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Synthesis and Chiral Recognition Property of 3-Acetylamino-3-deoxy-β-cyclodextrin

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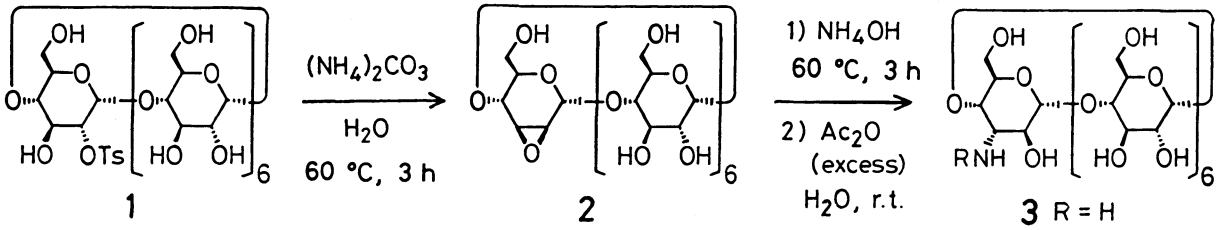
Mono(3-acetylamino-3-deoxy)-β-cyclodextrin (**4**) was firstly prepared via regioselective ring opening of manno-epoxide by ammonia. ^{1}H-NMR investigation clearly demonstrated that **4** recognized the chirality of mandelic acids and N-acetyl-phenylglycine by the formation of diastereomeric inclusion complexes.

Chiral recognition by organic host molecules has been extensively studied in recent years. Since cyclodextrins (CDs) are optically active hosts, they can form diastereomeric inclusion complexes with chiral guests, and the intrinsic chirality of CDs is reflected in the solubility, spectroscopic property, and reactivity of included guests.[1] Although efficient separation of some enantiomers[2] and high asymmetric inductions[3] by use of CD derivatives have been reported, there have been only few studies[4] on the chiral recognition by CDs on the basis of NMR spectroscopy.

We have recently reported[5] the regioselective preparation of mono(2-O-tosyl)-CDs, which are important intermediates of secondary-hydroxyl side modified CDs. This paper describes the first synthesis of mono(3-acetylamino-3-deoxy)-β-CD (**4**) from 2-O-tosyl-β-CD (**1**) and the ^{1}H-NMR spectroscopic properties of its inclusion complexes in aqueous solution.

The synthesis of **4** was carried out as shown in scheme 1. The 2-O-tosylate (**1**) was converted to 2,3-manno-epoxide (**2**) according to the known method.[6] Then, **2** was treated with 25% aqueous ammonia at 60 °C for 3 h to give mono-amino-CD in 70-80% yield[7] from **1**. The structure of this product was determined to be **3** containing 3-amino-3-deoxy-D-altrose residue, based on its ^{1}H- and ^{13}C-NMR spectra.[8] Its ^{1}H-NMR spectrum[9] showed a small, characteristic signal at δ 2.98 ppm (1H, dd, J=3.3 and 9.6 Hz), the expected position of a proton attached to C-NH_2 unit.



1 **2** **3** R = H **4** R = Ac

Scheme 1.

Spin-decoupling experiment demonstrated that this proton was attached to C-3,with coupling to protons at C-2 and C-4. The ^{13}C-NMR spectrum of **3** showed only one small signal of the carbon carrying the nitrogen at 53.3 ppm. Mono(2-amino-2-deoxy)-β-CD was not obtained. This regioselective addition, similar to the result reported,[6] is consistent with the diaxial opening rule of sugar epoxides.[10]

The amino group of **3** smoothly reacted with acetic anhydride in water to give acetamide (**4**)[11] in good yield. On the ^{1}H-NMR spectrum of **4**, anomeric (C-1) proton signals are separated into several doublets as shown in Fig. 1. A larger coupling constant ($J_{1,2}$=6.8 Hz) of a proton at 4.93 ppm suggests 1,2-trans configuration of its parent pyranose unit, while the other coupling constants ($J_{1,2}$=3.0-3.9 Hz) indicate the 1,2-cis configuration.[12] This spectrum confirms the assignment of structure **3**.[13] The molecular model of **4** constructed on the basis of the above result has a slightly oval and unsymmetrical macrocyclic ring.

In order to compare the complexation properties, mono(6-acetylamino-6-deoxy)-β-CD (**5**),[14] a primary-side modified isomer of **4**, was also prepared from 6-amino-CD.[15] In comparison with β-CD (**6**) or **5**, **4** is highly soluble in water.

