Estimation of Thermodynamic Parameters on Enantioselective Complexation Equilibria by Temperature-dependent FAB Mass Spectrometry

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The relative thermodynamic parameters, $\Delta\Delta G^{\circ}_{\mathrm{enan(R/S)}}$, $\Delta\Delta H^{\circ}_{\mathrm{enan(R/S)}}$, and $\Delta\Delta S^{\circ}_{\mathrm{enan(R/S)}}$, on the enantioselective host–guest complexation equilibria were estimated easily using the temperature-dependent FAB mass spectrometry coupled with the enantiomer labeled guest method.

Molecular recognition in solution, in particular chiral recognition is one of the fundamental and significant processes in living systems. Thermodynamic analyses of the host–guest complexation equilibria are very important in understanding and clarifying the essential properties of the molecular recognition phenomena. Thermodynamic parameters of the enantioselective complexation equilibria between various chiral hosts and guests have been estimated to clarify the mechanisms of the molecular recognitions, until now.[1,2]

We have proposed an evaluation method of the chiral recognition ability of chiral hosts toward chiral guests using FAB mass spectrometry (3-nitrobenzyl alcohol matrix, NBA), and investigated the chiral recognition of various hosts such as chiral crown ether derivatives[3] and oligosaccharide derivatives.[4] In the method, the FAB mass spectra of the NBA solution involving the chiral host (H) and the excess chiral guest (G_R, $G_{S\text{-d}n}$, n: number of deuterium atoms), which is an equimolar mixture of isotopically labeled and unlabeled enantiomers, are measured to observe two diastereomeric host–guest complex ions. The relative peak intensity $[I(H + G_R)^+/\,I(H + G_{S\text{-d}n})^+ = I_R/I_{S\text{-d}n}]$ is corresponding to the chiral recognition ability of the host toward the guest. Interestingly, the $I_R/I_{S\text{-d}n}$ values in the method were in good agreement with the ratio of association constants (K_R/K_S) in solution such as chloroform.[3,4] Recently, there appeared various mass spectrometry methods for chiral recognitions. However, most of them are based on the kinetic method handling the dissociation of the respective complexes by the collision in gas phase,[5–8] which are not suitable for the present evaluation of thermodynamic behaviors of the complexation in solution.

In this communication we report the successful estimation of the relative thermodynamic parameters of the enantioselective host–guest complexation equilibria on the basis of the $I_R/I_{S\text{-d}n}$ values at various temperatures in the FABMS method.

Permethylated oligosaccharide (**1**) (Chart 1)[4b] and isopropyl esters of amino acids were used as chiral host and guest, respectively. *S*-enantiomers of the guests were labeled with deuterium atoms (d_7). FABMS samples were prepared by mixing 20 µL of 0.2 M host in methanol, 40 µL of 0.67 M equimolar mixture of guest enantiomers in methanol, and 60 µL of NBA.[9] The thermally controlled FAB probe was altered to fix the sample solution on the tip during the measurement. Temperature of the probe was measured by a thermoelectric thermometer.

Typical temperature-dependent FAB mass spectra are shown in Figure 1 (guest, Val). The host–guest complex ion peaks are observed at m/z 1229, $(H + G_R)^+$ and 1236, $(H + G_{S\text{-d}n})^+$. The $I_R/I_{S\text{-d}n}$ values decreased with the rise of the temperature. The tendency was recognized in all case with the given guests. The decreasing of selectivity with raising temperature is one of the general behavior in molecular recognition.

A typical plotting of the logarithms of the $I_R/I_{S\text{-d}n}$ values against the reciprocal values of the absolute temperature ($1/T$) of the FAB probe is shown in Figure 2 (guest, Val). In all case

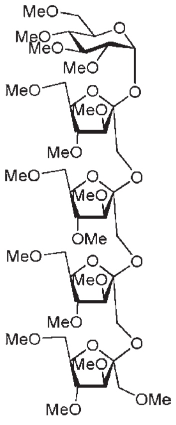

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Chart 1.

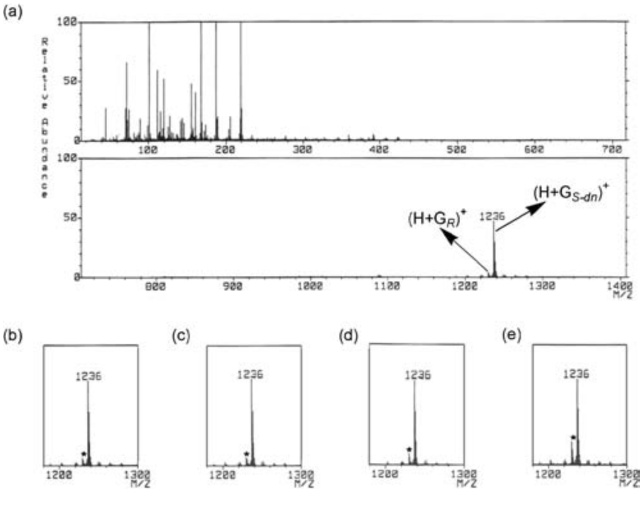

Figure 1. Typical FAB mass spectra. Host, **1**; guest, valine isopropyl ester hydrochloride (G_R:$G_{S\text{-d}7}$ = 1:1). (a) All real spectrum at 15 °C, (b) regional spectrum at 8 °C, (c) 15 °C, (d) 25 °C, and (e) 36 °C.

