Chiral Recognition in Molecular Complexation for the Crown Ether–Amino Ester System. A Facile FAB Mass Spectrometric Approach

Masami Sawada,*[a] Yoshio Takai,[a] Hitoshi Yamada,[a] Takahiro Kaneda,[a] Kimiko Kamada,[b] Takashi Mizooku,[b] Keiji Hirose,[b] Yoshito Tobe[b] and Koichiro Naemura*[b]

[a] *The Institute of Scientific and Industrial Research, Osaka University, Mihogaoka, Ibaraki, Osaka 567, Japan*
[b] *Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan*

Various degrees of chiral recognition properties of chiral crown ether hosts toward amino acid ester guests are directly, easily and reliably evaluated by the enantiomer deuterium-labelled racemic guest method using conventional FAB mass spectrometry.

Chiral recognition in molecular host–guest complexations is one of the highlights in modern organic chemistry. Various chiral crown ethers have been synthesized and various degrees of chiral recognition have been achieved.[1–3] Until recently, many methods were used for determining chiral recognition of chiral crown hosts. Examples are extraction/NMR,[2] extraction/polarimetry,[2] transport,[4] membrane electrode,[5] calorimetry,[6] LC,[7] and UV[8,9] methods and so on. Mass spectrometry has been primarily uninformative for this purpose due to its lack of mass differences. In the diol dimerization system or related aggregation systems, there appeared a few reports of specific observations of the chirality effect in CI mass spectrometry[10–12] and in tandem FAB mass spectrometry,[13,14] *etc.*[15] Recently, in more highly structured host–guest complex systems, chiral recognition has been detected by mass spectrometry (MS). One is by FABMS in the dimethoxyphenylene crown systems[12,16,17] and the other is by FTICRMS (Fourier transform ion cyclotron resonance mass spectrometry) in the pyridino crown system.[18] However, the former treats two FAB mass spectra and the latter treats two equilibrium constants. Both approaches inherently require two successive measurements and comparisons and then, may be classified into the indirect methods.

Here we report the successful detection of chiral recognition in the host–guest complexations by a *direct* method using conventional FAB mass spectromety (positive mode). The method particularly uses a racemic guest which contains an isotopically labelled enantiomer.[10,11] This is the first success of the combination of the enantiomer labelled racemic guest method and the highly structured host–guest complex ion system. Diastereoisomeric host–guest complex ions produced by a chiral crown ether host (H) and an enantiomer labelled racemic guest (G) (for example, a 1:1 mixture of G_R and $[^2H_n]G_S$) have different masses and then, simultaneously appear as a pair of complex ion peaks $[(H + G_R)^+$ and $(H + [^2H_n]G_S)^+]$. Since the complex ions are identified by the aid of the isotope tag, both the degree and direction of the chiral recognition properties of hosts toward guests can be directly evaluated using the ratio value of the corresponding peak intensities observed in one spectrum as $I[(H + G_R)^+]/I[(H + [^2H_n]G_S)^+]$.

Compounds **1–3** were selected as the amino ester (CH_3 and CD_3 esters) guests. Compounds **4–8** were chosen as the chiral crown ether hosts,[8,12,16,17] **9**, **10** (monensin methyl ester) as the chiral acyclic hosts, and **11** (18-crown-6) as an achiral host for the control experiments. A typical FABMS sample solution was prepared by mixing the following three solutions: a 5 μl portion of a 0.30 mol dm^{-3} (total) MeOH solution of a 1 : 1 mixture of (*R*)-**1** (CH_3 ester) and (*S*)-[$^2H_3$] **1** (CD_3 ester), a 5 μl portion of a 0.05 mol dm^{-3} $CHCl_3$ solution of (*R,R,R,R*)-**4**, and 30 μl of the *m*-nitrobenzyl alcohol (noba) matrix. The peak intensity ratios of the corresponding complex ions in FABMS were obtained (Fig. 1), averaged ($n = 2$), and listed in Table 1. The stability of the ratio value with scan times for one measurement was, for example, statistically given as 1.74 ± 0.03 (standard deviation; $n = 26$; scans 10–35) for the (*R,R,R,R*)-**4** and **3** combination.

When the quantity, $I[(H + G_R)^+]/I[(H + G_S)^+]$, is larger than unity ($I/I > 1.0$), a host binds more strongly to an (*R*)-enantiomer guest. The larger the value, the higher the degree of chiral recognition. Alternatively, $I/I < 1.0$ shows that a host binds more strongly to an (*S*)-enantiomer guest. The unity ($I/I = 1.0 \pm 0.1$) value indicates the non-chiral recognition ability of a host. Since **11** is achiral, the I/I value should have to be unity. It should be pointed out that the values generated by the present direct method are in good agreement with those measured by the indirect method (previously called the RPI method)[12,16,17] within a range of ±0.1: no appreciable differences seem to be observed for the direct and indirect methods.

