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Specific Recognition of β-Cyclodextrin by a Tetraphenylethene Luminogen through a Cooperative Boronic Acid/Diol Interaction

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Cyclodextrins (CDs) are cyclic oligosaccharides composed of six (α), seven (β), eight (γ), or more glucopyranoside units. CDs have been one of the most extensively studied hosts and widely applied across multiple fields including supramolecular chemistry,[1–3] and pharmaceutical[4] and biomedical science.[5,6] In such fields, the host–guest interaction between the hydrophobic cavity of CDs, and guest molecules with proper shape and size, nearly dominates the entire self-assembly process . Besides offering a hydrophilic environment, the multiple hydroxyl groups on the rim of CDs could function as reactive sites for covalent modification. Can these hydroxyl groups be involved in the host–guest interaction process? Or is there a third interaction existed between CDs and recognized molecules? Exploring and establishing such an interaction will surely contribute to fundamental supramolecular chemistry, bring innovation to the molecular recognition applications, and also help to understand the cooperative interactions in sophisticated biological-recognition events.

Enlightened by the reversible reaction between boronic acid and diols that forms cyclic esters in aqueous media,[7] and the boron-based recognition of monosaccharide[8] and oligosaccharide[9] that features dynamic covalent interactions,[10] we are interested in exploring whether such dynamic interactions can be applied to establishing an alternative binding type for CDs. Although there are a few reports on the combination of monoboronic acid derivatives with CDs, the rather weak binding affinity between them prevents the interaction from playing the key role.[11]

Our success in developing a "light-up" biosensor for D-glucose (Glu)[12] by a diboronic acid-containing tetraphenylethene moiety (TPEDB) prompted us to investigate the possible interaction between TPEDB and CDs. As shown in Figure 1 A, the fluorescence (FL) of TPEDB in carbonate buffer solution remained nearly unchanged at a molar ratio of less than 1 for TPEDB/β-CD, which is progressively intensified with the addition of β-CD. The highest FL intensity was recorded in the molar ratio of TPEDB/β-CD of 500, which was 10.4 times stronger than that of TPEDB. To our surprise, the increment of FL intensities of TPEDB in carbonate buffer solution was very small upon addition of analogues of β-CD, that is, α-CD and γ-CD (Figure 1 B and the Supporting Information; S1).

We then tried to understand and explain such unexpected specific recognition of β-CD from α- and γ-CDs experimentally and theoretically. We first supposed that the oligomerization (model 1 in Figure 2), which is well applied in the explanation of the specific detection of D-Glu by TPEDB, is the cause for this phenomenon. But this mechanism was firstly excluded because the condensation reaction between TPEDB and CDs is difficult to form due to the low affinity of boronic acid to *trans* diols in CDs. Furthermore, there would not be such remarkable difference when TPEDB interacted with α-, β-, and γ-CDs due to their structural similarity. Therefore, other mechanism(s) are responsible for the specific recognition of β-CD by TPEDB.

CDs are well known as host materials in supramolecular chemistry. Is the host–guest interaction responsible for the specific recognition of β-CD by TPEDB (see model 2 in Figure 2)? To verify our conjecture, three water-soluble tetraphenylethene (TPE) derivatives **1**–**3** (structures shown in Figure 3) were designed and successfully synthesized (see the Supporting Information; scheme S1).[13] The experimental results showed that addition of CDs to the aqueous solutions of these water-soluble TPEs caused a slight emission enhancement (Figure 3, and the Supporting Information; S2–S5). We thus concluded that the recognition is unlikely to be caused solely by the host–guest interaction, and the boronic acid groups are essential for the specific recognition.

A further question is rationally raised as to whether the two boronic acid groups are necessary for such recognition.