Table 1. Thermodynamic parameters on the enantioselective complexation equilibrium between host **1** and amino acid isopropyl ester hydroclorides (G_R:$G_{S\text{-d7}}$ = 1:1)

Guest	Ala	Val	Tle[b]	Met	Phe	
$\Delta\Delta G^\circ_{\text{enan(R/S)}}$[a] kJ·mol^{-1}	2 ± 0.5	4 ± 0.9	3 ± 1.3	3 ± 0.4	4 ± 0.7	2.7
$\Delta\Delta H^\circ_{\text{enan(R/S)}}$ kJ·mol^{-1}	17 ± 4.0	25 ± 4.5	21 ± 4.5	21 ± 5.0	13 ± 2.0	8.8
$\Delta\Delta S^\circ_{\text{enan(R/S)}}$ J·mol^{-1}·K^{-1}	54 ± 10	75 ± 15	54 ± 11	61 ± 12	31 ± 6	19
solvent	NBA	NBA	NBA	NBA	NBA	chloroform
method	FABMS	FABMS	FABMS	FABMS	FABMS	UV[c]

[a] $\Delta\Delta G^\circ_{\text{enan(R/S)}} = \Delta G^\circ_{\text{enan(R)}} - \Delta G^\circ_{\text{enan(S)}}$. [b] *tert*-Leucine(3-methylvaline)isopropyl ester hydrochloride. [c] The UV titration method. Ref. 4b.

with the given guests, good linear relationships were recognized (correlation coefficient, $R^2 = 0.85$–0.97).

Under the concentration conditions of excess guests for the host, the $I_R/I_{S\text{-d}n}$ values agreed approximately with the ratio of the K_R/K_S.[3,4] Therefore, the relationship is represented by Eq 1, where R is gas constant.

$$\Delta\Delta G^\circ_{\text{enan(R/S)}} = -RT\ln(K_R/K_S) \approx -RT\ln(I_R/I_{S\text{-d}n}). \quad (1)$$

Thermodynamic parameters are represented by the Eq 2.

$$\Delta\Delta G^\circ_{\text{enan(R/S)}} = \Delta\Delta H^\circ_{\text{enan(R/S)}} - T(\Delta\Delta S^\circ_{\text{enan(R/S)}}). \quad (2)$$

Then, using Eqs 1 and 2, 3 is derived.

$$\ln(I_R/I_{S\text{-d}n}) = -(\Delta\Delta H^\circ_{\text{enan(R/S)}}/R)(1/T) + T(\Delta\Delta S^\circ_{\text{enan(R/S)}}/R). \quad (3)$$

Therefore, $\Delta\Delta H^\circ_{\text{enan(R/S)}}$ and $\Delta\Delta S^\circ_{\text{enan(R/S)}}$ are calculated from the slope and the intercept of the fitted line. The $\Delta\Delta H^\circ_{\text{enan(R/S)}}$ and $\Delta\Delta S^\circ_{\text{enan(R/S)}}$ estimated on the basis of the $I_R/I_{S\text{-d}n}$ values in the FABMS method (NBA matrix) are summarized in Table 1. For the comparison, the thermodynamic parameters estimated on the basis of the K_R and K_S determined at various temperatures by the UV titration method are also described (guest, Phe; solvent, chloroform).[4b] The results by the FABMS method almost agreed with those in chloroform. Both $\Delta\Delta H^\circ_{\text{enan(R/S)}}$ and $\Delta\Delta S^\circ_{\text{enan(R/S)}}$ showed positive values, and the contribution of the enthalpy factors to chiral recognition was nearly the same degree as that of the entropy factors at 298 K. The fact suggests that the thermdynamic properties of the enantioselective complexation observed by FABMS are essentially parallel with that in solution. Therefore, the FABMS coupled with the enantiomer labeled guest method is a powerful tool for detecting chiral host–guest interactions in the host–guest complexation systems.

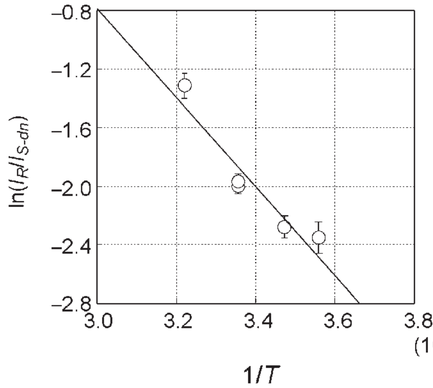

Figure 2. Plot of the logarithms of the $I_R/I_{S\text{-d}n}$ values against the reciprocal values of the absolute temperature ($1/T$). Host, **1**; guest, valine isopropyl ester hydrochloride (G_R:$G_{S\text{-d7}}$ = 1:1).

In conclusion, we have succeeded in the estimation of the relative thermodynamic parameters on the enantioselective complexation equilibria using the temperature dependent FAB mass spectrometry. This method will be expected to be one of the useful methods for studying chiral recognition in future because of the facile preparation of measuring samples and short-time measurements.

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9 FABMS measurement conditions: Instrument, a JEOL HX-100; mode, positive; accelerating voltage, 10 kV; mass range, m/z 100–2400; atom beam, Xe; emission current, 10 mA; ion source pressure, ca. 1–2×10^{-5} Torr; magnet scan rate, 10 s·scan^{-1}.

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