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Interaction of Pyromellitic Diimide Derivatives with β-Cyclodextrin and Anthracene-Appended β-Cyclodextrin: Rim Binding vs Inclusion Complexation

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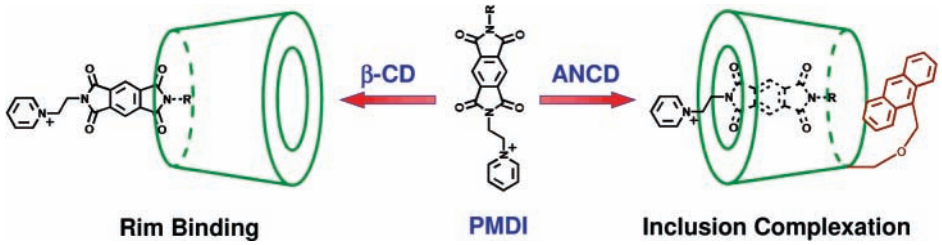
ABSTRACT



Complex formation of pyromellitic diimide derivatives with β-cyclodextrin and anthracene-appended β-cyclodextrin was studied with use of induced circular dichroism and ^{1}H NMR spectroscopies. It is revealed that pyromellitic diimides form rim-binding type complexes with β-CD and in these complexes the pyromellitic diimides lie just outside of the narrow rim of the CD. With anthracene-appended β-CD the pyromellitic diimides form true inclusion complexes. Implications of the formation of rim-binding type complexes are also discussed.

Cyclodextrins (CDs) are cyclic oligosaccharides having six, seven, or eight D-glucopyranose units linked by α-(1,4) linkages. CDs are shaped like truncated cones possessing a hydrophobic cavity lined on the interior with the H3 and H5 protons and glycosidic oxygen atoms of the glucose units. The primary hydroxyl groups of the glucose units are arranged on the narrow rim and the secondary hydroxyl groups are assembled on the wider rim of the cone. The most important attribute of CDs is their ability to form complexes with other molecules and almost all applications of CDs, either in research or in industry, are related to complex formation.[1] In most of the CD complexes, the guest molecules are either completely or partially encapsulated into the CD cavity and hence these are generally known as inclusion complexes. Nearly a thousand papers appear every year on CD systems and about 22% of these papers deal with studies of inclusion complexes,[2] leading to the common belief that all CD complexes are inclusion complexes. In this Letter, we try to show that β-CD can form non-inclusion-type complexes also. Our studies with pyromellitic diimide derivatives (PMDIs) show that β-CD can form non-inclusion-type complexes wherein the PMDIs lie just outside of the narrow rim of β-CD. We also show that PMDIs can form true inclusion complexes with β-CD if the narrow rim is blocked by substitution with a relatively large molecule like anthracene.

PMDI derivatives employed in this study (see the Supporting Information for structures and synthesis) have a

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2-(ethyl)pyridinium group attached to one of the nitrogen atoms, which makes them water soluble. The other nitrogen is attached to the 2-propyl, *n*-butyl, or *n*-hexyl group. Synthesis and characterization of anthracene-appended β-CD (designated as ANCD in this paper) was reported previously.[3] All PMDIs exhibited similar absorption spectra (λ_{max} = 314 nm, $\epsilon_{max} \approx 2800$ M^{-1} cm^{-1}). Upon addition of β-CD, absorption spectra of PMDIs exhibited changes indicative of complex formation. In this paper complex formation is studied by induced circular dichroism (ICD) and ^{1}H NMR techniques.

PMDI derivatives do not exhibit circular dichroism, but when associated with β-CD or ANCD they exhibited ICD. Figure 1A shows ICD spectra of the PMDIs in the presence

