Measurement of Chiral Recognition Properties of Crown Ethers Using Matrix Assisted Laser Desorption Ionization Mass Spectrometry

REGULAR PAPER

Measurement of Chiral Recognition Properties of Crown Ethers Using Matrix Assisted Laser Desorption Ionization Mass Spectrometry

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Hydrogen bonding host–guest complex ions between chiral crown ethers and chiral amino acid ester salts, detected by matrix assisted laser desorption ionization (MALDI) mass spectrometry (MS) with a DIIBA or MSA matrix, were studied on the view point of chiral recognition properties of the chiral crown hosts. The chiral recognition property (I_R/I_{S-d_n} value $\cong 1.0$) obtained by the present MALDI-MS is sharply different from the I_R/I_{S-d_n} value obtained by FAB-MS or ESI-MS ($\neq 1.0$) in the same host–guest combinations. The direct comparison on the basis of the I_R/I_{S-d_n} values suggests that MALDI-MS is not a suitable measurement tool for chiral host–guest interactions probably because of the particular way of sample preparation involving a crystallization process.

1. Introduction

Matrix assisted laser desorption ionization (MALDI) has been one of the typical soft ionizations in modern organic mass spectrometry (MS)[1-4] and has been becoming a versatile tool for detecting various non-covalent complex ions.[5-7] Further, MALDI-MS has been recognized as suitable for high throughput screening of combinatorially synthetic compounds because of the high sensitivity and the simplicity of operation for continuous measurements.[8-10] It is then expected that chiral interactions between chiral hosts and chiral guests can be detected by MALDI-MS, and also expected that a rapid methodology for screening the chiral recogniton properties will be developed. To our knowledge, until now there is no reports of semiquantitative or qualitative measurements of diastereomeric host–guest complex ions by MALDI-MS.

In a previous series of papers, we have already reported fast atom bombardment (FAB) and electrospray ionization (ESI) mass spectrometric studies on chiral recogniton behavior of chiral crown ether hosts and cyclic oligosaccharide hosts (H) toward chiral amino acid and their ester guests (G).[11-15] Therein, we characteristically used a racemic guest whose enantiomer was deuterium labeled (G_R: $G_{S-d_n} = 1:1$). The chiral recognition ability of a given host toward a given guest has been evaluated in terms of the relative peak intensities of the corresponding diastereomeric host–guest complex ions on the respective mass spectrum.

$$I[(H+G_R)^+]/I[(H+G_{S-d_n})^+]=I_R/I_{S-d_n}=IRIS \quad (1)$$

Here, I represents peak intensity of a target host–guest complex ion appeared.

MALDI-MS is less quantitative than FAB-MS, but more suitable to measure many different samples on a sample plate. Therefore, MALDI-MS seems to offer a valuable screening strategy for measuring chiral interactions among various host–guest combination
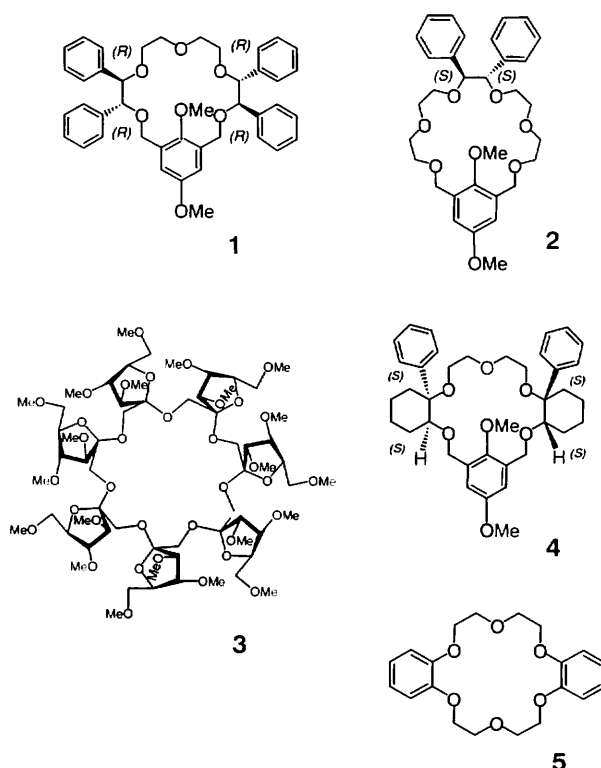
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Fig. 1. Chiral and achiral crown ether hosts studied.

systems.

