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Bifunctional β-Cyclodextrins with Two Imidazolyl Groups Specifically Attached to C3 Positions

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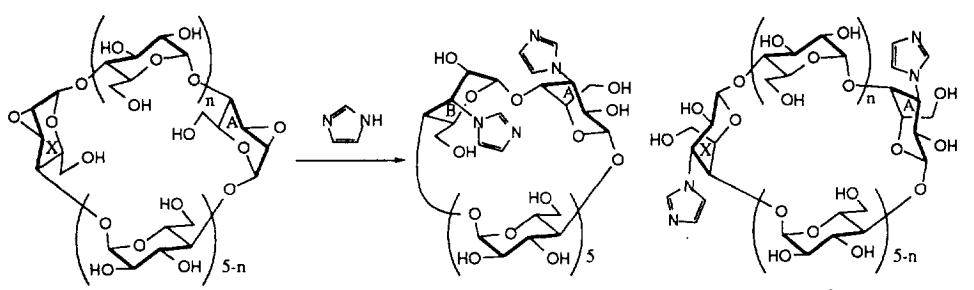
Abstract: By reacting $2^A,3^A$; $2^X,3^X$-dimannoepoxido-β-cyclodextrins with imidazole, $3^A,3^X$-diimidazolyl-$3^A,3^X$-dideoxy-(2^AS),(2^XS),(3^AR),(3^XR)-β-cyclodextrins (X = B, C, D) were prepared and their conformational behavior was also described.

Bifunctional cyclodextrins have attracted special attention in biomimetic research since natural enzymes generally use the action of two or more functional groups to achieve catalysis. By introducing a pyridoxamine moiety and an ethylenediamine group onto β-cyclodextrin, Tabushi *et al.*[1] revealed the stereospecific transamination of α-ketoacids. Breslow *et al.* demonstrated simultaneous bifunctional catalyses of bis(imidazolyl)-β-cyclodextrins in the hydrolysis of cyclic phosphate esters[2] and in the enolization of ketones.[3] These studies have been confined to the primary hydroxyl side of cyclodextrins, while bifunctionalization on the secondary hydroxyl side has seldom been reported. If the two functional groups are attached regiospecifically to the ring carbons rather than to the methylene carbons of a cyclodextrin, they should have less freedom and more rigid geometry and can therefore serve as preferential candidates to elucidate the geometric requirements for some bifunctional catalyses. Recently, we worked out an efficient method for regiospecific preparation of a set of dimannoepoxido-β-cyclodextrins[4] and clarified the opening reaction of 2,3-mannoepoxide ring.[5,6] Here we describe the regio- and stereo-specific introduction of two imidazolyl groups to two C3 positions of β-cyclodextrin and the interesting conformational behavior of the bis(imidazolyl)-β-cyclodextrins **2**a-c.



1(a~c) **2a** **2b, 2c**

a: n = 0, X = B; b: n = 1, X = C; c: n = 2, X = D

A solution of $2^A,3^A$; $2^B,3^B$-dimannoepoxido-β-cyclodextrin **1**a (138 mg) in 13 mL of pH 7.0 imidazole-HCl buffer (1.1 mole/L) was heated at 75 ℃ for a week. The reaction mixture was diluted with water and chromatographed on a reverse-phase column (Lobar Column LiChroprep Rp-18, size B, Merck). After elution with water (1 L), a linear gradient elution from water (1 L) to 20 % aqueous methanol (1 L) afforded **2**a (121 mg, 78%). Similarly, **2**b (72 mg, 68%) and **2**c (94 mg, 68%) were obtained from their corresponding dimannoepoxide **1**b (94 mg) and **1**c (123 mg), respectively. Pure imidazole as a solvent gave similar results, whereas DMF enabled no obvious reaction. The structures of **2**a-c were confirmed by their FAB mass spectra, ^{1}H and ^{13}C NMR spectra (Fig. 1, only the cyclodextrin parts were shown).

