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Restriction of guest rotation based on the distortion of a cyclodextrin cavity

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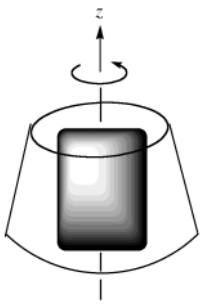
Significant restriction of the rotation of an intermolecular guest upon binding into a distorted cyclodextrin cavity has been observed for the first time.

Most enzymes bind substrates in their hydrophobic pockets and promote the reaction of bound substrates in a strictly controlled manner. It is not rare that enzymes control multiple reactants so exactly as to give only one isomeric product during the formation of multiple chiral centers. In the last three decades, bioorganic chemists have been investigating the main factors that predominate in enzyme reactions and have created artificial enzymes by mimicking the enzyme actions with synthetic model compounds.[1–3] In this endeavour, cyclodextrins (CDs) are the first and also the most profoundly studied class of apoenzyme mimics.[4,5] Cyclodextrins have a closed-up belt-type structure usually composed of 6–8 glucopyranose units. Their cavity can accommodate a variety of guest molecules of suitable size and shape, mainly *via* hydrophobic interactions. Since the hydrophobic binding force is non-directional, the C_n symmetry of the CD cavity leaves appreciable freedom for the bound substrates to rotate around the *z* axis (Scheme 1).[6] However, this rotation should be properly controlled in order to develop more efficient and sophisticated enzyme mimics. However, this problem has been essentially ignored up to now. The only work dealing with this problem appeared ten years ago, concluding that the hosts having larger binding constants restrict the molecular motion of guests more significantly.[7] Since the binding site of an enzyme is usually unsymmetrical rather than symmetrical, a cyclooligosaccharide with a distorted hydrophobic cavity may serve as a better model for enzymes than a C_n symmetrical CD. We found that distorting the hydrophobic cavity of β-CD remarkably reduces the rotation of bound 2-naphthalenesulfonate, but does not necessarily increase the binding strength. Herein, we describe NMR evidence for this first example of cavity-based restriction of guest rotation.



Scheme 1 In principle, a guest in a CD cavity has appreciable freedom to rotate around the *z* axis.

One glucose of β-CD can be readily converted to altrose.[8] The resultant mono-*altro*-β-CD **1** shows distinct NMR signals (Fig. 1, bottom) for all its protons. Though it no longer has C_n symmetry, the difference between the glucose units is not very significant. As a result, the signals of all the non-anomeric C–H protons are crowded in the narrow range of δ 3.9–3.5. However, significant changes occur in the NMR spectrum of **1** upon complexation with sodium 2-naphthalenesulfonate (Na–Nas). By following the spectral change upon addition of Na–Nas to the host solution, a binding constant of 176 M^{-1} can be derived, slightly smaller than that of β-CD–Nas.[9] In the NMR spectrum of 90% **1**–Nas complex and 10% **1** (Fig. 1), the originally overlapped signals in the range δ 3.9–3.5 are more widely dispersed over the range δ 4.2–2.69, and all the H-1 protons are clearly separated. Obviously, the guest Nas exercises a very strong anisotropic effect on each sugar unit of the host.

In order to further understand this phenomenon, the NMR spectrum of the complex has been assigned in detail with the aid of various techniques (the assignment is partially depicted in Fig. 1). As is clear from Fig. 1, inclusion complexation causes significant shifts for the inner-directed H-3 and H-5 protons. The drastic upfield shifts of protons 3C, 5C, 3D, 5D, 3G and 5G

