Chiral molecular recognition in electrospray ionization mass spectrometry

Masami Sawada,*[a] Yoshio Takai,[a] Takahiro Kaneda,[a] Ryuichi Arakawa,*[b] Masanori Okamoto,[c] Hidekazu Doe,[c] Takekiyo Matsuo,[d] Koichiro Naemura,*[e] Keiji Hirose[e] and Yoshito Tobe[e]

[a] *Materials Analysis Center, The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan*
[b] *Department of Applied Chemistry, Faculty of Engineering, Osaka University, Toyonaka 560, Japan*
[c] *Department of Chemistry, Faculty of Science, Osaka City University, Osaka 558, Japan*
[d] *Department of Physics, Faculty of Science, Osaka University, Toyonaka 560, Japan*
[e] *Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka 560, Japan*

Non-covalently bound complex ions detected by ESIMS are demonstrated as intermolecularly interacted (highly structured) host–guest complex ions on the basis of successful cross-chiral relationships (purely stereochemical grounds).

Much attention has been paid to non-covalently bound complexes detected by electrospray ionization (ESI) mass spectrometry (MS)[1–7] in the fields of organic chemistry and biochemistry because of their correspondence to solution-phase behaviour.[8,9] Since the ESI process does not involve any high-energy excitation process, one can often detect weakly bound complexes or associations in solution. Therefore, ESI mass spectrometric observations of macrocyclic host–guest complexes have been active and fundamental challenges.[10,11] However, it remains still unclear whether such a 1 : 1 complex ion detected by ESIMS, for example, a β-cyclodextrin–phenylalanine complex ion, is a structure-specific ion (highly stuctured host–guest complex ion) or a structure non-specific one (anomalous aggregate ion)[12–15] Here, on the basis of purely stereochemical aspects, we describe the first direct evidence that in the host–guest combination system of chiral crown ethers with chiral amino esters, structure specific host–guest complex ions are detected by ESIMS.

The chiral recognition of crown ethers toward amino esters is evaluated using the peak intensity ratio of the diastereomeric host–guest complex ions, $I[(H + G_R)^+]/I[(H + [^2H_3]G_S)^+]$ (abbreviated as IRIS), using fast atom bombardment (FAB) mass spectrometry coupled with the enantiomer-labelled (EL) guest method.[16] It is assumed that a given host–guest complex ion is highly structured due to multiple intermolecular interactions. In this case, if the (*R*)-host can complex the (*R*)-guest by a factor of 5.0 better than the (*S*)-guest (IRIS value = 5.0), the (*S*)-host which corresponds to the enantiomer of the (*R*)-host should complex the (*S*)-guest just by a factor of 5.0 better than the (*R*)-guest (IRIS value = 0.20). Consequently, if complex ions detected by ESIMS are highly structured, such a cross-chiral relationship eqn. (1) should hold for an enantiometic pair of given hosts.

$$(\mathrm{IRIS}_{(R)\text{-host}}) \times (\mathrm{IRIS}_{(S)\text{-host}}) = 1.0 \qquad (1)$$