The information about the fine structures of **2**a-c was obtained from ^{1}H and ^{13}C NMR spectra. Each signal was assigned based on 2D COSY and ROESY experiments. Fig. 1 shows that all the sugar residues in each compound are different from each other, indicating the destruction of the C_7 symmetry of native β-cyclodextrin by the introduction of the imidazolyl groups. The resonances associated with the functional sugar residues are subjected to significant shifts. Large downfield shifts of H3 protons (1-1.3 ppm) and of C3 carbons (~14 ppm) are assigned for all the functional sugar residues, indicating that all the imidazolyl groups are attached to C3 positions. On the basis of the axial attack[7,8] of imidazole at C3 of the mannoepoxide unit, the formation of altroside is expected for each functional sugar residue in **2**a-c, which can also be derived from the ^{1}H-^{1}H coupling constants given in Table 1 and the close similarity of the ^{13}C NMR spectra of **2**a-c to those of 2- or 3-imidazolyl-altro-β-cyclodextrin.[6]

Table 1. Coupling Constants (Hz) of the Modified Sugar Units in Compounds **2**a-c

Compound	**2**a		**2**b		**2**c	
	A	B	A	C	A(or D)	D(or A)
$J_{1,2}$	6.9	2.7	7.1	7.6	7.2	6.8
$J_{2,3}$	~11.0		11.2	11.7	11.1	11.0
$J_{3,4}$	~3.2		2.1	2.5	2.3	2.1

The conformational behavior of the modified altrosides is of interest. In the case of mono-manno-β-cyclodextrin, the $^4C_1$ altroside resulting from diaxial opening of the epoxide ring usually undergoes a subsequent chair inversion to $^1C_4$ conformation.[8] This appears to be the case in compounds **2**b and **2**c. Each altroside unit in these compounds demonstrates ^{1}H-^{1}H coupling constants of $J_{1,2}$ 6.8-7.6 Hz and $J_{2,3}$ 11.0-11.7 Hz, suggesting the axial orientation of H1, H2 and H3 protons, and of $J_{3,4}$ 2.1-2.5 Hz, indicating an equatorial orientation of H4. These results are in agreement with the promise that all the modified altrosides in **2**b and **2**c have a predominant conformation of $^1C_4$. In contrast, compound **2**a shows two altrosides of different conformation. The coupling constants of the sugar unit A, which are similar to those of **2**b and **2**c, indicate a $^1C_4$ conformation. The altroside unit B, however, exhibits a coupling constant $J_{1,2}$ of 2.7 Hz, which corresponds to an equatorial-equatorial interaction. This observation suggests that the unit B has a $^4C_1$ conformation, which can be further confirmed by NOE experiments. For a 3-imidazolyl altroside, the $^4C_1$