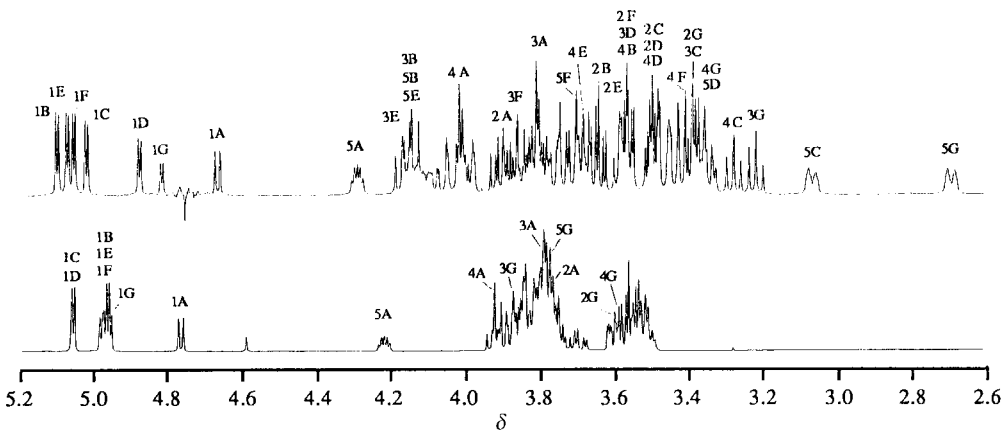


Fig. 1 500 MHz ^{1}H NMR spectra of mono-*altro*-β-CD **1** (bottom) and of its 2-naphthalenesulfonate inclusion complex **2** (top, 90% binding) in D_2O, assigned based on 1D TOCSY, 2D COSY, HMBC and NOE experiments. The sugar units are labeled clockwise A–G (viewed from the primary hydroxy side), starting from the altrose unit. The numbers denote the positions to which the corresponding protons are attached.

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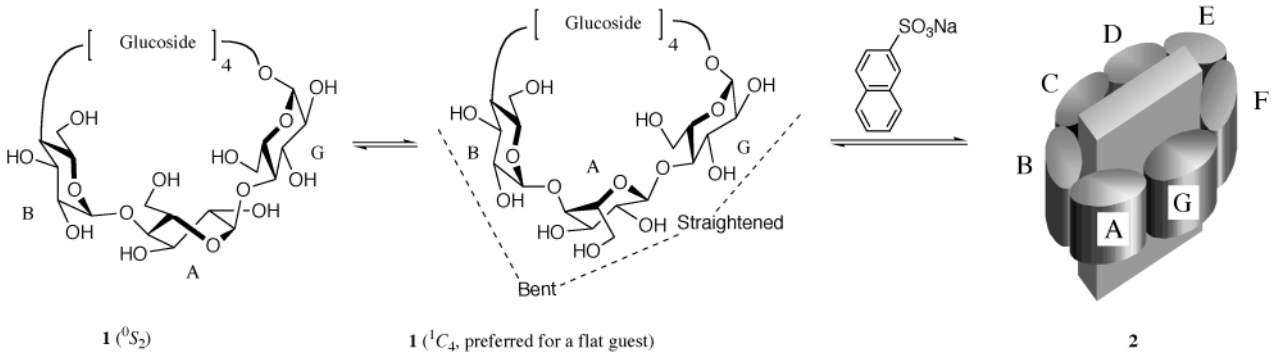
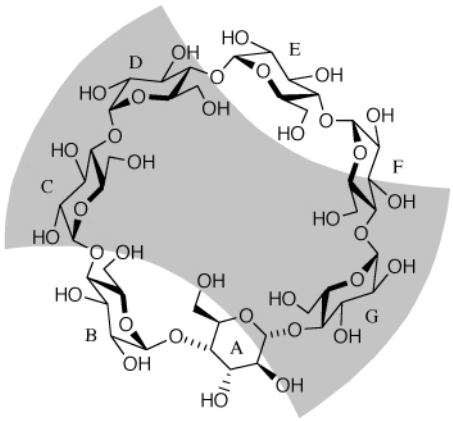


1 ($^0S_2$) **1** ($^1C_4$, preferred for a flat guest) **2**

Scheme 3 Mono-*altro*-β-CD **1** and its inclusion complex with sodium 2-naphthalenesulfonate. **2** is a sketch (view from the 6-OH side) for the proposed structure of the **1**–Nas complex: the cylinders denote pyranosides while the plate represents Nas.



