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Guest-Induced Dynamic Self-Assembly of Two Diastereomeric Cage-Like Boronic Esters

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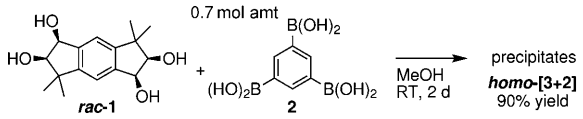
Guest-induced dynamic self-assembly of several different macrocyclic host molecules starting from the same set of components is an active area of research in the field of supramolecular chemistry.[1] In case that chiral, racemic components are employed, formation of diastereomeric host molecules becomes possible, which makes the dynamic self-assembly more intriguing. However, the diastereoselective self-assembly using racemic substrates is still rare,[2] and moreover, selective formation of each diastereomer by the addition of an appropriate guest molecule has remained as a challenging subject due to the difficulty in discriminating diastereomeric structures by non-covalent host–guest interactions.[3]

We recently reported the dynamic self-assembly of macrocyclic boronic esters based on the reversible formation of boronic ester in the presence of appropriate guest molecules.[2d,4] In this system, two types of macrocyclic boronic ester of different size could be produced diastereoselectively by the addition of appropriate guest molecules, for which precipitation of the complex played an important role for selective assembly. To realize more precise discrimination of host–guest interaction, we thought of using 1,3,5-benzenetri(boronic acid) **2**[5] instead of 1,4-benzenedi(boronic acid), because the expected cage-like structure has an internal space surrounded by chiral tetrols from three directions. In this paper, we report disubstituted benzene-induced selective formation of two diastereomeric cage-like boronic esters from racemic tetrol **1**[6] and 1,3,5-benzenetri(boronic acid) **2**.

When racemic tetrol **1** and 0.70 molar amount of tri(boronic acid) **2** were mixed in methanol at room temperature (Scheme 1), the mixture became gradually heterogeneous,



Scheme 1. Self-assembly of ***homo*-[3+2]**.

but the filtrated solid was soluble in several organic solvents such as chloroform, toluene, etc. FAB-MS and ^{1}H, ^{13}C NMR spectral data suggested the formation of a single, highly symmetric product, 3:2 complex of tetrol **1** and tri(boronic acid) **2** (abbreviated as ***homo*-[3+2]**). It was also confirmed by ^{1}H NMR that methanol was not included in this isolated ***homo*-[3+2]**. It should be noted that in the previous **[2+2]** formation from 1,4-benzenedi(boronic acid) and tetrol **1**, addition of appropriate guest molecules was necessary and polymeric boronates insoluble in all organic solvents examined were obtained in methanol. On the other hand, this ***homo*-[3+2]** structure is thought to be thermodynamically more stable than polymeric boronates and was constructed without adding guest molecules.

Single crystal of this ***homo*-[3+2]** suitable for X-ray diffraction analysis was successfully obtained by the slow vapor diffusion of *n*-pentane into a toluene solution of ***homo*-[3+2]**.[7] As shown in Figure 1, the complex has the expected cage-like structure and is composed of three molecules of tetrol **1** and two molecules of tri(boronic acid) **2**, and one molecule of toluene was observed in its internal space, suggesting the presence of π–π interactions with the phenyl

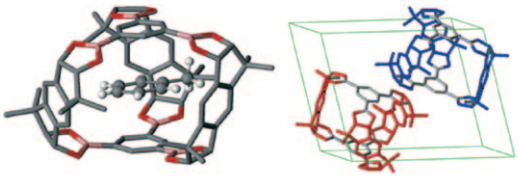


Figure 1. X-ray structure of ***homo*-[3+2]·toluene** (white, hydrogen; pink, boron; gray, carbon; red, oxygen).

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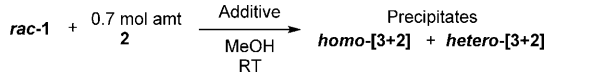
rings of two tri(boronic acid) groups. The distance between these phenyl rings and the toluene is 3.5 Å, which is ideal for this.[8] It also turns out that methyl group of the toluene faced to a space between two tetrol units. The most remarkable is the fact that the three tetrol units in ***homo*-[3+2]** are derived from the same enantiomer of the tetrol **1**, which suggested that the diastereoselective self-assembly occurred during the formation of this **[3+2]** structure.

