Matrix Effects on the Chiral Recognition Determined by the Relative Peak Intensity of Diastereomeric Host–Guest Complex Ions Using the FAB Mass Spectrometry/Enantiomer Labeled Guest Method

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The FAB mass spectrometry (MS)/enantiomer labeled (EL) guest method is one of the useful techniques to easily evaluate chiral discrimination ability of a chiral host (H) toward chiral guests (Gα, Gβ). In this paper, the matrix dependency of the relative peak intensity (IRIS) of the diastereomeric host–guest complex ions [(H+Ga)+ and (H+Gβ)+] was investigated (host, MeFruNys; guest, Phe-O-iPr+). The IRIS values of spectra measured using NBA, NPOE, and DTDE matrices agreed almost with the ratio of concentrations of the complex ions calculated from the association constants (Kα and Kβ) in chloroform at 298 K. While, the IRIS values of spectra using glycerol matrix reached almost unity. It was assumed that the IRIS values depend upon the matrices used since the difference of solvation ability of the matrices affects the actual concentration of the guest concerning in the complexation. And then, it was recommended that NBA is the best matrix for chiral recognition mass spectrometry studies.

1. Introduction

“The chiral recognition mass spectrometry” is one of the topics in various fields such as analytical, biological and organic chemistry.1–5) We proposed the enantiomer-labeled guest method to evaluate chiral recognition ability of a given chiral host toward chiral guests using FAB mass spectrometry, and then, the chiral recognition behavior of various chiral crown ethers, permethylated oligosaccharides, and modified carbohydrates has been investigated by the method.5–15)

In our method, the FAB mass spectra of a mixture of three components in matrix, a chiral host (H), and an equal amount of an (S)-enantiomer labeled guest with deuterium atoms (Gβ-d8+) and an unlabeled (R)-enantiomer guest (Gβ), were measured at room temperature. The relative peak intensity ([I(H+Ga)+]/[I(H+Gβ-d8)+]) of the diastereomeric 1:1 host–guest complex ions with different molecular weight (ΔMW=n, n: the number of deuterium atoms) corresponds to the chiral recognition ability. Thus, the chiral recognition ability can be easily evaluated in a short time from a single mass spectrum. This method is called “FAB mass spectrometry (MS)/enantiomer labeled (EL) guest method”. If the initial concentration of the host becomes small enough when compared with the concentration of the guest pair in 3-nitrobenzyl alcohol (NBA), the IRIS value was in good agreement with the ratio of the association constants (Kα/Kβ) in organic solvents such as chloroform, acetone, methanol/chloroform etc. Therefore, it was concluded that the IRIS value corresponded to the ratio of the concentration of the complex ions under competitive host–guest complexation equilibrium.6, 7, 11)

It has been reported that the appearance of ion peaks depends upon the kind of matrices.16) However, there was only few reports for the IRIS values on the basis of spectra measured using matrices except NBA.17) In this paper, we reported the matrix effects on the IRIS values in the case of a permethylated oligosaccharide host, 1S-fructofuranosylnystose (MeFruNys), which has remarkable high chiral recognition ability, with an amino acid ester salt guest, 2-propyl phenylalanate hydrochloride [Phe-O-iPr+ (Cl–)] (Chart 1).

Chart 1. Chiral host and chiral guest.
2. Experimental

2.1 Materials

Permethylated \(^{1}F\)-fructofuranosylnystose, deuterium-labeled propyl (S)-phenylalanate hydrochloride, and propyl (R)-phenylalanate hydrochloride were synthetic samples which have already been described elsewhere.\(^5,\)\(^13\) For 18-crown-6, a commercial sample (Alrich) was used without further purification. For matrices, glycerol (G), \(\alpha\)-thioglycerol (TG), 2-nitrophenyl \(n\)-octyl ether (NPOE), 2,2'-dithiodiethanol (DTDE), 3-nitrobenzyl alcohol (NBA), diethanolamine (DEA), and triethanolamine (TEA), commercial samples (Tokyo Kasei) were used without further purification. Methanol (Nakalai) was used after distillation.

2.2 FAB mass spectrometry: the enantiomer labeled guest method

Positive ion FAB mass spectra were obtained using a JEOL JMS-500 spectrometer (A) and a JEOL SX-102 spectrometer (B). The instrumental conditions were as follows: (A) acceleration voltage, 3 kV; mass range, \(m/z\) 20–2300; beam, Xe; emission current, 20\,\mu A; source pressure, ca. \(10^{-8}\) Torr; magnet scan rate, 7 s. (B) Acceleration voltage, 10 kV; mass range, \(m/z\) 100–2400; beam, Xe; emission current, 10 mA; source pressure, ca. \(1–2\times10^{-5}\) Torr; magnet scan rate, 10 s. Calibration was carried out with CsF.