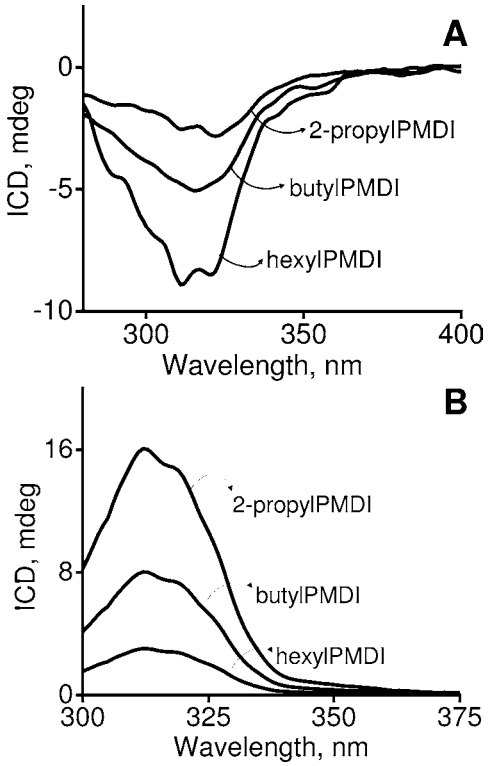

Figure 1. ICD of PMDIs (3.5×10^{-4} M) in the presence of (A) β-CD (1.4×10^{-3} M) and (B) ANCD (1.2×10^{-5} M).

of β-CD and Figure 1B shows ICD spectra of PMDIs in the presence of ANCD. ICD spectra shown in parts A and B of Figure 1 differ in several respects. (1) The β-CD:PMDI systems exhibit negative ICD signals where the signal intensity increased with alkyl chain length. (2) The ANCD:PMDI systems showed strong positive ICD signals where the signal intensity decreased with alkyl chain length. (3) For β-CD:PMDI, millimolar amounts of β-CD were required to obtain ICD signals whereas for ANCD:PMDI good ICD signals were obtained with 10^{-5} M ANCD.

Achiral molecules complexed with CDs often exhibit induced CD spectra, the sign and intensity of which are very sensitive to the orientation of the achiral molecule. The orientation of the guest is usually deduced by using the rules derived for ICD of chiral supramolecular systems, which were initially derived for CD complexes[4] and then generalized for complexes of chiral macrocycles.[5] The rules predict the following: (1) the sign of ICD is positive for a transition polarized parallel to the axis of the macrocyclic host and negative for that polarized perpendicular to the axis; (2) the sign of ICD is reversed when a chromophore moves from the inside of the host cavity to the outside, keeping the direction of the transition moment unchanged; (3) the absolute value of ICD is greater when a chromophore exists on the outside of the narrower rim than when it is on the outside of the wider rim; and (4) the ICD value of a transition polarized perpendicular to the axis of a macrocycle is $-1/2$ of that of a parallel-polarized one and the sign of ICD changes at 54.7°. These rules were successfully applied for the conformational analysis of several CD-appended systems and inclusion complexes.[6]

For PMDIs, the lowest energy absorption (314 nm) is polarized along the long axis connecting the two imide nitrogen atoms.[7] Thus in a parallel orientation we would expect positive ICD if PMDI is inside the cavity and negative ICD if PMDI is outside. Geometrical considerations (see the Supporting Information for molecular dimensions) suggest that PMDI cannot be accommodated within the β-CD cavity in a perpendicular manner. On the basis of these factors and the ^{1}H NMR data (vide infra), the strong positive ICD of ANCD:PMDIs is assigned to parallel orientation of PMDI within the cavity and the negative ICD for the β-CD:PMDI systems is assigned to parallel orientation outside the cavity as shown in Figure 2. An orientation in which PMDI lies just outside of the wider rim (for β-CD:PMDI) is ruled out based on geometrical considerations (vide infra). If PMDI is sitting outside the cavity as shown in Figure 2, encapsulation of small molecules into the cavity is not expected to affect this binding process. Preliminary experiments showed that addition of toluene (1.75×10^{-3} M) into the 2-propyl-PMDI/β-CD system, for example, resulted in very little change in the ICD signal. The association constants (K_a) were determined from Benesi−Hildebrand plots of the ICD data, assuming 1:1 stoichiometry. For β-CD:PMDI systems K_a values were 300 (2-propyl), 700 (*n*-butyl), and 1800 (*n*-hexyl) M^{-1} and increased in the order 2-propyl < *n*-butyl < *n*-hexyl. For ANCD:PMDI systems the order was reversed and K_a values were 1249 (2-propyl), 596 (*n*-butyl), and 533 (*n*-hexyl) M^{-1}.