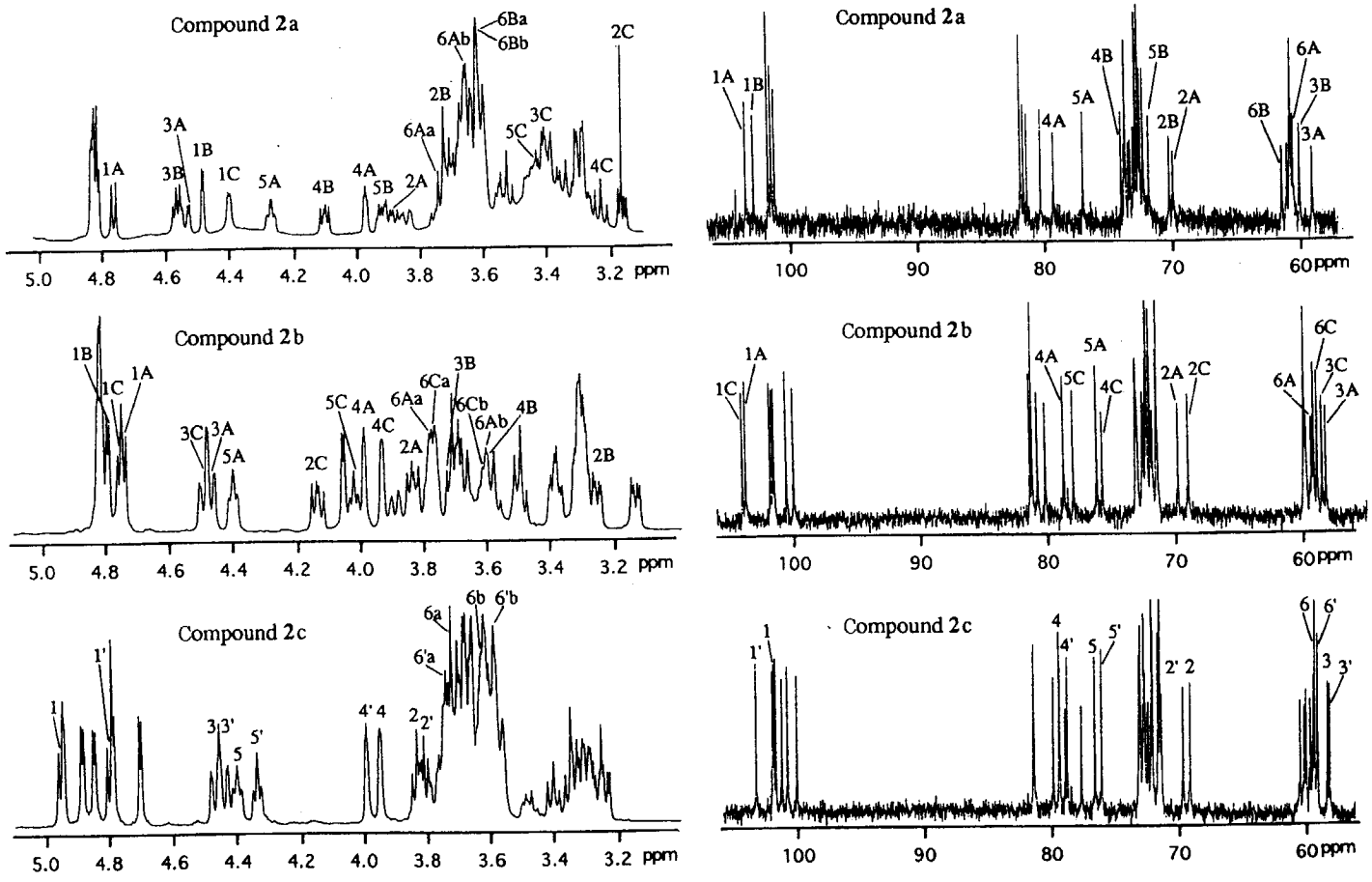


Fig. 1 ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra of compounds **2**a-c in $(CD_3)_2SO$-D_2O.

conformation locates the axial H5 and 3-imidazolyl group close enough to give obvious NOE enhancements while directing the equatorial H1 and H3 protons apart from each other. The situation of the $^1C_4$ conformation is just reverse. Indeed, the irradiation of H5B gave notable NOE enhancements of the protons of the imidazolyl group on the sugar B, whereas on irradiating the H1B, no obvious NOE signal of the H3B proton was observed. Every other modified altroside residue showed significant NOE enhancements between the H1 and H3 protons but no important signals between the H5 and imidazolyl protons. These results are consistent with the assignments of the conformations. The formation of compound **2**a represents the first example that a cyclodextrin epoxide undergoes a ring opening without subsequent inversion of its $^4C_1$ conformation. This retention of the $^4C_1$ conformation, although its reason has not been deciphered, makes **2**a different from **2**b and **2**c in two respects. (i) Compound **2**a possesses a less deformed hydrophobic cavity than **2**b and **2**c do since the inversion of the $^4C_1$ conformation deforms the cyclodextrin cavity significantly, while the retention of the $^4C_1$ conformation does not. (ii) The orientations of the imidazolyl groups are different: the one on the sugar B of compound **2**a is directed towards the cavity of cyclodextrin, while all the others of compounds **2**a~c are positioned nearly parallel to the cavity. Therefore, different binding and catalytic properties are expected from these rigid bifunctional cyclodextrins.

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