We next examined addition of an appropriate guest molecule that could work as a template for the formation of cyclic boronic esters. As shown in Table 1, selective precipitation of the ***homo*-[3+2]** was again observed on addition of excess amount of benzene or toluene, with its equimolar amount included as confirmed by NMR and elemental analysis. However, the chemical shifts of both benzene and toluene were identical with those measured in the absence of the host, suggesting exchange of benzene and toluene with solvent ($CDCl_3$) takes place rapidly. Interestingly, addition of 13 molar amounts of cumene based on tetrol **1** completely suppressed the formation of ***homo*-[3+2]** and a complex mixture of polymeric and oligomeric boronates was obtained.[9] These results suggest that interaction of cumene with partially formed host molecules inhibits further assembly to give ***homo*-[3+2]**.

Table 1. Template-induced selective formations of each diastereomer of **[3+2]**.



Entry	Additive (Molar amount based on **1**)	Results (precipitates) ***homo*-[3+2]**	***hetero*-[3+2]**
1	benzene (100)[a]	84 %[c]	ND
2	toluene (100)[a]	78 %[c]	ND
3	cumene (13)[a]	complex mixture	
4	*p*-xylene (13)[a]	86 %[d]	ND
5	*m*-xylene (13)[b]	trace	89 %[c]
6	*m*-xylene (0.33)[b]	97 %[e]	trace
7	*o*-xylene (13)[b]	trace	87 %[c]
8	*o*-xylene (0.33)[b]	trace	90 %[c]

[a] Reaction was carried out for 1 d. [b] Reaction was carried out for 3 d. [c] Equimolar amount of additive based on **[3+2]** was observed. [d] 0.3 molar amount of *p*-xylene based on ***homo*-[3+2]** was observed. [e] 0.2 molar amount of *m*-xylene based on ***homo*-[3+2]** was observed.

Furthermore, examination of the effect of disubstituted benzenes revealed a very unique feature of this system. Although *p*-xylene had little influence on the formation of ***homo*-[3+2]**,[10] when 13 equivalents of *m*-xylene or *o*-xylene were employed as a guest molecule, a different boronic ester was precipitated as a major product (Table 1, entries 5 and 7). Although this new product was indicated to be composed of three molecules of tetrol **1** and two of tri(boronic acid) **2** by FAB-MS just as before, it has three sets of signals for each proton and carbon, which suggested the new product was ***hetero*-[3+2]**, the diastereomer of ***homo*-[3+2]**. The presence of one molecule of guest molecules contained within ***hetero*-[3+2]** was confirmed by NMR in these cases although complete displacement of these guest molecules by $CDCl_3$ was again observed. In addition, these boronic esters, ***homo*-** and ***hetero*-[3+2]**, were stable in aprotic solvent such as $CDCl_3$ and C_6D_6 without any interconversion for several days even in the presence of these guest molecules. It should be emphasized that only 0.33 molar amount of *o*-xylene based on tetrol **1** (the theoretical minimum amount) could work very well for the formation of ***hetero*-[3+2]** while the same amount of *m*-xylene resulted in the selective formation of ***homo*-[3+2]** (Entry 6). Thus, *o*-xylene has a stronger inducing ability for this boronic ester than *m*-xylene.

The structure of ***hetero*-[3+2]** was confirmed by X-ray diffraction analysis of a single-crystal obtained by the slow vapor diffusion of diethyl ether into a chloroform solution of the product (Figure 2).[7] The three tetrol units in the product are composed of two molecules of one enantiomer and one molecule of the opposite enantiomer of the tetrol **1**. More interestingly, a single crystal of ***hetero*-[3+2]** was composed of only its one enantiomer, that is, ***hetero*-[3+2]** is a relatively rare, racemic mixture although ***homo*-[3+2]** is a common, racemic compound. These results suggested that the selective formation of each diastereomer of **[3+2]** is accomplished depending on the substitution pattern of added xylenes. Furthermore, treatment of **1** and **2** in $CD_3OD/[D_{10}]o$- or *m*-xylene(2:1) first resulted in the formation of a mixture of ***homo*-** and ***hetero*-[3+2]** in solution. From this mixture, ***hetero*-[3+2]** selectively precipitated out and ***homo*-[3+2]** remained in the solution after several hours (Figure S6). Thus, the selective formation of ***hetero*-[3+2]** in the presence of *o*- or *m*-xylene was induced during the crystallization process.