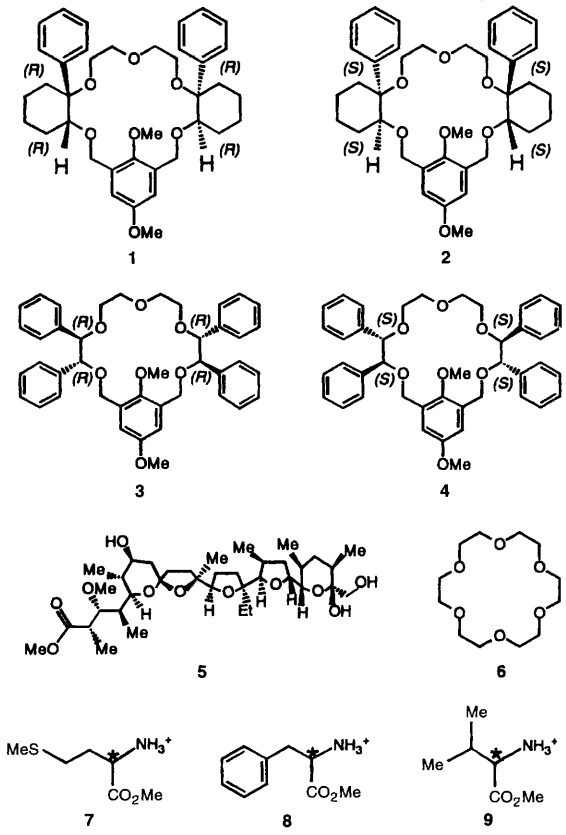
We used enantiomeric pairs of crown ether hosts (**1**, **2** and **3**, **4**)[16–18] and amino ester hydrochloride guests (**7–9**). Host **6** was chosen as a typical achiral crown ether host for control experiments. Here, a 1 : 1 mixture of an unlabelled (CH_3 ester) and a labelled (CD_3 ester) guest enantiomer was complexed with a target crown ether host. An ESIMS sample solution was prepared by mixing the two solutions. For example; (1) 200 ml of a 1 mmol dm^{-3} MeOH solution of a 1 : 1 mixture of (*R*)-**7** and (*S*)-[$^2H_3$]**7** guests, (2) 20 ml of a 1 mmol dm^{-3} MeOH solution of host **1**. A laboratory-made electrospray interface connected to a sector-type mass spectrometer (JEOL D300) was employed.[19] ESI conditions are flow rate 2 μl min^{-1}, electrospray voltage 3.5 kV, N_2 gas for desolvation at 70 °C, and voltage difference between the first and the second skimmers 40 V. The IRIS values are summarized in Table 1 and a typical ESI mass spectrum is shown in Fig. 1.

As seen in the Table, hosts **1** and **2** indicate clear chiral recognition behaviour toward the guests, and their IRIS values satisfactorily provide the cross-chiral relationship for each guest in each solvent [eqn. (2)].

$$(\mathrm{IRIS}_{(\text{host }\mathbf{1})}) \times (\mathrm{IRIS}_{(\text{host }\mathbf{2})}) = 1.0 \pm 0.1 \qquad (2)$$

Therefore, it is evidenced from purely stereochemical grounds that the complex ions detected by the positive ion ESIMS are intermolecularly interacted (highly structured) host–guest complex ions at least in the combinations of hosts **1**, **2** and guests **7**, **8**.

It is worthwhile to note the following two findings. One is that the IRIS value does not vary with solvent changes. The value is almost equal from aqueous MeOH to acetonitrile, supporting our previous prediction such that solvent effects on the chiral recognition are small (small solvent effects on $\Delta\Delta G_{enan}$).[16] Secondly IRIS value is much smaller than the



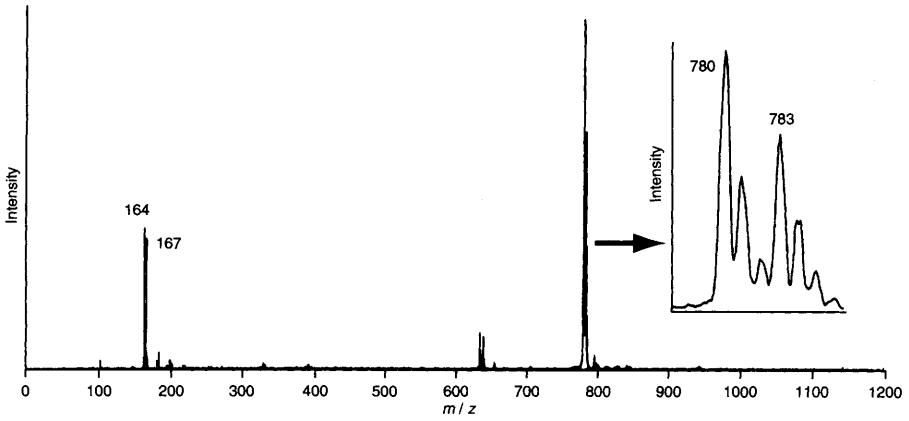


Fig. 1 ESI mass spectrum of host **1** with a 1 : 1 mixture of (*R*)-**7** and (*S*)-[$^2H_3$]**7** (CD_3 ester) guests (in MeOH). (*R*)-**7** and (*S*)-[$^2H_3$]**7** guest cations appear at *m/z* 164 and 167, and the corresponding host–guest complex cations with host **1** appear at *m/z* 780 and 783, respectively