2.2.1 Preparation of the sample solutions

A sample solution was prepared by mixing two solutions and a matrix. The three solutions were as follows: (1) 10 \,\mu L of a 0.67 M MeOH solution of a 1/1 mixture of (S)-Phe-O-iPr\(_{d}\)\(_{2}\)\(_{2}\) (Cl) and (R)-Phe-O-iPr\(_{d}\)\(_{2}\)\(_{2}\) (Cl)\(_{2}\); (2) 5 \,\mu L of a host MeOH solution (concentrations 0.02, 0.2, 1, 2 M); (3) 15 \,\mu L of a matrix. The mixed solution was treated with an ultrasonic homogenizer and stood overnight. After vaporization of MeOH, the initial concentration of the guest in the matrix is 0.44 M, and the initial concentrations of the host in the matrix are 0.0067, 0.067, 0.53, and 0.67 M, respectively. The mol ratio of the guest against the host are 66, 66, 75, and 65, respectively. The accuracy of the 1/1 equivalent concentration of (R)- and (S)-enantiomers of the amino acid ester salts was confirmed on the basis of the IRIS value with 18-crown-6, which is an achiral host, and was experimentally obtained as unity (1.00±0.03).

2.2.2 FABMS measurements

A 1 \,\mu L of the above mixed solution was deposited on a FAB probe tip. The spectra were measured at room temperature. The spectral data were averaged from 10th to 40th scans (\(n=31\)). The chiral recognition ability of MeFruNys was evaluated on the basis of the relative peak intensity of the observed complex ions \([H+G_S]^+\) (m/z 1275) and \([H+G_S-d_{2}]^+\) (m/z 1282).

3. Results and Discussion

3.1 Matrix effects on IRIS

The mass spectra of the mixed solution of MeFruNys (H) with Phe-OiPr\(_{d}\)\(_{2}\)\(_{2}\) (Cl)\(_{2}\) (Ga\(_S\)\(_{d}\)\(_{2}\)\(_{2}\)) and Ga\(_{d}\)\(_{2}\)\(_{d}\)\(_{2}\) (m/z 1282). The diastereomeric host–guest complex ions were clearly observed with different mass number by 7 except the case of the basic matrices such as DEA and TEA. In the case of DEA and TEA matrices, it is assumed that the host cannot bind to the guest since most of the guest cations are deprotonated by the matrices which have strong proton acceptability. Therefore, the complex ions may be little produced. The IRIS values are summarized in Table 1. All the IRIS values were smaller than 1.0, thus, the host was estimated to be S-enantiomer selectivity toward the guest. However, the magnitude of the IRIS values was different from each other. The ordering of the IRIS values was G > TG > DTDE > NPOE > NBA. From the above results, it is clarified that the IRIS values depend upon the matrix.

3.2 Concentration effects on IRIS

As previously reported,\(^5\)\(^13\) the IRIS values from measurements using NBA matrix change depending upon the initial concentration of the host under the conditions that the concentration of 1/1 enantiomer guest pair was fixed. Moreover, the change in the IRIS values were corresponding to the change in the concentration ratio of the complex ions calculated using the initial concentration of the host and guests, and the association constants (\(K_R\) and \(K_S\)) in chloroform. Thus, the IRIS values reflect the concentration ratio of the complex ions in the matrix.

As shown in Table 1, the IRIS values reached unity as the initial concentration of the host increased, except G and basic matrices. Thus, the IRIS values depend upon the concentration of the host and the guest in the matrices. The change is the similar manner as that of other examples in the previous reports. Therefore, it was indicated that the IRIS values reflect the concentration ratio of the complex ions in their matrices.

3.3 Correlation between IRIS and \(K_R/K_S\) values in solution

The association constants between MeFruNys and each enantiomer of Phe-OiPr\(_{d}\) (Pic\(_{d}\)\(_{d}\)) were determined in chloroform at 298 K \((K_R=650\, M^{-1}\), \(K_S=2650\, M^{-1}\), \(K_R/K_S=0.32)\).\(^13\) Figure 2 shows a simulated plot of the concentration ratio of the complex ions, \([H+G_S]/[H+G_S^*]\) against \([H+S]_0\), where \(K_R\) and \(K_S\) and \([G^*]_0\) are kept constant. \(K_R/K_S=0.32\), \([G^*]_0=0.44\, M\). The plotting curves are calculated from the different magnitudes of association constants: Curve A, \(K_R=650\, M^{-1}\), \(K_S=2650\, M^{-1}\), curve B, \(K_R=63\, M^{-1}\), \(K_S=205\, M^{-1}\), curve C, \(K_R=0.65\, M^{-1}\), \(K_S=2.05\, M^{-1}\). The IRIS values on the basis of the spectra measured under the corresponding concentration conditions are also shown in Fig. 2. The IRIS value using an NPOE, DTDE or NBA matrix changes along the curves. The facts suggest that the IRIS values reflect the \([H+G_S]/[H+G_S^*]\) in the matrix.