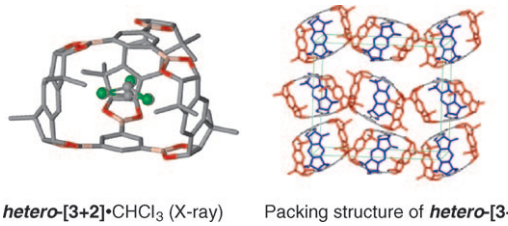


Figure 2. X-ray structure of ***hetero*-[3+2]·CHCl$_3$** (white, hydrogen; pink, boron; gray, carbon; red, oxygen; green, chlorine).

The X-ray structures of ***homo*-** and ***hetero*-[3+2]** gave us a possible answer to the question why the selective formation of each diastereomer of **[3+2]** occurs. As shown in Figure 3, the space between two tetrol units have two types; a narrow one and a wide one (type A and B) depending on the combination of the enantiomers.[11] Although ***homo*-[3+2]** has only type A, ***hetero*-[3+2]** was composed of one type A and two type Bs. As mentioned in the case of toluene complex, a substituent of benzene ring would face to the space to minimize steric hindrance between a host molecule and the substituent. Probably, the two methyl groups of *o*-

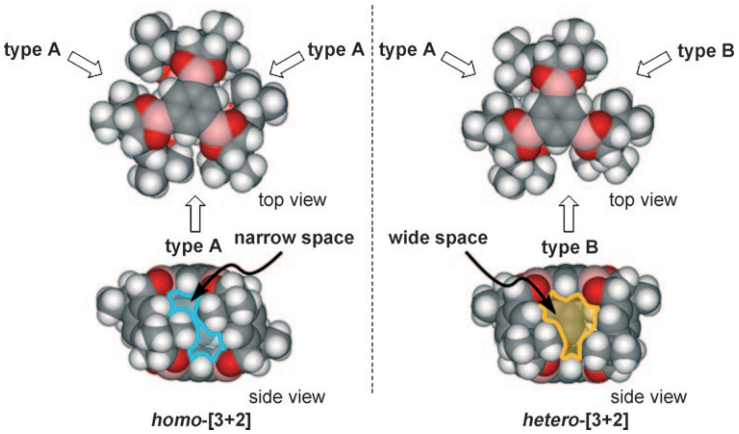
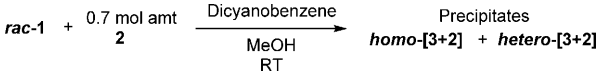


Figure 3. Two types of the space between two tetrol units (type A: narrow, type B: wide).

or *m*-xylene would fit into two type B spaces, decreasing the steric repulsion.

Similar tendency of diastereoselectivity was observed by using dicyanobenzenes as a guest molecule. Although *p*-dicyanobenzene had little influence on the formation of ***homo*-[3+2]**, only 0.33 molar amount of *o*-dicyanobenzene induced the selective formation of ***hetero*-[3+2]** (Table 2, entries 1 and 3). Dicyanobenzenes have a stronger inducing ability for assembly than xylenes and 0.33 molar amount of *m*-dicyanobenzene produced ***hetero*-[3+2]** as a major product. Thus, two diastereomeric host molecules were constructed with recognition of the substitution pattern of disubstituted benzenes in general.

Table 2. Dicyanobenzene-induced selective formation of each diastereomer of **[3+2]**.