Complex formation between these hosts and chiral aromatic guests in aqueous solution was investigated by ^{1}H-NMR spectroscopy.[8] Mandelic acid (MA), methyl mandelate (MM), and N-acetyl-α-phenylglycine (APG) were employed as chiral guests. The concentrations of the guests were equal to or slightly lower than those of the hosts (ca. 0.02-0.04 mol dm^{-3} in D_2O). Upon complexation, most proton signals of the hosts moved upfield[16] due to the ring current effects of the aromatic guests. As shown in Fig. 2, the methine proton signals of DL-MA and DL-APG in the complexes are split into two peaks for the all hosts. These splittings are resulted from the difference in the induced shifts of the D- and L-isomers by the formation of diastereomeric host-guest complexes. The differences between two peaks by use of **4** as a host are much larger than those by use of **5** or **6** and the largest splitting (0.07 ppm) is observed for DL-APG with **4**. As shown in Fig. 2, the methine proton signal of DL-MM is also split into two peaks in the presence of **4**, while such a splitting is not observed in the presence of **5** or **6**. In cases where **4** is a host, the two peaks of the racemates clearly correspond to the signals of the two enantiomers for the respective guests. This indicates that each of the enantiomeric guests is included with a particular geometry into the cavity of **4**. In all cases, phenyl protons of the guests show little upfield shifts (0 - 0.02 ppm) and no enantiomeric differences.

The above observations clearly show that the secondary acetamide (**4**) has higher ability to discriminate between D- and L-isomers of these guests than β-CD (**6**) or the primary acetamide (**5**). This complexation property of **4**, different from that of **5**, is probably resulted from the inversion of C-2 and C-3 configurations of one sugar residue. Therefore, selective modification of the secondary-hydroxyl side of CDs seems to be an effective approach to increase the ability of chiral recognition. Our present study exhibits an attractive possibility of **4** as chiral NMR shift reagent. Further investigations are now in progress to elucidate the binding modes of chiral guests with **4**.

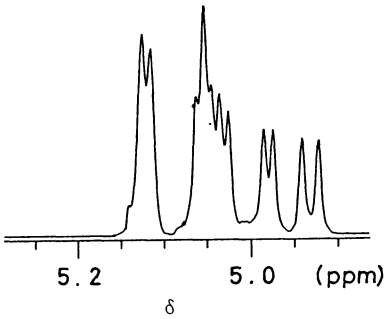


Fig. 1.
^{1}H-NMR spectrum of **4** (360 MHz, D_2O).
Only anomeric proton signals are shown.