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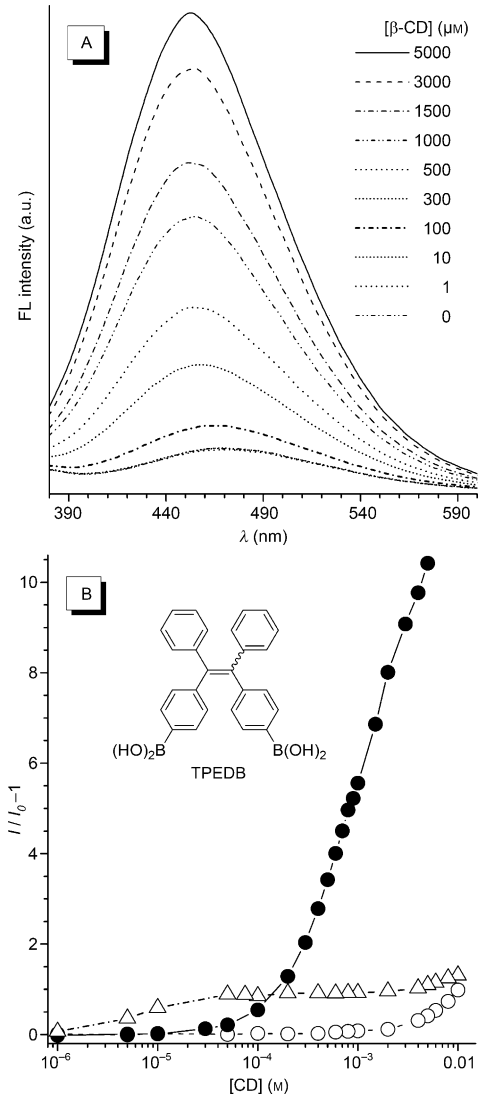

Figure 1. A) FL spectra of TPEDB (10 μM) in carbonate buffer (0.2 M, pH 10.5) containing 0.5 vol% DMSO in the presence of different amount of β-CD. B) Variation in the FL intensity (I) of TPEDB (10 μM) with their peaked values as a function of the concentration of CDs; α-CD (○), β-CD (●), and γ-CD (△). I_0 presents the intensity in absence of CDs. Inset: chemical structure of TPEDB.

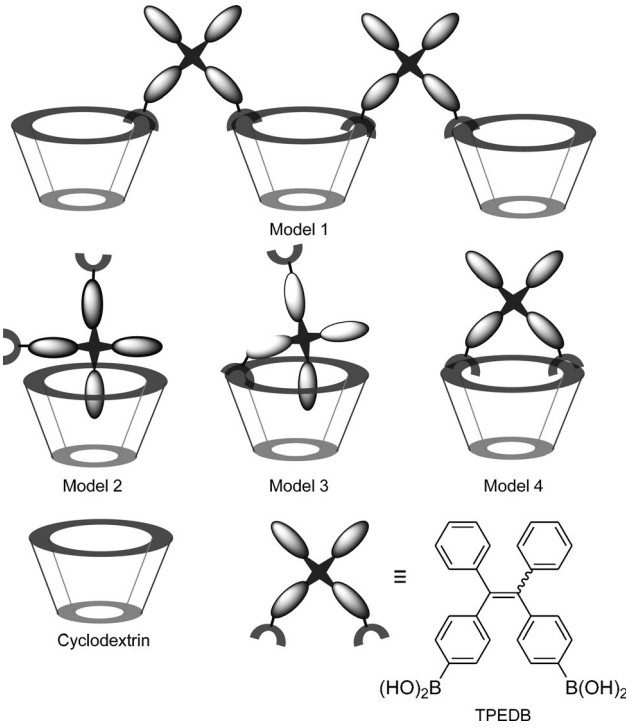

Figure 2. Supposed interaction of TPEDB and β-CD.

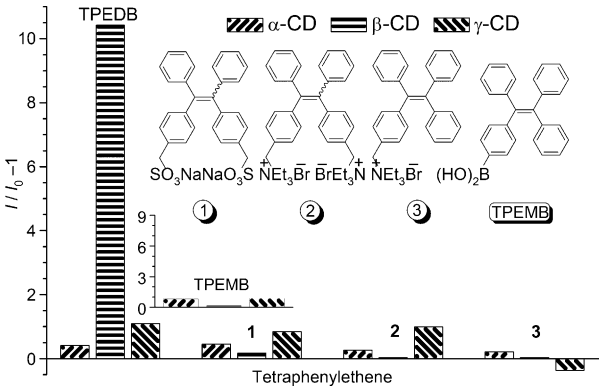

Figure 3. FL responses of water-soluble TPE derivatives (10 μM) in carbonate buffer (0.2 M, pH 10.5) containing 0.5 vol% DMSO to CDs (5.0 mM). Inset: chemical structures of TPE derivatives of **1**–**3**, and TPEMB; FL response of TPEMB (10 μM) in carbonate buffer containing 20 vol% DMSO to CDs (5.0 mM).

To answer this question, and to further uncover the underlying recognition mechanism, monoboronic acid-functionalized TPE (TPEMB) was prepared (see the Supporting Information; Scheme S1).[12] The emission behavior of TPEMB was similar to compounds **1**–**3** when CDs were added into its aqueous solution (Figure 3, see the Supporting Information; S6 and S7), ruling out the dual recognition mechanism including the cavity of CDs (host–guest interaction) and monoboronic acid reaction with diols (model 3 in Figure 2), which is used to interpret the findings of borate-CDs complex-based chiral separation of diol enantiomers by capillary electrophoresis.[14] It is further concluded that the two boronic acid groups are prerequisite for the specific recognition of β-CD.