Scheme 2 The anisotropic effect that **1** experiences in the complex: the shaded region denotes a shielding field while the unshaded region represents a deshielding field.

imply that the sugar units C, D and G are under a strong shielding effect from Nas, while the large downfield shifts of protons 3B, 5B, 3E and 5E are indicative of a strong deshielding effect. Careful examination of the NMR data thus reveals that the host molecule in the complex is under an extremely unusual anisotropic effect, as represented in Scheme 2. The protons in the shaded region are shifted upfield while those in the non-shaded region are shifted downfield. Sugar G is located in the center of the lower right half of the shielding region and is subjected to the strongest shielding effect and the largest upfield shifts are for H-3 and H-5 of sugar G ($\Delta\delta$ −0.77 and −1.18 ppm, respectively). The effect becomes much weaker for the neighboring sugar units A and F, and gradually becomes deshielding when crossing the two units. On the opposite side of G, both C and D lie in the upper left half of the shielding region. Accordingly, protons H-4C and H-1D, although outward-directed, exhibit a remarkable upfield shift. The inward-directed H-3 and H-5 protons of the two sugar residues are still strongly shielded, but obviously to a smaller extent than the corresponding protons of sugar G. The shielding effect is weak for H-4D and H-1C and becomes deshielding for H-1E and H-4B. Both the sugar units B and E are fully under a deshielding effect with their inward-directed protons H-3 and H-5 being significantly shifted downfield. As a result, each pyranoside in the inclusion complex experience different anisotropic effects, which represents, to the best of our knowledge, an unprecedented strongly anisotropic effect of an intermolecular guest within a cyclooligosaccharide host.

Based on the above result, the structure of the complex (**2**) can be visualized as shown in Scheme 3. The pyranose G and disaccharide C–D are situated on either side of and nearly parallel to the naphthalene ring, while the naphthalene species directs its 1-9-8 and 4-10-5 rims towards between the sugar units B and A or E and F but much closer to the B and E units. Although Scheme 3 represents a static situation rather than a dynamic one, it probably represents the most probable rotamer, if indeed there is any rotation of the guest in the CD cavity, outweighing any others for the complex to a very large extent. Were mono-*altro*-β-CD not restricting the guest rotation, as in the case of β-CD, the ring-current effect of the guest would be averaged so that each sugar unit would be subjected to a similar shielding effect rather than the observed anisotropic effect, and the inward-oriented protons of all the sugar units would give NOE on irradiation at the naphthalene protons. Irradiation at the 1-H of the guest gave cross peaks at the frequencies corresponding to protons H-3 and H-5 of B and E whereas no cross peaks correlating with the protons of C, D and G were observed, which supports the above assertion.

It is not surprising that the rotation of the bound guest is substantially restricted as the host adopts a distorted conformation and **2** is the complex structure expected from the host conformation. The altrose portion of **1** is an equilibrium of the $^0S_2$ and $^1C_4$ conformers with an approximate 2 : 1 preponderance of the latter (Scheme 3).[10] The $^0S_2$ makes the overall shape of **1** closely resemble that of β-CD, while the $^1C_4$ conformer straightens the A–G disaccharide but bends the A–B disaccharide, and leads to a mussel-shaped ellipse shape for the cavity with its longer axis passing through residues B and E. It is reasonable to deduce that $^1C_4$ is the preferential conformer enabling the host to accommodate the flat guest Nas, by accommodating the guest plane along its longer axis. Indeed, the binding of Nas into the cavity of **1** increased the coupling constants $J_{1,2}$ and $J_{2,3}$ of the altroside, suggesting a significant enrichment of the $^1C_4$ conformer upon inclusion.

In conclusion, the introduction of an altrose unit to β-CD narrows the hydrophobic cavity and enables it to substantially reduce the rotation of the bound flat Nas guest. In this sense, the binding of mono-*altro*-β-CD **1** is more like an enzyme process than that of normal CDs.

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