Table 1 lists the results of a survey of the chiral recognition properties of the hosts toward the guests employed. Host (*R,R,R,R*)-**4** exhibits the highest degree of (*R*)-enantiomer predominance toward guests **2** and **3** in the present experiments. Enantiomeric host (*S,S,S,S*)-**4** also has the highest (*S*)-enantiomer predominance as expected from a cross-chirality relationship (see Table 1, footnote). Host (*S,S*)-**6** shows relatively higher (*R*)-enantiomer selectivity, but host (*S,S*)-**8** switches the predominance-direction to a relatively lower but definitive (*S*)-enantiomer selectivity, probably due to different sites and groups of chiral barrier substituents attached to the crown ring. The (*S*)-enantiomer preference of host (*S,S,S,S*)-**7** appears only toward guest **1**, but clearly is absent toward guests **2** and **3**. Less effective hosts (*S,S,S,S*)-**5** and (*R,R,R,R*)-**9** provide very small complex ion peaks

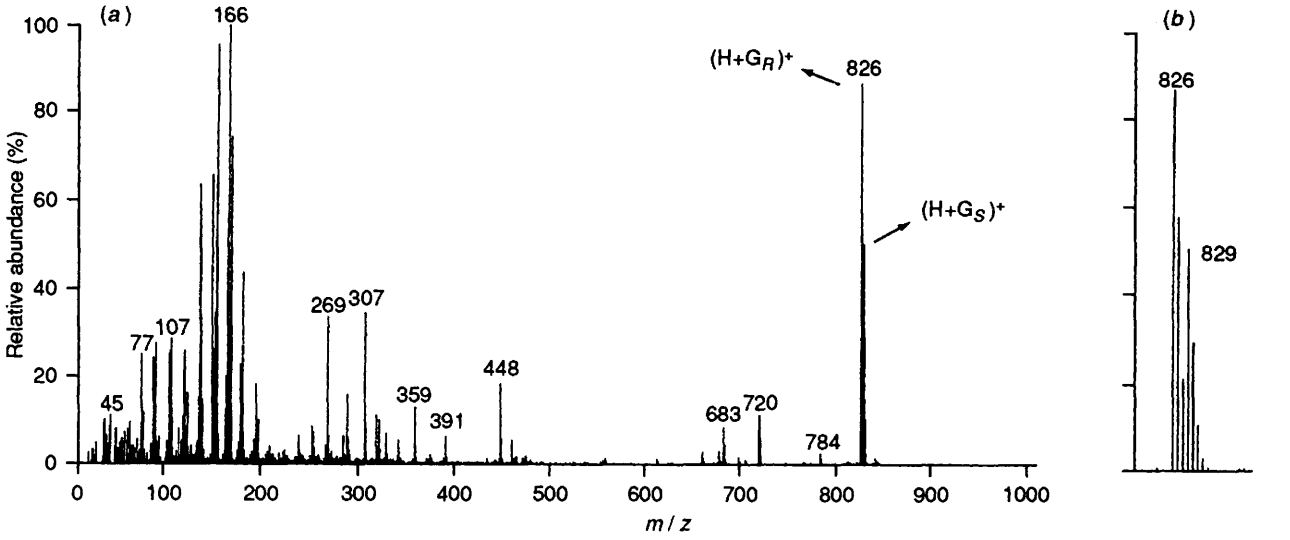

Fig. 1 (*a*) A FAB mass spectrum using the enantiomer labelled racemic guest method: host = (*R,R,R,R*)-**4** and guest = a 1 : 1 mixture of (*R*)-**3** and (*S*)-[$^2H_3$] **3** (20 scan). (*b*) An expansion of the host–guest complex ion region.

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

	Guest		
Host	**1**	**2**	**3**
(*S,S,S,S*)-**4**	0.63, 0.66[b]	0.51, 0.52[b] (0.6)	0.50, 0.51[b]
(*R,R,R,R*)-**4**	1.42, 1.56[b]	1.75, 1.90[b] (1.6)	1.76, 1.90[b]
(*S,S,S,S*)-**5**			*ca.* 0.8[c]
(*S,S*)-**6**	1.47 (1.4)	1.50 (1.4)	1.33
(*S,S,S,S*)-**7**	1.36	0.98 (1.1)	1.05
(*S,S*)-**8**	0.76	0.81 (0.9)	0.78
(*R,R,R,R*)-**9**			*ca.* 1.0[c]
10			*ca.* 0.5[c]
11	0.99	0.98	0.97

[a] Generally, the value is uncorrected by natural isotope abundance for convenience. Averaged with two measurements using two sample solutions prepared separately. For one measurement, the *I/I* value is obtained from an average of those of three scans (Nos. 10, 20, 30). Difference of two measurements is within ±0.03. The corresponding values using the internal standard host method are given in parentheses.[16,17] [b] Peak intensity is corrected by natural isotope abundance. After the correction, each cross chiral relationship satisfactorily holds between (*R,R,R,R*)-**4** and (*S,S,S,S*)-**4** hosts: for guest **1**, 0.66 × 1.56 = 1.03; for guest **2**, 0.52 × 1.90 = 0.99; for guest **3**, 0.51 × 1.90 = 0.97. [c] Host–guest complex ion peaks are less intense.