To collect additional information about the specific interaction mechanism between TPEDB and β-CD, an induced circular dichroism (ICD) technique was used. It is well known that CDs are chiral hosts and capable of inducing the circular dichroism signals of bound achiral guests, although they have no signals in the detectable wavelength of the equipment. Furthermore, a general relationship between the sign, intensity of the ICD signal, and the spatial arrangement of guest molecules and CDs has been well documented.[15] Delightfully, TPEDB possesses different ICD responses upon addition of CDs, which enabled us to distinguish their mutual interactions.

As shown in Figure 4A, a negative ICD signal of TPEDB was recorded when β-CD was added, suggesting that there is interaction between its phenyl rings and the β-CD cavity.

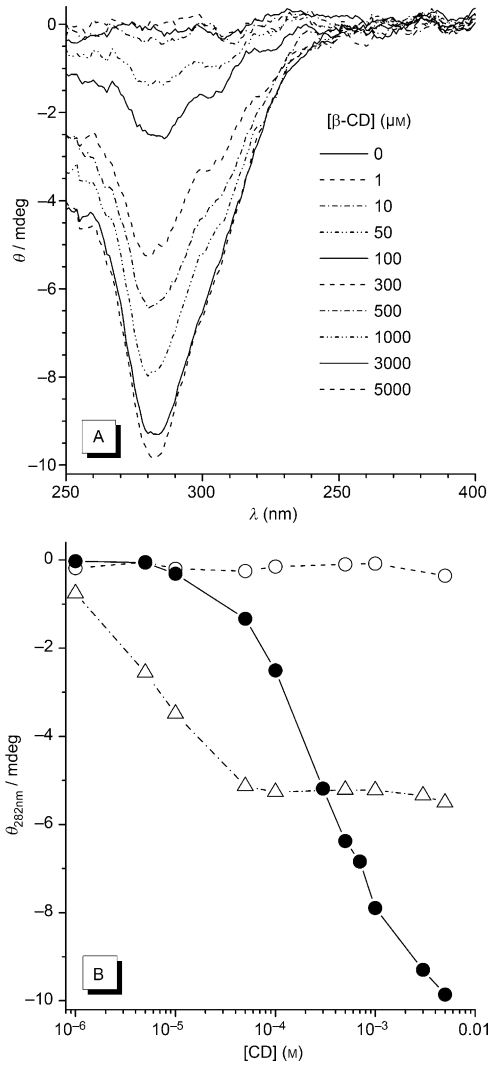

Figure 4. A) ICD spectra of TPEDB (10 μM) in carbonate buffer (0.2 M, pH 10.5) containing 0.5 vol% DMSO in the presence of different amount of β-CD. B) Variation in the ellipticity values (θ) with CD concentrations; α-CD (○), β-CD (●), and γ-CD (△).

Moreover, the signal became progressively stronger with each addition of β-CD. However, almost no ICD signals of TPEDB were observed upon addition of α-CD, but a smaller negative signal of TPEDB was recorded for γ-CD, which was gradually intensified until reaching the plateau at a γ-CD concentration of 50 mM (Figure 4B and the Supporting Information; S8). For comparison, the ICD signals of **1**–**3**, and TPEMB upon addition of CDs were also measured (see the Supporting Information, Figure S9). Similar phenomena (like the ICD signals of TPEDB upon addition of α- and γ-CDs) were observed but rather weaker negative ICD signals of TPEs were induced by β-CD. These results further confirmed that the two boronic acid groups on TPEDB play a critical role in the interaction between TPEDB and β-CD.

The FL and ICD responses of TPEs are consistent on β- and γ-CDs but different on α-CD, shedding light on the binding model of TPEDB and CDs. As a classical polyarylvinyl propeller, TPEs are racemic mixtures of two rapidly interconverting enantiomers of *M*- and *P* helicities with opposite arrangement of phenyl rotors.[16] The absences of ICD signal of TPEs upon addition of α-CD could be due to the understanding that the interaction of α-CD with both conformations of TPEs is identical, and thus balances the positive and negative circular dichroism signals.[17] Meanwhile, the α-CD could interact with one phenyl ring on the TPEs regardless of helicity, which would partially restrict the rotation of this phenyl ring but leave three phenyl rings freely rotated, resulting in a weak FL according to the restriction of intramolecular rotation (RIR) mechanism[18] of aggregation-induced emission.[19] γ-CD, however, possesses a relatively larger cavity than α- and β-CDs. Thus, it could probably interact with two phenyl rings of TPEs simultaneously and be able to enrich one enantiomer conformation by enantioselective complexation. Furthermore, such an interaction would also boost the emission of TPEs by confining the rotation of the phenyl rings in a larger degree than that of α-CD, resulting in a relatively higher ICD signal and stronger FL.