Here, we selected the typical host–guest combination systems between chiral crown ethers (1–4 in Fig. 1) and chiral amino acid ester hydrochloride salts (in Table 1), which had been previously investigated both by FAB-MS and ESI-MS.[11), 14), 15)] Our primary purpose in this paper is to judge whether MALDI-MS is a rapid measurement tool for chiral host–guest interactions which many analytical chemists and organic chemists, *etc.* want to know.[16), 17)]

2. Experimental

2.1 Materials

Chiral crown ethers (1–4) and chiral amino ester salts (both labeled and unlabeled ones) were synthetic compounds, which had been already reported elsewhere.[11), 14), 15), 18)] As matrices for MALDI, commercially available (Aldrich) 2,5-dihydroxybenzoic acid (DHBA), 5-methoxysalicylic acid (MSA), and α-cyano-4-hydroxycinnamic acid (CHCA) were used without further purification.

2.2 MALDI mass spectral measurements

Positive ion MALDI-MS was performed using a Voyager-DE™ RP MALDI time-of-flight (TOF) mass spectrometer equipped with a delayed extraction system (PerSeptive Biosystems, Inc.). Measurement conditions were as follows: acceleration volt, 20 kV; N_2 laser wave length, 337 nm; pulse width, 3 ns; laser power, 2,000 unit (DHBA, MSA) and 1,500 unit (CHCA). The ions were generated by irradiating various positions on the sample surface area with a joy stick and accumulated ($n=256$). The spectra were primarily obtained with a reflector-mode and sometimes checked with a linear-mode.

2.3 Enantiomer labeled (EL)-guest method

The method characteristically requires isotope label-

ing of one of the guest enantiomers and handles the complexation of a given host (H) with a given 1 : 1 guest mixture of an unlabeled (R)-enantiomer (G_R^+) and a deuterium labeled (S)-enantiomer (G_{S-dn}^+). The chiral recognition ability of the host is quantitatively estimated from the I_R/I_{S-dn} value (Eq. (1)).

2.4 Preparation of sample solutions for the MALDI-MS/EL-guest method

An equivolume (50 μL) of (i) a 1 : 1 racemic mixture resulted from an each 100 mM CHCl$_3$–MeOH (1 : 1) solution of deuterium labeled (S)- and unlabeled (R)-guests, and (ii) a 10 mM CHCl$_3$–MeOH (1 : 1) solution of a given host were mixed. Then, a 20 μL of this host–guest solution and a 80 μL of a 125 mM CHCl$_3$–MeOH (1 : 1) solution of DHBA matrix were mixed. After vibration of the mixture, the concentration of each component became as follows: [H]=1 mM, [G_R]=[G_{S-dn}]=5 mM, [matrix]=100 mM. That is, the molar ratio of the components were 1 : 5 : 5 : 100 ([H] : [G_R] : [G_{S-dn}] : [matrix]). At the preliminary stage of the experiments, a slightly modified stoichiometry such as 1 : 5 : 5 : 50–1,000 was tested with DHBA. Due to relatively abundant peaks appeared to the complex ions, the stoichiometry of 1 : 5 : 5 : 100 was selected in this paper.

About 0.3 μL aliquots of the final mixture were placed on one of the sample spots on a gold-sample plate (max 100 spots) and dried in air at room temperature during overnight.

