A New Reagent to Evaluate Optical Purity of Organic Amines by FAB Mass Spectrometry

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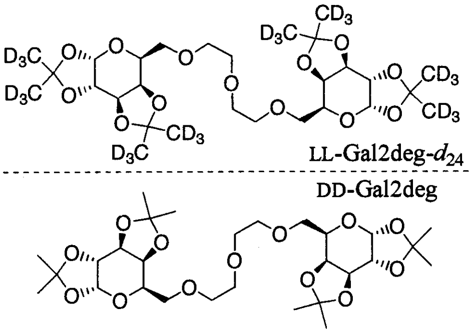
Optical purity (enantiomeric excess: ee) of organic amine salts such as 1-(1-naphthyl)ethylamine hydrochloride was determined by FAB mass spectrometry using a deuterium-labeled/unlabeled enantiomer pair of a newly synthesized saccharide derivative (DD-Gal2deg/LL-Gal2deg-d_{24}), podands.

Chiral recognition is one of significant and fundamental processes in living systems and one of important subjects in chemistry and biochemistry. Chiral recognition is based on the difference of thermodynamic stabilities of diastereomeric complexes of a chiral host with chiral guests. Optical purity (ee) of chiral compounds is evaluated by the detection of the difference using chromatography,[1] capillary electrophoresis,[2] and spectrometric methods such as NMR.[3] Recently, the evaluation by mass spectrometry (ESIMS,[4] ESIMS/MS,[5] FABMS,[6] LSIMS,[7] FTICRMS[8] etc.) has been paid great attention because of the high-sensitivity and facile measurements. The "deuterium-labeled method" proposed by us has a lot of advantages such as the easy, short-time, and direct measurements.[9–12] However, the recent ESIMS measurements, compared with the detection by FABMS ones, gave clear depression of the chiral recognition properties with this method for the simple host–guest complexation systems.[13]

We already reported that the deuterium-labeled/unlabeled enantiomer pairs of crown ether derivatives were very useful as reagents for evaluating ee of amino acid esters before.[13,14] However, they were, in general, not so powerful for the ee-evaluation of primary (simple) alkyl amine salts. Now, we report that a newly synthesized labeled /unlabeled enantiomeric pair of an acyclic host containing galactose moieties (DD-Gal2deg/LL-Gal2deg-d_{24}) is very useful as a new podand type of ee-evaluation reagents toward 1-(1-naphthyl)ethylamine hydrochloride (NEA^+Cl^-) and secondary amine derivatives such as proline ester hydrochloride by FAB mass spectrometry.



The podand containing galactose-end groups capable of chiral recognition (DD-Gal2deg), which was designed in consideration of binding ability toward various organic ammonium ions (flexible oxyethylene chain), C_2 symmetry, and steric effect (steric hindrance) on complexation, was synthesized by

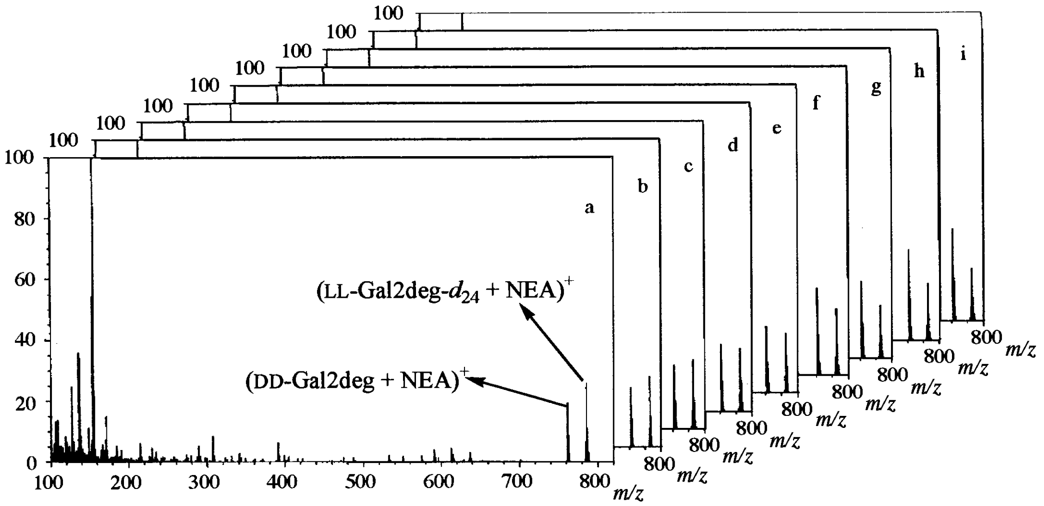


Figure 1. FAB mass spectra of the DD-Gal2deg/LL-Gal2deg-d_{24} equimolar mixture with NEA^+ (NBA matrix).
(a) R 100 % ee, (b) R 75 % ee, (c) R 50 % ee, (d) R 25 % ee, (e) 0 % ee, (f) S 25 % ee, (g) S 50 % ee, (h) S 75 % ee, (i) S 100 % ee of NEA^+.

two steps of (i) acid-catalyzed acetalization of galactose and (ii) etherization with *p*-tosyl diethylene glycol by the Williamson method.[15] The deuterated enantiomer (LL-Gal2deg-d_{24}) was labeled by acetalization using acetone-d_6 (D content: 98.8 D%). The podand flexibly changes the linear structure to form the pseudo-cyclic complex. The flexibility of conformation would give great difference in the stability of the diastereomeric complex.