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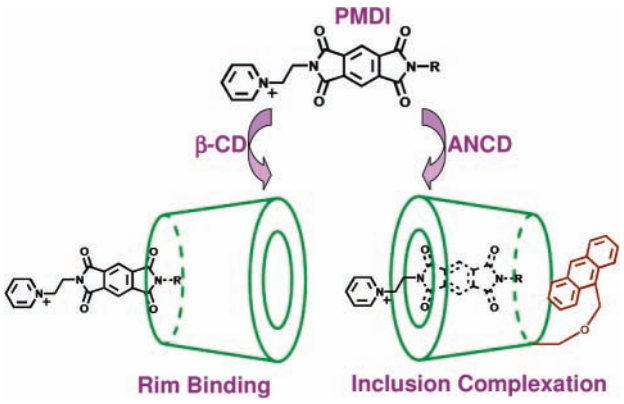

Figure 2. Scheme showing different types of binding for β-CD: PMDI and ANCD:PMDI systems.

Orientations for the complexes shown in Figure 2 are confirmed by ^{1}H NMR. ^{1}H NMR of *n*-butylPMDI in D_2O in the presence of increasing amounts of β-CD and ANCD is given in the Supporting Information and important changes observed in the chemical shift values of the various protons caused by the addition of CD are shown in Figure 3. Upon addition of β-CD small changes are observed for the alkyl (0.06−0.14 ppm for protons a, b, and c) and aromatic (0.09 ppm for proton e) protons (Figure 3A). Protons of the pyridinium group (h, i, and j) are unaffected indicating that this moiety is placed away from the CD. The effect of addition of β-CD on the ^{1}H NMR of 2-propylPMDI and *n*-hexylPMDI was also very samll. Addition of ANCD, on the other hand, led to drastic shifts in the signals of all protons except for the pyridinium protons (Figure 3 B). The alkyl protons experienced considerable broadening, loss of splitting pattern, and shifts in the 0.3−0.7 ppm range. The aromatic proton is shifted by 0.4 ppm along with broadening, indicating that this moiety is tightly bound within the CD cavity. Results similar to these are obtained for complex formations of ANCD with 2-propylPMDI[3] and *n*-hexylPMDI.

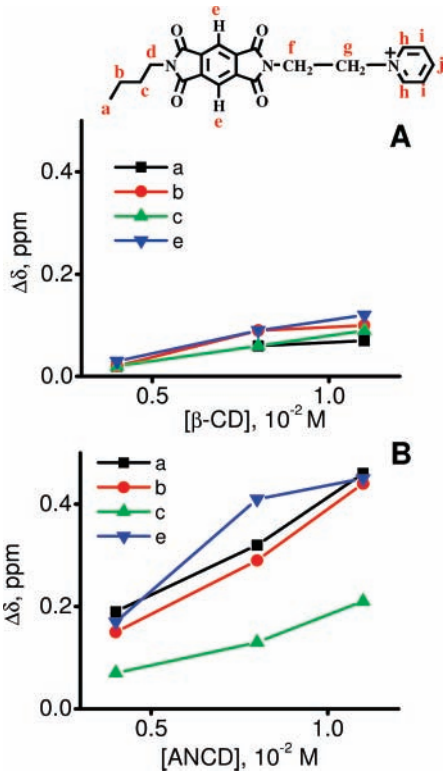

Figure 3. Changes in the ^{1}H NMR chemical shifts of butylPMDI upon addition of (A) β-CD and (B) ANCD. Assignments of the various protons are also indicated.

In the conformation shown for β-CD:PMDI systems (Figure 2) most parts of the PMDI molecule are exposed to water. Native β-CD contains about six water molecules inside the cavity. When the alkyl group inserts into the cavity through the narrow rim as shown in Figure 2, a few water molecules might be displaced, but the alkyl chain is still exposed to water that can enter and leave the cavity through the wider rim. The microenvironment around the PMDI chromophore does not change much and hence changes observed for the aromatic protons are very small.