3. Results and Discussion

The MALDI-TOF mass spectrum of host 1 with a racemic methionine methyl ester hydrochloride salt guest [(R)-Met-OMe$^+$: (S)-Met-OMe-d_3^+ =1 : 1] with a MSA matrix is shown in Fig. 2. Further, for compari-
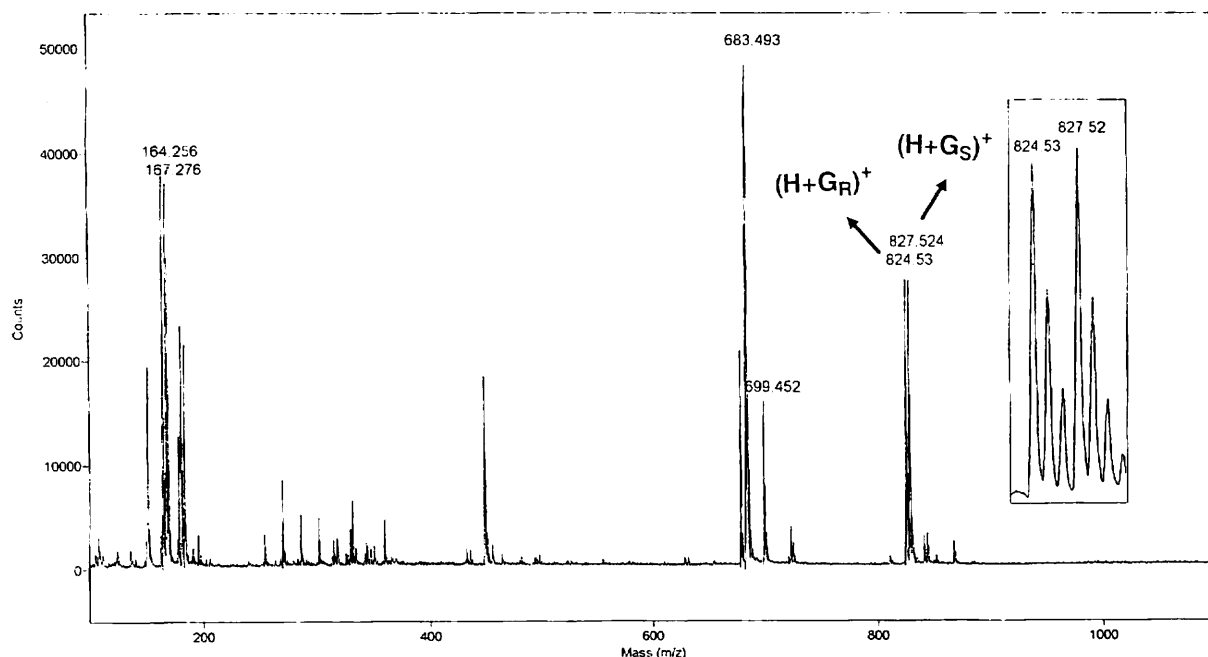

Fig. 2. A MALDI-TOF mass spectrum (MSA matrix) of chiral crown host 1 (H) with a 1 : 1 mixture of Met-OMe·Cl⁻ (G_R : G_{S-d3}) whose enantiomer is deuterium labeled [(R)-Met-OMe⁺ : (S)-Met-OMe-d₃ =1 : 1]. Peaks at *m/z* 824 and *m/z* 827 are the corresponding host–guest complex ions: (H+G_R)⁺ and (H+G_{S-d3})⁺ ions, respectively. A peak at *m/z* 683 is (H+Na)⁻.
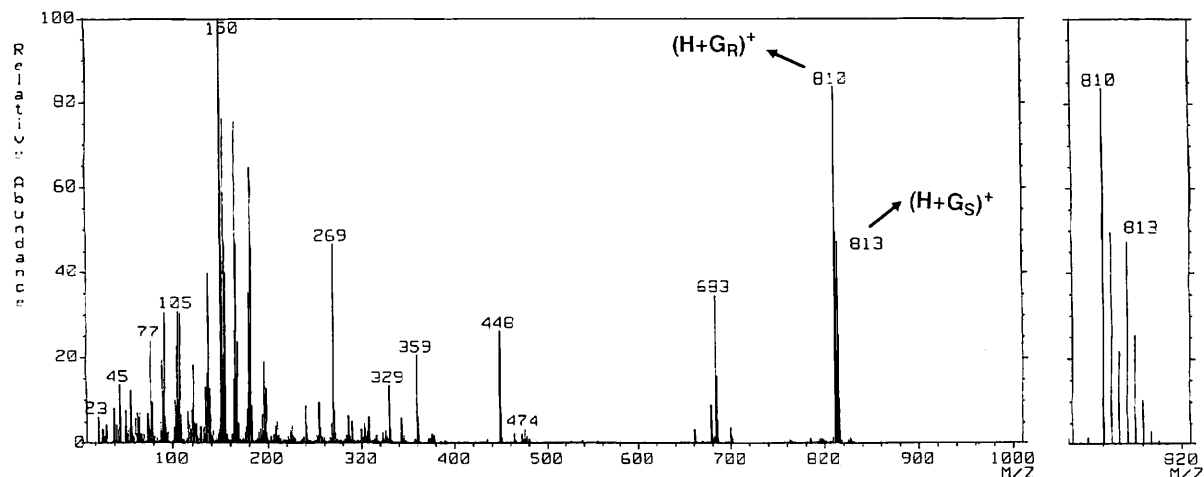
Fig. 3. A FAB mass spectrum (NBA matrix) of chiral crown host 1 (H) with a 1 : 1 mixture of Met-OH·OTs⁻ (G_R : G_S-d3) whose enantiomer is deuterium labeled [(R)-Met-OH⁻ : (S)-Met(CH₃S-d₃)-OH⁺ = 1 : 1]. Peaks at m/z 810 and m/z 813 are the corresponding host–guest complex ions: (H+G_R)⁺ and (H + G_S-d3)⁺ ions, respectively.