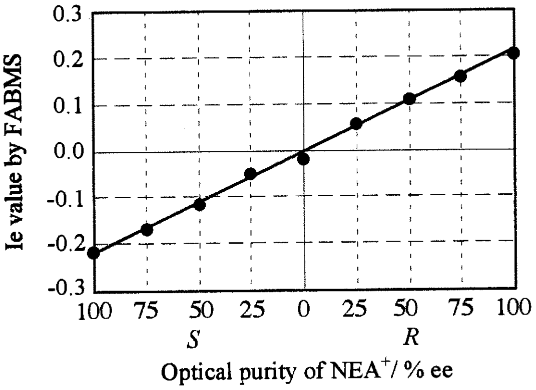


Figure 2. Correlation between optical purity (% ee) of NEA$^+$ and Ie values in FAB mass spectra. The % ee value can be determined within the error of ± 3 % ee in this case.[19]

FAB mass spectra in 3-nitrobenzyl alcohol (NBA) matrix of an equimolar mixture of DD-Gal2deg/LL-Gal2deg-d_{24} pair compounds and given NEA hydrochlorides prepared as various ee values were measured (Figure 1).[16] Intensity excess (Ie) values calculated from peak intensity of two observed complex ions (DD-Gal2deg+NEA)$^+$ and (LL-Gal2deg-d_{24}+NEA)$^+$ showed a good linear correlation (n = 9, $R^2 = 0.9966$) with optical purity (% ee) of NEA$^+$ (Figure 2).[17] The definition of Ie values corresponds to that of enantiomeric excess (ee: |R-S|/|R+S|) as the following equation.[18]

$$\mathrm{Ie} = \frac{\mathrm{I(DD\text{-}Gal2deg + NEA)^+ - I(LL\text{-}Gal2deg\text{-}}d_{24}\mathrm{ + NEA)^+}}{\mathrm{I(DD\text{-}Gal2deg + NEA)^+ + I(LL\text{-}Gal2deg\text{-}}d_{24}\mathrm{ + NEA)^+}}$$

Here, I means the respective peak intensity.

Therefore, optical purity of a given ee-unknown NEA$^+$ can be determined using the equation: % ee = $|\mathrm{Ie}|/|\mathrm{Ie}_{100}| \times 100$.[4] The accuracy of the estimated optical purity strongly depends on the magnitude of the absolute Ie value ($|\mathrm{Ie}_{100}|$) in 100 % ee. The $|\mathrm{Ie}_{100}|$ value of Gal2deg enantiomer pair with proline 2-propyl ester was larger than that with NEA$^+$ (Table 1). The fact suggested that the present linear Gal2deg enantiomer pair is useful for the ee-evaluation of secondary amine salts which had been difficult in the case of the previous crown ether enantiomer pairs.[13]

In summary, we synthesized a new deuterium-labeled/unlabeled enantiomeric pair compounds (podands) containing galactose-end groups capable of chiral recognition, and demonstrated the potential utility for determining the optical purity of primary and secondary alkyl ammonium compounds can be determined by FAB mass spectrometry using the pair.

References and Notes

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15 DD-Gal2deg: ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 5.53 (d, 1H, $^3J_{1,2}$ = 5.0 Hz, H1), 4.59 (dd, 2H, $^3J_{2,3}$ = 2.3 Hz, $^3J_{3,4}$ = 7.9 Hz, H3), 4.30 (dd, 2H, $^3J_{1,2}$ = 5.0 Hz, $^3J_{2,3}$ = 2.3 Hz, H2), 4.26 (dd, 2H, $^3J_{3,4}$ = 7.9 Hz, $^3J_{4,5}$ = 1.7 Hz, H4), 3.98 (m, 2H, H5), 3.72-3.60 (m, 12H, OCH_2), 1.54 (s, 6H, CH_3), 1.44 (s, 6H, CH_3), 1.34 (s, 6H, CH_3), 1.33 (s, 6H, CH_3) from TMS; $[\alpha]_D^{20}$ = –69.4° (*c* = 0.471, $CHCl_3$); Anal. Found: C, 56.69; H, 8.00 %. Calcd for $C_{28}H_{46}O_{13}$: C, 56.94; H, 7.85 %. LL-Gal2deg-d_{24}: ^{1}H-NMR, same as DD-Gal2deg except for CD_3; $[\alpha]_D^{20}$ = +64.0° (*c* = 0.307, $CHCl_3$); Anal. Found: C, 55.92; H, 7.62 %. Calcd for $C_{28}H_{34}D_{24}O_{13}$: C, 54.74; H (containing D), 7.55 %.
16 Sample concentration conditions: [DD-Gal2deg] = [LL-Gal2deg-d_{24}] = 0.0133 M; [(*R*)-NEA$^+$Cl$^-$] + [(*S*)-NEA$^+$Cl$^-$] = 0.0133 M in NBA.
17 The isotope proportion of the complex ion of LL-Gal2deg-d_{24} with NEA$^+$ depends on the D content (98.8 D%). The peak intensity of the complex ion was corrected from the natural isotopic abundance of unlabeled complex ion and the D contents. Typical examples of corrected Ie values were as follows, R 100 % ee: $\mathrm{Ie_{obs}}$ = –0.143, $\mathrm{Ie_{cor}}$ = –0.217; S 100 %: $\mathrm{Ie_{obs}}$ = –0.143, $\mathrm{Ie_{cor}}$ = –0.217.
18 Generally, Ie = $(I_R/I_S - 1)/(I_R/I_S + 1)$; here, I_R/I_S is the chiral recognition ability previously used in the literature.[9–14]
19 The larger the $|\mathrm{Ie}_{100}|$ value is, the smaller the error of Ie value is.