The strong FL intensity and high ellipticity value of TPEDB upon addition of β-CD are extraordinary. The interaction mechanism between them should be different from that of TPEs with other two CDs. On the bases of above results, we speculate that TPEDB may be anchored on the outside edge of β-CD through the host–guest-aided cooperative boronic acid/diols dynamic covalent-binding interaction in the aqueous solution with a pH of 10.5 (model 4 in Figure 2, the Supporting Information, Scheme S2).[8,9] The phenyl rings on TPEDB could probably first interact with the β-CD aided by the host–guest interaction, and then the diboronic acids react with the adjacent two hydroxyl groups on the alternative glucoside units to form cyclic boronate, although the diols possess *trans* configuration with dihedral angles of near 61°. Furthermore, the overall interaction strength will be amplified through the binding cooperativity.[20] When the TPEDB is fixed on the β-CD by the boronate bonds, the intramolecular rotations of its phenyl rings will be restricted, which will activate the RIR process and open up the radiative decay channel. The ICD signal will also be intensified by the bonding interaction at the same time, probably due to fixing of one enantiomer with the aid of host–guest interactions.

To ascertain the binding sites of TPEDB on the β-CD, we optimized the geometry of the former and analyzed the crystal structure of the latter. According to the optimized geometry of TPEDB (see the Supporting Information; Figure S10), the distance between two oxygen atoms in separated boronic acids is 13.98 and 10.08 Å for the *trans*- and *cis* isomers, respectively. The average distances of the pairs of 2,3-diols on separated glucosides measured from the crystal

structure of β-CD are 5.43, 9.73, and 12.15 Å, respectively.[21] The diols with the distance of 9.73 Å, which lie in the alternate glucosides of β-CD are well matched to react with the boronic acids of the *cis*-TPEDB. In contrast, the distance mismatch of 2,3-diols in the alternate glucosides of α- and γ-CDs for diboronic acids of TPEDB is probably responsible for the failure of forming the host–guest interaction-aided boronic acid/diol dynamic covalent bond.

The optimized structure of the 1:1 complex formed by TPEDB with a *cis* conformation and β-CD suggests that the TPE moiety is tilted above the entrance of the nanocavity of β-CD, and blocks the attack from another TPEDB on the wider rim of the β-CD (see the Supporting Information, Figure S11). Therefore, the formation of the 2:1 complex was disfavored. Furthermore, the non-linear regression analysis of the fluorescence changes of TPEDB versus concentration of β-CD also indicates the formation of the 1:1 stoichiometric complex between TPEDB and β-CD with an overall binding constant (K) of 686 M^{-1} (assuming that TPEDB consists of an equal molar ratio of the *cis*- and *trans* isomer;[22] see the Supporting Information, Figure S12).[23]

Since the diols on β-CD possess a *trans* configuration, the boronic acid/diols reaction is a dynamic process with a low binding constant.[9c] The addition of more reactive and favorable *cis* diols, such as monosaccharide, to the system of TPEDB and β-CD will destruct the boronate bonds and form a new compound of TPEDB and monosaccharide.

The FL intensity of the system decreased upon addition of the monosaccharide of D-Glu, D-mannose (Man), D-galactose (Gal), or D-fructose (Fru; Figure 5A and the Supporting Information; S13). This result indicates that the diboronic acids on the TPEDB are more likely to react with the *cis* diols on the monosaccharide than the *trans*-2,3-diols on the β-CD. When the boronic acids on TPEDB with a concentration of 10 μM are bound by the diols on the monosaccharides, the phenyl rings of the resultant compounds could rotate more freely, which may activate the non-radiative decay and lead to the emission decrease. The FL attenuation rates follow the order of Fru > Gal > Man > Glu, which is consistent with the binding constants (K_a) of saccharide with phenylboronic acids ($K_{a,\ sugar}/M^{-1} = 160$ for Fru, 15 for Gal, 13 for Man, and 4.6 for Glu).[24] The ICD of TPEDB and β-CD also disappeared after the addition of D-Fru. (see the Supporting Information, Figure S14), further suggesting the destruction of the system. Addition of Fru to the systems of TPEDB and α-CD or γ-CD has increased the FL slightly, confirming our speculation that boronic acid/diol-binding does not contribute to the boosted emission in these systems (see the Supporting Information, Figure S15). The slight increment of FL could probably be attributed to increased viscosity of the media after the addition of sugar.