Table 1. Change in the $I_R/I_{S\text{-}dn}$ Values Using MALDI, ESI, and FAB Mass Spectrometry

System	MALDI			ESI[14]	FAB[11, 14, 15]	K_R/K_S [=11]
Host+EL-Guest⁺ (counter anion: Cl⁻)	Matrix			Solvent	Matrix	Solvent
	DHBA	MSA	CHCA	MeOH	NBA	CD₃OD/CDCl₃ (10/1)
1 [Pgly-OMe]⁺ ᵃ	1.0	1.0	ca. 1.0*	1.5	2.0	2.0
[Met-OMe]⁺	1.0	1.0	ND ᵇ	1.2	1.6	
[Met-OH]⁻ ᶜ	ca. 1.0*	ca. 1.0*			2.0	
2 [Pgly-OMe]⁻	1.0			ND ᵇ	0.81	
3 [Pgly-OMe]⁻	ca. 1.0*			0.8 ᵈ	0.76 ᵉ	
4 [Met-OMe]⁻	ca. 1.0*			0.69	0.22	0.22
[Phe-OMe]⁻	ca. 0.9*			0.72	0.22	
5 [Pgly-OMe]⁻	1.0			1.0	1.0 ᶠ	1.0 ᶠ

ᵃ Pgly-OMe·Cl⁻: phenylglycine methyl ester hydrochloride. ᵇ ND: not detected.

ᶜ Methionine p-toluenesulfonate. ᵈ [Pgly-OPrⁱ]⁺ was used in acetone.

ᵉ [Pgly-OPrⁱ]⁺ was used. ᶠ Unity by definition. * Small host–guest complex ion peaks.

= Ratio of equilibrium constants (K_R and K_S).

son, the FAB mass spectrum of host 1 with a racemic methionine p-toluenesulfonic acid salt guest [(R)-Met-OH⁻ : (S)-Met(CH₃S-d₃)-OH⁻ = 1 : 1] with a NBA matrix is shown in Fig. 3.[14]

The chiral recognition behavior (the $I_R/I_{S\text{-}dr}$ value) obtained by MALDI-MS is summarized in Table 1, and is compared with the results by FAB-MS and ESI-MS in the same host–guest combination systems.[11, 14, 15] As seen in Table 1, the $I_R/I_{S\text{-}dn}$ values are almost unity in spite of the different matrices utilized. The host–guest complex ions could be detected by MALDI-MS in the present study, although the peaks are not always abundant (Table 1). However, their chiral recognition properties could not be detected anymore by this type of MALDI-MS. This is in sharp contrast to the fact that the corresponding chiral recognition properties could be clearly and successfully detected by FAB-MS (or ESI-MS).

The reason is not clear at present. In the case of MALDI-MS, the crystallization process of the sample solution through solvent vaperization on the sample plate is inevitably involved. The matrix and the guest (salt) compounds, which are of relatively lower solubil-

ity, are crystallized ahead of the remaining relatively soluble host compound. As a result, host–guest competitive conditions in solution are completely broken (for example, [H]/[G] becomes larger (>10)) and then, at the final stage, equal concentration of the diastereomeric host-guest complex ions {[(H+G_R)⁺]/[(H+G_S-dn)⁺] ≈ 1.0} are formed and crystallized. It is considered that the complex ions are then observed as $I_R/I_{S\text{-}dn}$ = 1.0 by the present MALDI-MS/EL-guest method.

These findings concludingly suggest that MALDI-MS is suitable for detecting non-covalent host–guest complex ions, while it is not inherently suitable for measuring chiral host–guest interactions.

Acknowledgments

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