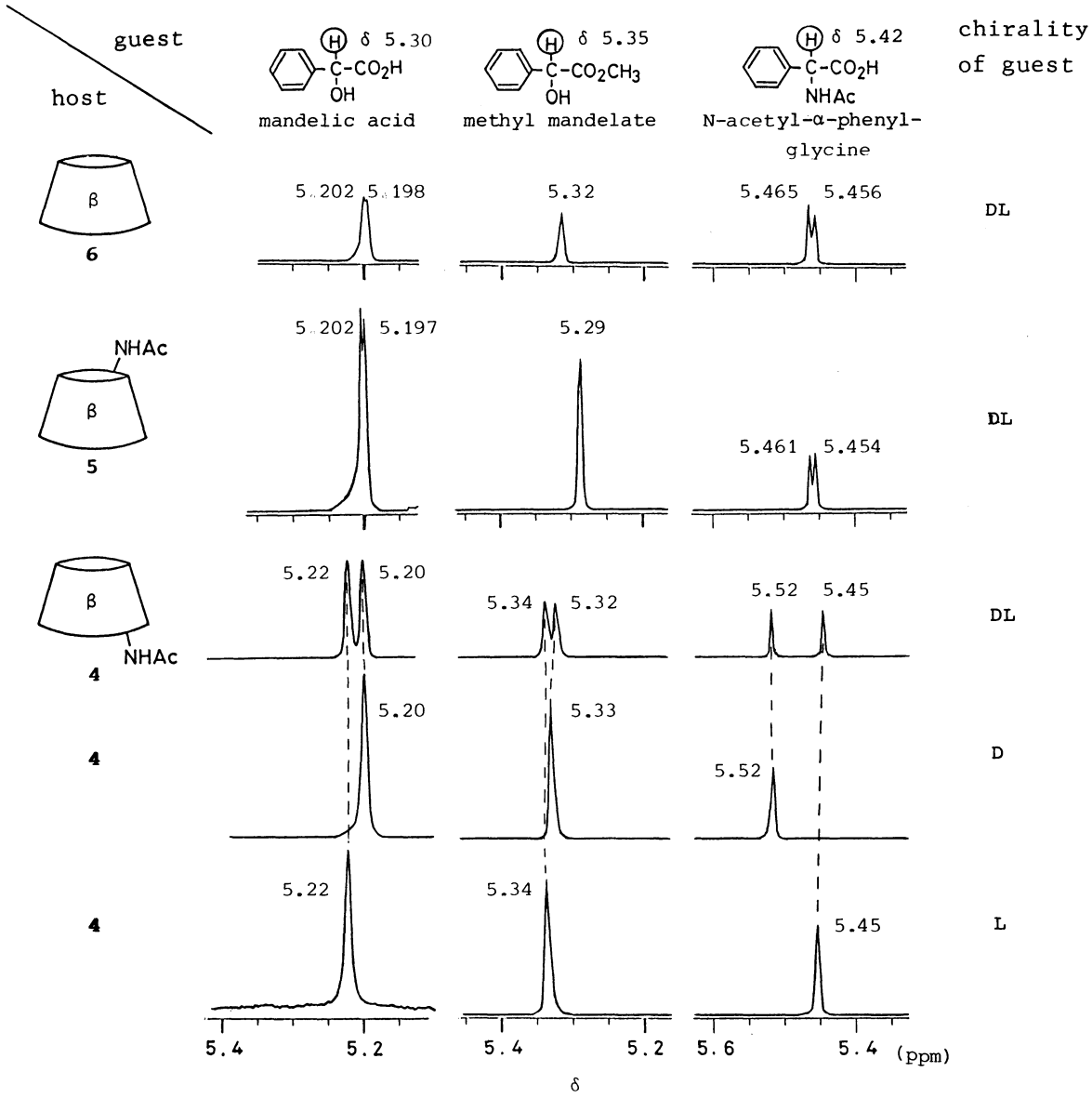


Fig. 2. ^{1}H-NMR spectra of inclusion complexes in D_2O (360 MHz).
Only methine signals of guests are shown.

References

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5) T. Murakami, K. Harata, and S. Morimoto, Tetrahedron Lett., 28, 321 (1987).
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7) The amino-CD was isolated by SP-Sephadex C-25 (cation-exchanger) column chromatography, eluted with 0.5% aqueous ammonia.
8) All ^{1}H-NMR spectra were measured on a Nicolet NT360 Fourier-transformed NMR system (360 MHz) at 20 °C. ^{1}H-Chemical shifts were referenced to external tetramethylsilane in $CDCl_3$.
9) ^{1}H-NMR (D_2O) data of **3**: δ 2.98 (dd, J=3.3, 9.6 Hz, 1H), 3.55-3.70 (m, 14H), 3.74-4.00 (m, 28H), 4,22 (m, 2H), 5.00 (d, J=3.8 Hz, 1H), 5.03 (d, J=3.8 Hz, 1H), 5.04 (d, J=4.9 Hz, 1H), 5.05 (d, J=4.3 Hz, 1H), 5.13 (d, J=3.6 Hz, 2H).
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11) Physical data for **4**: mp 235-240 °C (dec.); $[\alpha]_D^{25}$ +136°(c 1.0, H_2O); Elemental analysis, Found $C_{44}H_{73}NO_{35}\cdot 2H_2O$; ^{1}H-NMR ($D_2O$) δ 2.02 (s, 3H), 3.56-3.70 (m, 14H), 3.78-4.00 (m, 28H), 4.20 (m, 1H), 4.93 (d, J=6.8 Hz, 1H), 4.98 (d, J=3.9 Hz, 1H), 5.03 (d, J=3.6 Hz, 1H), 5.05 (d, J=3.0 Hz, 1H), 5.06 (d, J=3.1 Hz, 1H), 5.12 (d, J=3.4 Hz, 2H); ^{13}C-NMR (D_2O/DSS) δ 23.5, 52.4, 61.2, 61.8, 71.3, 72.9, 73.3, 73.7, 74.1, 74.5, 77.4, 79.6, 81.3, 82.1, 82.2, 82.4, 102.5, 102.7, 102.9, 103.1, 103.2, 105.2, 175.6; IR (KBr) 1640, 1550 cm^{-1} (amide group).
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13) The anomeric proton of the altrosamine unit of **3** could not be observed owing to the overlap with a large HDO peak at 4.81 ppm.
14) Satisfactory ^{1}H- and ^{13}C-NMR, IR spectral and analytical data were obtained for **5** : mp 285-288 °C (dec.); $[\alpha]_D^{26}$ +154 ° (c 0.80, H_2O).
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16) P.V. Demarco and A.V. Thakkar, Chem. Commun., 1970, 2; D.J. Wood, F.E. Hruska, and W. Saenger, J. Am. Chem. Soc., 99, 1735 (1977) ; Since the system is in the NMR chemical shift fast-exchange limit, the proton signals appear at the weighed averages of the chemical shifts of the free and the complexed forms.

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