Furthermore, the emission of the system of TPEDB and β-CD also decreased upon addition of guest molecules with high complexation constants, such as DL-phenylalanine (DL-Phe), L-phenylalanine (L-Phe), *trans*-cinnamic acid (*t*-Ca), and 1-adamantecarboxylic acid (Ada), regardless of the addition sequence (Figure 5B, S16, and S17).[25] The higher

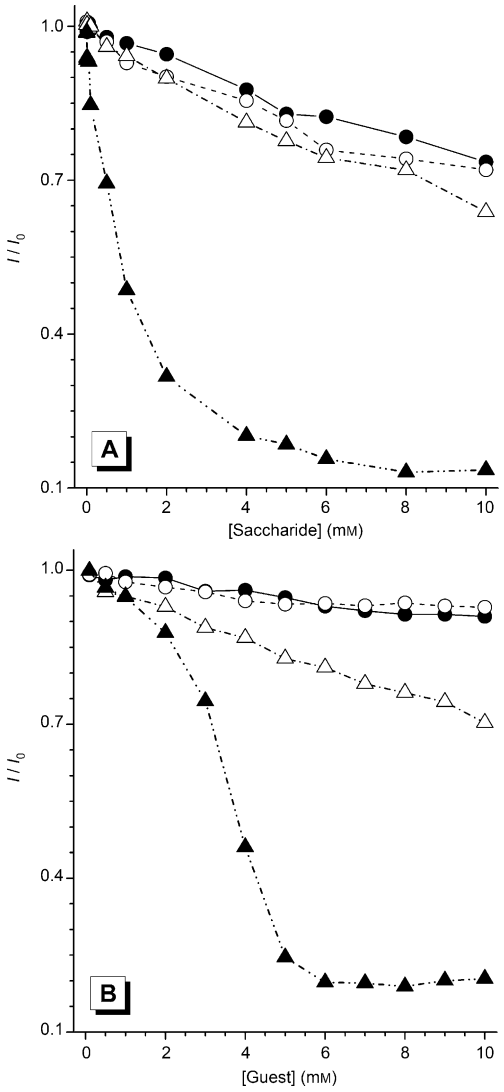

Figure 5. A) Variation in the FL intensity (I) of the mixture of TPEDB (10 μM) and β-CD (5.0 mM) at 452 nm as a function of the concentration of monosaccharide in a carbonate buffer containing 0.5 vol% DMSO (pH 10.5). I_0 is the intensity in absence of a monosaccharide, Glu = D-glucose (●), Man = D-mannose (○), Gal = D-galactose (△), Fru = D-fructose (▲). B) Variation in the FL intensity (I) of the mixture of TPEDB (10 μM) and β-CD (5.0 mM) at 452 nm as a function of the concentration of guest molecular in a carbonate buffer containing 0.5 vol% DMSO (pH 10.5). I_0 is the intensity in absence of a guest molecular. DL-Phe = DL-phenylalanine (●), L-Phe = L-phenylalanine (○), *t*-Ca = *trans*-cinnamic acid (△), Ada = 1-adamantecarboxylic acid (▲).

binding constants between guests and β-CD enables the former to enter the hydrophobic cavity of β-CD, which will destruct or prohibit the formation of the 1:1 emissive complex of TPEDB and β-CD.[26] A similar attenuated ICD signal was also observed when Ada was mixed into the solution of TEPDB and β-CD (see the Supporting Information, Figure S18).

In summary, we have systematically investigated the interactions between TPEDB and CDs and developed a conceptually new binding model for β-CD based on host–guest interaction-aided boronic acid/diol-binding. The two boronic

acids on TPEDB could cooperatively bind to two pairs of alternative diols on a β-CD, in which the FL was intensified due to the RIR process. Thus, specific recognition of β-CD was realized from α- and γ-CDs due to the fit-distance-matching of diboronic acid and alternative diols on its wide rims. Meanwhile, the interaction was proven to be a dynamic process. The speculation had been validated by various control experiments. This specific recognition process through the cooperativity of weak interactions is significant for biological science to realize enzyme function and biomolecular assembly, and so on. We are working on an application of TPEDB that includes an interaction with biologically important conjugates, such as polysaccharide and polyols.

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Keywords: cooperative effects · cyclodextrins · host–guest systems · molecular recognition · tetraphenylethene

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