Table 1 $I[(H + G_R)^+]/I[(H + [^2H_3]G_S)^+]$ values determined by the enantiomer labelled guest method in ESI mass spectrometry[a]

		Guest		
Host	Solvent	**7**	**8**	**9**
1	MeOH	1.47 (1.01)	1.36 (0.98)	1.13 (0.92)
	MeOH	1.9[b] (0.95)		
	MeCN	1.67[c] (1.07)		
	aq. MeOH(AcOH)[d]	1.53[e] (1.06)		
	MeOH–$CHCl_3$[f]	1.52 (1.03)		
2	MeOH	0.69 (1.01)	0.72 (0.98)	0.81 (0.92)
	MeOH	0.5[b] (0.95)		
	MeCN	0.64[c] (1.07)		
	aq. MeOH(AcOH)[d]	0.69[e] (1.06)		
	MeOH–$CHCl_3$[f]	0.68 (1.03)		
3	MeOH	1.22 (1.00)	1.06 (1.07)	1.24 (0.89)
4	MeOH	0.82 (1.00)	1.01 (1.07)	0.72 (0.89)
5	MeOH	0.86	0.98	0.89
6	MeOH	1.05	1.06	0.93
	MeOH–$CHCl_3$[f]	0.96		

[a] The IRIS values are evaluated by the corresponding peak intensity ratio. A value in parentheses shows the value of the cross-chiral relationship based on eqn. (1). Unless otherwise noted, [G] : [H] = 10 : 1 = 0.91 mmol dm^{-3}: 0.091 mmol dm^{-3}. [b] [G] : [H] = 1000 : 1 = 9.9 mmol dm^{-3} : 0.099 mmol dm^{-3}: data are less reliable than the others because of relatively smaller peaks of the complex ions, compared with those of the guest ions appeared. [c] [G] : [H] = 20 : 1 = 1.82 mmol dm^{-3} : 0.091 mmol dm^{-3}. [d] Solvent composition (vol%) : MeOH (96.5), H_2O (1.75), AcOH (1.75). [e] [G] : [H] = 10 : 1 = 0.88 mmol dm^{-3} : 0.88 mmol dm^{-3}. [f] Solvent composition (vol) : MeOH(10)–$CHCl_3$(1).

concentration ratio calculated from their thermodynamic competitive equilibrium in a given solution. For example, in the case of host **1** with guest **7**, the ratio of the ion concentrations generated, $\{[(H + G_R)^+]/[(H + G_S)^+]\}$, is assumed to be 5.0 in a MeOH–$CHCl_3$ (10 : 1) solution at 25 °C,[16] but the IRIS value was found to be 1.5 by ESIMS at ambient temperature. In the case of host **3** with guest **9**, the relevant value is assumed to be *ca.* 2.0, but the corresponding IRIS value was to be 1.2 by ESIMS: the reported data of K_R/K_S = 2.0/1.0 = 2.0 in a MeOH–$CHCl_3$ (10 : 1) solution for the complexation between host **3** and phenylglycine methyl ester ammonium ion[16] is tentatively used for calculations instead of guest **9**. These findings show that the IRIS value by ESIMS is substantially suppressed, which does not simply reflect the concentration ratio of the diastereomeric host–guest complex ions under given conditions in solution. This is considered as a reflection of dynamic processes involved in the electrospray ionization mechanism. Consequently, the results suggest that the minimum chiral recognition ability of $\Delta\Delta G_{enan} \geqslant 1.0$ kcal mol^{-1} (cal = 4.184 J), which corresponds to $K_R/K_S \geqslant 5$ (*K* is equilibrium constant in solution), may be required for the clear ESIMS detection of chiral recognition. This must be a quantitative criterion for practical applications in the future screening.

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