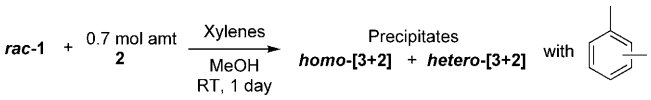


Entry	Dicyanobenzene (Molar amount based on **1**)	Results (precipitates)	
		***homo*-[3+2]**	***hetero*-[3+2]**
1	*p*-dicyanobenzene (1.0)[a]	90 %[c]	ND
2	*m*-dicyanobenzene (0.33)[b]	32 %[d]	68 %[d]
3	*o*-dicyanobenzene (0.33)[b]	trace	94 %[e]

[a] Reaction was carried out for 1 d. [b] Reaction was carried out for 3 d. [c] 0.3 molar amount of *p*-dicyanobenzene based on ***homo*-[3+2]** was observed. [d] 0.7 molar amount of *m*-dicyanobenzene based on **[3+2]** was observed. [e] Equimolar amount of *o*-dicyanobenzene based on ***hetero*-[3+2]** was observed.

These results suggest that it would be possible to apply this phenomenon for selective inclusion of *o*- or *m*-xylene from their mixture with *p*-xylene. In fact, when **1** and **2** were mixed in the presence of 5 molar amounts each (against tetrol **1**) of two xylenes in MeOH, completely selective inclusion of *o*- or *m*-xylene over *p*-xylene was achieved during the precipitation process. Furthermore, *o*-xylene was included preferentially over *m*-xylene (Table 3).

Table 3. Selective inclusion of xylenes.[a]



Added xylenes	Detected xylenes in precipitates[b]	Total yield (*homo*/*hetero*)
o- and *p*-xylene	*o*-xylene/*p*-xylene, >95:<5	83 % (1:5.7)
m- and *p*-xylene	*m*-xylene/*p*-xylene, >95:<5	90 % (1:23)
o- and *m*-xylene	*o*-xylene/*m*-xylene, 6:1	84 % (1:7.2)

[a] 5 molar amounts each of two xylenes for tetrol **1** were used. [b] One molecule of *o*- or *m*-xylene was included in one molecule of **[3+2]**.

In conclusion, we have achieved the guest-induced, selective formation of two diastereomeric cage-like boronic esters. The recognition of substitution pattern of disubstituted benzenes was realized in this system.

Experimental Section

Self-assembly of *homo*-[3+2] in MeOH: 1,3,5-benzenetri(boronic acid) **2** (34.3 mg, 0.16 mmol) was added to a methanol solution (6.8 mL) of tetrol **1** (62.3 mg, 0.22 mmol). The reaction mixture became homogeneous in a moment, and in a few seconds precipitation started to appear. After the mixture was stirred at room temperature for 2 days, ***homo*-[3+2]** was obtained as a white powder by filtration followed by drying in the air (69.4 mg, 90 %).

Self-assembly of *hetero*-[3+2]·*m*-xylene in MeOH-*m*-xylene (95:5): 1,3,5-benzenetri(boronic acid) **2** (31.8 mg, 0.15 mmol) was added to a methanol (6.3 mL) and *m*-xylene (0.33 mL, 2.7 mmol) solution of tetrol **1** (60.3 mg, 0.22 mmol). The reaction mixture became homogeneous in a moment, and in a few seconds precipitation started to appear. After the mixture was stirred at room temperature for 3 days, ***hetero*-[3+2]·*m*-xylene** (89 %) and ***homo*-[3+2]·*m*-xylene** (trace) was obtained as a white powder by filtration followed by drying in the air (73.9 mg).

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Keywords: boronic esters · cage compounds · diastereoselectivity · self-assembly · supramolecular chemistry

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[9] We defined here that polymeric boronates were insoluble in all organic solvents examined and that oligomeric boronates were soluble in several organic solvents and broadening signals were observed in their ^{1}H NMR spectra.

[10] A 0.3 molar amount of *p*-xylene against ***homo*-[3+2]** was observed in the complex by ^{1}H NMR, suggesting *p*-xylene did not influence the formation of ***homo*-[3+2]**.

[11] The space between the same enantiomer of tetrol **1** is narrow (type A) and that between the opposite enantiomer of **1** is wide (type B).

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