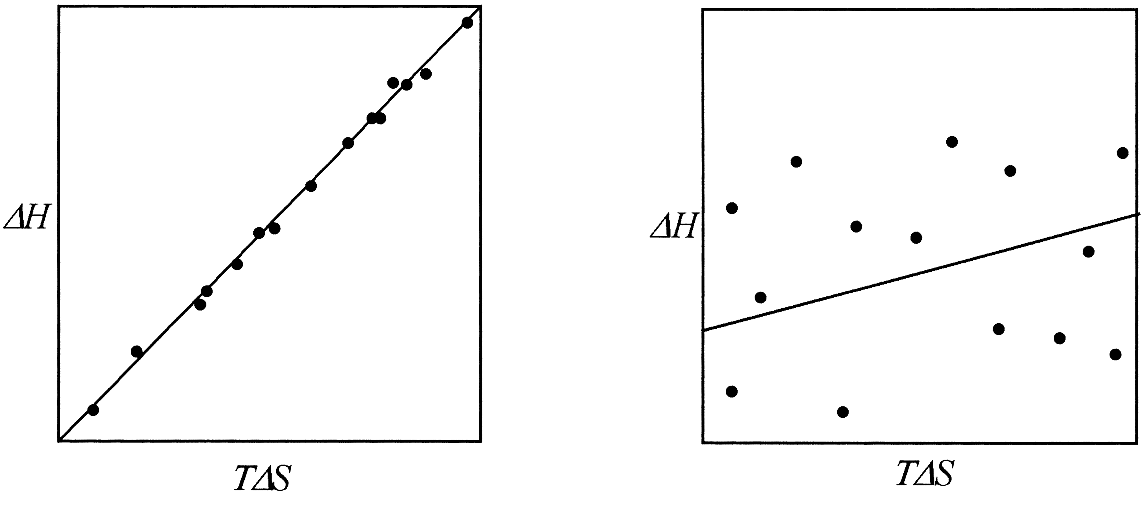
If in a series of reactions $|\delta b|$ is much larger than $|\delta a|$ and $|\delta c|$, ($|\delta a - \delta c|$) will be much smaller than $|\delta \Delta H|$ or $|\delta (T\Delta S)|$. Thus, plotting $\delta \Delta H$ vs. $\delta(T\Delta S)$ gives a straight line. The slope of the line and the correlation coefficient of the plot are both near to unity (Fig. 1a). Any variation in ΔH is nearly offset by a corresonding variation in ΔS, resulting in a good EEC.

On the other hand, if $|\delta a - \delta c|$ is equal to or greater than $|\delta b|$, $|\delta \Delta H|$ and $|\delta (T\Delta S)|$ will be comparable to or smaller than $|\delta a - \delta c|$. Then, there is poor relationship between $\delta \Delta H$ and $\delta(T\Delta S)$, if ($\delta a - \delta c$) varies scholastically among the series of reactions. Thus, poor or no EEC is exhibited, shown by a very poor correlation coefficient in the ΔH–$T\Delta S$ plot (Fig. 1b). The slope of the plot is not generally around unity, either.

In addition to the above two situations, when $|\delta b|$ is only modestly larger than $|\delta a|$ and $|\delta c|$, fair EEC will occur. The correlation coefficient is modest in the ΔH–$T\Delta S$ plot, and the slope of the plot can also be a little away from unity.

Indeed, all of the above three types of EEC have been observed in CD complexation, as shown before.

3. Enthalpy–Entropy Compensation in Cyclodextrin Complexation. First, let us examine a set of published data. The stabilization energies (ΔH_v) for the α-CD complexation with benzoic acid and phenol in vacuo were calculated to be -21.4 and -5.0 kJ/mol.[16] However, the enthalpy changes (ΔH_w) for the α-CD complexation with the same substrates in water were measured to be -42.5–-38.2 and -19.7–-7.5 kJ/mol.[6] Similarly, ΔH_v for the β-CD complexation with benzoic acid and phenol were both -1.67 kJ/mol, while ΔH_w were -32–-6.2 and -12.2–-11.0 kJ/mol. Obviously, ΔH_w is always much larger than ΔH_v and the variation in ΔH_w among different substrates is also much larger than that in ΔH_v. Because the difference between ΔH_w and ΔH_v can only be caused by the involvement of water molecular reorganization in the liquid-phase reaction, which includes the release of water molecules bound in the CD cavity and a collapsing of the water shell around the substrate, it can be concluded that the enthalpy change from the water molecular reorganization can



(a) (b)

Fig. 1. Theoretical ΔH–$T\Delta S$ plots for the good (a), and poor (b) enthalpy–entropy compensation. Herein, the plot between ΔH and $T\Delta S$ is equivalent to the plot between $\delta \Delta H$ and $\delta(T\Delta S)$.

dwarf the gas-phase host-guest interactions. Meanwhile, the free-energy change from the water molecular reorganization is always zero. Thus, it is understandable why EEC occurs in CD complexation.

However, it can be expected that for different classes of substrates, the magnitudes of the enthalpy and entropy changes contributed from the water molecular reorganization are different. Thus, the significance of EEC can be different for different classes. If the contribution from the water molecular reorganization is large, EEC will be good. If the contribution from the water molecular reorganization is small, EEC will be poor.

From the regressions, good EEC takes place in CD complexation with hydrophobic compounds, while poor EEC occurs in CD complexation with relatively hydrophilic ones. This observation can be rationalized if we consider the interaction between the substrate and water. As seen, the non-compensated portion of the enthalpy, $\int(h_{X/w}dn_{X/w} + h_{Y/w}dn_{Y/w} + h_{XY/w}dn_{XY/w})$, is determined by the interactions between the host and guest and their interactions with the environments. Thus, the interaction between the substrate and water can affect the value of the non-compensated portion. The stronger is the interaction, the greater is the influence. As a result, a stronger will lead to a larger value of the non-compensated enthalpy, which can unfavorably affect the linearity in the ΔH–$T\Delta S$ plot, as shown in Fig. 1b. Therefore, a larger interaction between the substrate and water disfavors the occurrence of compensation. The more hydrophilic is the substrate, the worse is the compensation. When the interaction between the substrate and water is very strong, like that in CD complexation with ionic inorganic substrates, the non-compensated portion becomes so large that no EEC is exhibited at all.

Admittedly, the present theory of enthalpy–entropy compensation does not mention the driving forces of cyclodextrin complexation, which have been discussed before in other places.[17] However, because enthalpy–entropy compensation is not only observed in cyclodextrin systems, any theory of enthalpy–entropy compensation should not rely heavily on the particular driving forces of cyclodextrin complexation. Moreover, it is known that the free energy of cyclodextrin complexation does not have any simple relationship with the corresponding enthalpy or entropy. Therefore, the driving forces of complexation cannot be used to explain the compensation. In fact, the cause of enthalpy–entropy compensation, mentioned as solvent molecule reorganization in the present paper, does not contribute to the free energy at all and, therefore, is not related to any driving force leading to complexation.

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