suggesting the important role of a missing $-CH_2OCH_2-$ unit for sufficient complexation ability.[2] The (*S*)-selectivity of host **10**, though having small complex ion peaks, is consistent with the reported (*S*)-direction.[19]

Association constants (*K*) determined using H NMR titration procedures in solution[16,20] are as follows: (*i*) $K(R)$ = 2.0 dm^3 mol^{-1} for host (*R,R,R,R*)-**4** with guest (*R*)-**3** and $K(S)$ = 1.0 dm^3 mol^{-1} for the same host with the enantiomeric guest (*S*)-**3** in CD_3OD–$CDCl_3$ (10/1 vol %) solution at 25 °C: $K(R)/K(S)$ = 2.0; and (*ii*) $K(R)$ = 1.5 × 10^2 dm^3 mol^{-1} for host (*S,S*)-**6** with guest (*R*)-**1** and $K(S)$ = 1.2 × 10^2 dm^3 mol^{-1} for the same host with the enantiomeric guest (*S*)-**1** in $CDCl_3$ at 25 °C: $K(R)/K(S)$ = 1.3. These thermodynamic properties in solutions parallel the present FABMS results.

In summary, FAB mass spectrometry plays a powerful role for unequivocal identification of chiral recognition in host–guest complexations. The enantiomer labelled racemic guest method can directly, easily and reliably determine which diastereoisomeric host–guest complex ion is more stable. The present approach will provide direct conclusions useful for the future design of the related host–guest complexation systems.

Received, 15th August 1994; Com. 4/04992F

References

1 D. J. Cram, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1009.
2 E. P. Kyba, J. M. Timko, L. J. Kaplan, F. de Jong, G. W. Gokel and D. J. Cram, *J. Am. Chem. Soc.*, 1978, **100**, 4555.
3 J. F. Stoddart, *Top. Stereochem.*, 1988, **17**, 207.
4 M. Newcomb, J. L. Toner, R. C. Helgeson and D. J. Cram, *J. Am Chem. Soc.*, 1979, **101**, 4941.
5 W. Bussmann and W. Simon, *Helv. Chim. Acta*, 1981, **64**, 2101.
6 R. B. Davidson, J. S. Bradshaw, B. A. Jones, N. K. Dalley, J. J. Christensen, R. M. Izatt, F. G. Morin and D. M. Grant, *J. Org. Chem.*, 1984, **49**, 353
7 L. R. Sousa, G. D. Y. Sogah, D. H. Hoffman and D. J. Cram, *J. Am Chem. Soc.*, 1978, **100**, 4569.
8 T. Kaneda, K. Hirose and S. Misumi, *J. Am. Chem. Soc.*, 1989, **111**, 742.
9 K. Naemura, K. Ueno, S. Takeuchi, Y. Tobe, T. Kaneda and Y. Sakata, *J. Am. Chem. Soc.*, 1993, **115**, 8475.
10 H. M. Fales and G. J. Wright, *J. Am. Chem. Soc.*, 1977, **99**, 2339.
11 F. J. Winkler, D. Stahl and F. Maquin, *Tetrahedron Lett.*, 1986, **27**, 335.
12 M. Sawada, in *Biological Mass Spectrometry: Present and Future*, ed. T. Matsuo, R. M. Caprioli, M. L. Gross and T. Seyama, Wiley, Amsterdam, 1994, ch 3.19, p. 639 and references cited therein.
13 G. Hofmeister and J. A. Leary, *Org. Mass Spectrom.*, 1991, **26**, 811
14 T. T. Dang, S. F. Pedersen and J. A. Leary, *J. Am. Soc. Mass Spectrom.*, 1994, **5**, 452.
15 E. N. Nikolaev, G. T. Goginashivili, V. L. Tal'rose and R. G. Kostyanovsky, *Int. J. Mass Spectrom. Ion Process.*, 1988, **86**, 249.
16 M. Sawada, Y. Okumura, M. Shizuma, Y. Takai, Y. Hidaka, H. Yamada, T. Tanaka, T. Kaneda, K. Hirose, S. Misumi and S. Takahashi, *J. Am. Chem. Soc.*,1993, **115**, 7381.
17 M. Sawada, Y. Okumura, H. Yamada, Y. Takai, S. Takahashi, T. Kaneda, K. Hirose and S. Misumi, *Org. Mass Spectrom.*, 1993, **28**, 1525.
18 I.-H. Chu, D. V. Dearden, J. S. Bradshaw, P. Huszthy and R. M. Izatt, *J. Am Chem. Soc.*, 1993, **115**, 4318.
19 H. Tsukube and H. Sohmiya, *J. Org. Chem.*, 1991, **56**, 875.
20 Y. Takai, Y. Okumura, T. Tanaka, M. Sawada, S. Takahashi, M. Shiro, M. Kawamura and T. Uchiyama, *J. Org. Chem.*, 1994, **59**, 2967.