The conformation shown in Figure 2 for ANCD:PMDI is a closed conformation. The anthracene moiety present at the small rim acts as a lid for the CD. The PMDI is inserted into the cavity through the wider rim with the alkyl group near the narrow rim and the pyridinium group remaining in the aqueous phase near the wider rim. The aromatic moiety of PMDI is relatively large and provides a tight fit near the wider rim. In such a conformation all water molecules present in the cavity would be displaced to the outside and the cavity becomes highly hydrophobic, leading to substantial shifts in the NMR signals. As the alkyl chain becomes larger, more and more of the aromatic moiety will be displaced to the outside of the wider rim. The cavity becomes more open leading to a decrease in hydrophobicity resulting in lower association constants and NMR shifts.

For β-CD complexes the most probable binding involves insertion of the nonpolar part of the guest into the cavity with the polar group exposed to bulk water just outside the wider rim.[8] For β-CD:PMDI systems the binding mode that emerges from ICD and NMR studies and shown in Figure 2 is exactly opposite. It is not clear as to why PMDIs associate with β-CD in this fashion, although some conclusions can be drawn from general considerations. The most hydrophobic part in 2-propylPMDI, for example, is the 2-propyl group. The pyridinium moiety is very hydrophilic and prefers to be in water. The imide moieties have two carbonyl groups each, capable of hydrogen bond formation with water, making them relatively hydrophilic. In the conformation shown in Figure 2, the imide group at the pyridinium end remains unaffected. The imide group at the 2-propyl end can engage itself in hydrogen bonding interactions with the primary OH groups at the narrow rim. Since the diameter of the narrow rim (5.6 Å) and the O−O distance of the imide group are similar (4.6 Å), H-bonding can result in the formation of a rigid structure. The OH groups at the wider

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rim are engaged in strong intramolecular H-bonding (between the 2-OH and 3-OH of adjacent glucose units) and hence not available for H-bonding with PMDI. Thus the imide group of the PMDI is sitting at the narrow rim, H-bonded to the primary OH groups with the 2-propyl group projecting slightly into the cavity. The association constants for 2-propanol, 1-butanol, and 1-hexanol with β-CD are respectively 2.6, 16.6, and 219 M^{-1}.[8] Thus, stabilization resulting from insertion of the 2-propyl group into the cavity is small and the major factor contributing to the association of 2-propylPMDI may be arising from the rigid hydrogen bonding interactions of the imide group with primary OH groups. Hence we categorize these as rim-binding-type complexes. K_a values in these systems increase with an increase in alkyl chain length due to the cooperative interactions of hydrogen bonding and alkyl group insertion. When the anthracene group is attached to one of the primary OH groups, the AN moiety undergoes partial self-inclusion through the narrow rim[3] forcing the PMDI molecule to approach the cavity through the wider rim with the more hydrophobic alkyl chain entering it first. The ANCD:PMDI systems are true inclusion complexes (Figure 2). In this conformation one of the imide groups is forced inside the CD cavity and no hydrogen bonding interaction is available to it. The cavity is highly hydrophobic, which stabilizes the alkyl groups and compensates for the loss of hydrogen bonding interaction suffered by one of the imide groups. As the alkyl chain length increases, the aromatic moiety of PMDI is gradually pushed out leading to a decrease in the hydrophobicity of the cavity, which results in a reduction in the ICD signal intensity, ^{1}H NMR shifts, and K_a values.

In this Letter, we have described rim-binding-type complexes of β-CD with alkylPMDIs and tried to elucidate the structures of these complexes. A large number of CD complexes are reported in the literature and at least in some of these cases where the substrates are loaded with hydrogen bond acceptor groups, non-inclusion complexes of the type described here are probable. It should be mentioned here that binding of guests to the rim of β-CD has been reported, but in most of these cases the studies are carried out at high pH values where the OH groups deprotonate.[9,10] The case presented here is clearly different. The rim-binding-type association described here could be very important in the context of designing supramolecular structures. For example, in the rim-binding conformation, most of the CD cavity is empty and one can design specific guests capable of inclusion into the cavity, thereby leading to the formation of CD-based ternary systems of well-defined structure and function. Such systems are obviously important from the supramolecular point of view. We are currently engaged in the design of such systems.

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Supporting Information Available: Structures of molecules and synthetic procedures, details of ICD and NMR experiments, Benesi−Hildebrand plots, and molecular dimensions of β-CD and PMDI. This material is available free of charge via the Internet at http://pubs.acs.org.

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