3.4 Contribution of matrix to the complexation

In general, the contribution of the solvents to host–guest complexations cannot be neglected.\(^16\) The complexation via electrostatic interactions is influenced by polarity of the solvent.\(^19\) However, the influence on the relative values such as \(K_R/K_S\) is set off.\(^20\)

The significant factors in solvent effects for complexation\(^21\) are permittivity and solvation ability. The relative permittivity \(\varepsilon_r\) of G and NBA are 42.5 and 22 (25°C), respectively.\(^22\) Their activity coefficients are calculated to be 1.61 and 1.59, respectively, by the Kirkwood equation on the basis of their relative perm-
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Fig. 1. FAB mass spectra of MeFruNys (H) with Phe-O-iPr⁺ (Cl−) (G₉⁺ and Gₛ₋₄₋⁺) in various matrices. (a) Glycerol, (b) α-thioglycerol, (b) 2-nitrophenyl n-octyl ether, (c) 2,2’-dithiodiethanol, (d) 3-nitrobenzyl alcohol, (e) diethanolamine, and (f) triethanolamine. (H+G₉)⁺ m/z 1275, (H+Gₛ₋₄₋)⁺ m/z 1282.

Table 1. IRIS Values of MeFruNys with Phe-O-iPr⁺ in Various Matrices

<table>
<thead>
<tr>
<th>[H]₀ (M)</th>
<th>Matrix</th>
<th>G</th>
<th>TG</th>
<th>NPOE</th>
<th>DTDE</th>
<th>NBA</th>
<th>DEA</th>
<th>TEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0067</td>
<td>0.89</td>
<td>0.46</td>
<td>0.31</td>
<td>0.32</td>
<td>0.17</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0.067</td>
<td>0.86</td>
<td>0.59</td>
<td>0.35</td>
<td>0.38</td>
<td>0.18</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0.33</td>
<td>0.93</td>
<td>0.60</td>
<td>0.36</td>
<td>0.44</td>
<td>0.27</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>0.67</td>
<td>0.90</td>
<td>0.62</td>
<td>0.42</td>
<td>0.50</td>
<td>0.29</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>18-Crown-6</td>
<td>1.00</td>
<td>0.99</td>
<td>1.03</td>
<td>0.99</td>
<td>0.99</td>
<td>1.03</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

[G⁺]₀ = [G₉⁺]₀ + [Gₛ₋₄₋⁺]₀ = 0.44 M. a [H]₀ = 0.067 M.
Therefore, the influence of the permittivity are elucidated to be small.

The solvation ability is interpreted on the basis of “donor-acceptor” concept, which is useful for explanation of various reactions and equilibria. In this case, the matrices are regarded as donor solvents for cations. The donating power of solvents can be presumed by the number of hydroxy-oxygen and nitrogen atoms which have lone pair. G is presumed to have stronger donating power than NPOE, DTDE, and NBA, since G possesses three oxygen atoms. Thus, G may form solvation with the cation guest more tightly. Therefore, the host and the matrix may bind to the guest in the additional competitive equilibrium system (Chart 2). In the system, if the matrix has strong donating power to the guest, the concentration of the guest which can be bound by the host decreases apparently.

The concentration ratios of the complex ions are plotted versus [H]0, where $K_R$ and $K_S$ are kept as $K_R = 650 \text{ M}^{-1}$, $K_S = 2050 \text{ M}^{-1}$, and curve (C) $K_R = 6.5 \text{ M}^{-1}$, $K_S = 2.05 \text{ M}^{-1}$. $[G_R][G_A] + [G_A][G_S] = 0.44 \text{ M}$ and $[G_R][G_A] + [G_A][G_S] = 0.22 \text{ M}$; curve E, $[G^+]_b = 0.044 \text{ M}$. The concentration of the host under our typical measuring conditions is shown by an arrow and a dotted line.

The initial concentration of the host under our typical measuring conditions (FABMS) is shown by an arrow and a dotted line. As the concentration of the guest decreases, the concentration ratio of the complex ions under the conditions shown by the arrow approaches unity. Since the IRIS values reflect the concentration ratio of the complex ions, the IRIS values also approaches unity as the concentration of the guest for that of the host decreases. Therefore, it could be concluded that the IRIS values depend upon the solvation ability of the matrix.

4. Summary

We clarified that the IRIS values of the FABMS/EL guest method depend upon the matrix utilized in FAB mass spectrometry. It was presumed that the IRIS values show the matrix dependency since the actual concentration of the chemical species in complexation is related to the solvation ability of the matrix. In general, as the donor numbers of nitro compounds such as nitrobenzene and nitromethane are small, the compounds do not solvate with metal ions. Therefore, their solvents are often used in the Lewis acid-catalyzed reactions such as Friedel–Crafts reaction etc. As NPOE and NBA also possess the nitro group, the matrices may not contribute to host–guest complexation by electrostatic interaction. In the host–guest complexation of the crown ether and alkylated carbohydrate hosts with the cationic guests, NBA, NPOE, and DTDE are good matrices. We would like guests to recommend especially NBA as the matrix which is suitable to the host–guest complexation sys-
tems by the FABMS/EL guest method.

References


Keywords: FAB mass spectrometry, Chiral recognition, Deuterium labeling, Matrix, Solvent effect, Host–guest complex