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Crystallization-Controlled Dynamic Self-Assembly and an On/Off Switch for Equilibration Using Boronic Ester Formation

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Abstract: Macrocyclic boronic esters of different sizes can be prepared selectively from the same starting diboronic acid and 1,2-diol by means of an interesting dynamic self-assembly phenomena. More specifically, two kinds of macrocyclic boronic esters could be formed diastereoselectively and nearly quantitatively under neutral conditions by the addition of an appropriate guest molecule that acts as a template. Although a mixture of tetrol **1** and di(boronic acid) **2** in methanol gave only insoluble polymeric boronic esters, a soluble macrocyclic boronic ester, homo-[**2+2**], was obtained selectively in the presence of toluene as a guest molecule. Furthermore, when benzene was employed as a guest molecule, the selective formation of another macrocyclic boronic ester, hetero-[**3+3**], occurred. Interestingly, each of these macrocycles could be converted into the other in the presence of methanol and the appropriate guest molecule; however, under aprotic conditions, guest molecules encaged by the macrocyclic boronic ester could be exchanged without affecting its structure. Thus the presence or absence of a protic solvent could be used as a regulator to switch on or off the dynamic equilibrium of the system. In addition, investigation of the effect of reaction time, direct observation of the reaction mixture by NMR spectroscopy, and carrying out the reaction using optically active tetrol suggested that precipitation plays an essentially important role in the selective formation of the macrocyclic boronic esters. Thus, although both of [**2+2**] and [**3+3**] were present as solutes in the reaction mixture, the type of added guest molecule induced the selective precipitation of only one form of macrocyclic boronic ester, hence displacing the equilibrium of the system.

Keywords: boron · cage compounds · diastereoselectivity · dynamic covalent chemistry · self-assembly

Introduction

Considered one of the most interesting research topics in the field of supramolecular chemistry, dynamic self-assembly can enable the adaptive recognition of different guest molecules by supramolecular host structures that are derived from a given set of building blocks.[1] Most of the reported examples are based on the coordination of multidentate nitrogen ligands to metal ions,[2,3] and relatively few examples are known in which reversible covalent linkages[4] such as S–S[5] or C=N[6] bonds are employed for the dynamic construction of host molecules. In these cases, the reaction is usually carried out under either acidic or basic conditions, and the yield and the selectivity of formation of the host molecule are often dissatisfying. It is well known that boronic esters can easily be prepared by mixing boronic acids and alcohols with azeotropic removal of water or in the presence of a dehydrating agent, and in favorable cases using 1,2- and 1,3-diols, cyclic boronic ester formation occurs spontaneously even in the absence of a dehydrating agent.[7,8] The overall process is an equilibrium, and this reversible reaction has previously been employed to build complex structures such as macrocycles,[9] dendrimers,[10] helicates,[11] nanotubes,[12] capsules,[13] porous covalent organic frameworks,[14] and polymers.[15]

In a recent communication,[16] we reported that boronic ester formation can be used to achieve the dynamic self-assembly of organic molecules into macrocycles through dynamic covalent-bond formation.[9b] This system has shown interesting novel features, such as the formation of two kinds of host boronic ester in nearly quantitative yield simply by mixing the tetrol **1** and the di(boronic acid) **2** under neutral conditions in the presence of the appropriate guest molecules, and the possibility to switch on/off the

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equilibration between these two host molecules in the presence or absence of methanol. Herein, we report a detailed investigation of the condensation between tetrol **1** and 1,4-benzenedi(boronic acid) **2**, including self-assembly phenomena in the presence of several guest molecules and X-ray crystallographic analysis of the two products. More specifically, our investigations on the influence of reaction time, the direct monitoring of the reaction mixture by NMR spectroscopy, and the use of optically active tetrol revealed the important role played by precipitation phenomena in the selective preparation of the two kinds of host molecules. To investigate dynamic self-assembly phenomena for this system at thermodynamic equilibrium, mixing conditions were chosen so that all components were sufficiently soluble.

Results and Discussion

Formation of boronic ester in the presence of several additives: We expected that, with an appropriate combination of di(boronic acid) and bis(1,2-diol), it should be possible to create a self-assembling system that adapts its final shape to a guest molecule used as template (Figure 1).

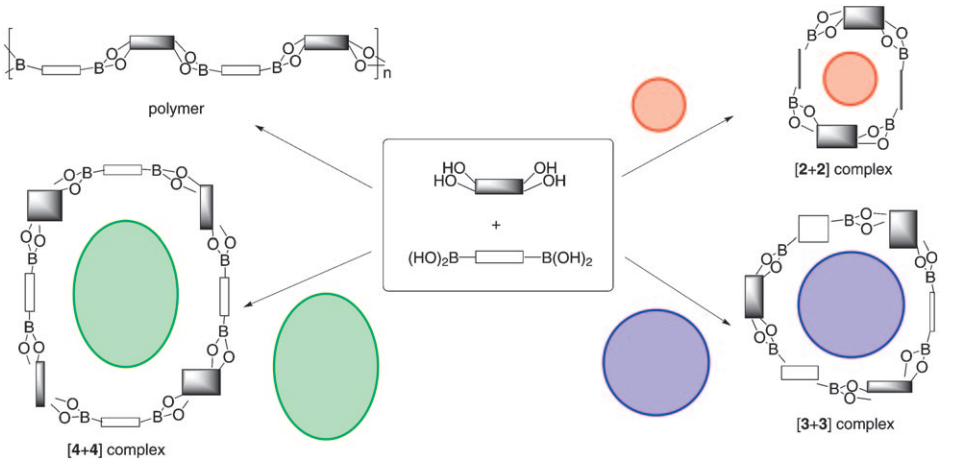
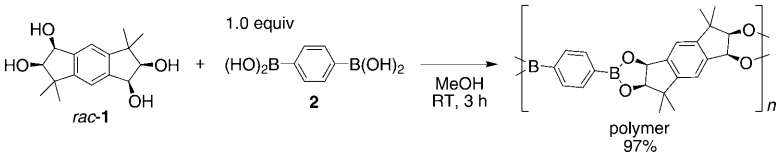


Figure 1. Proposed dynamic self-assembly based on the formation of boronic ester.

We selected a racemic tetrol **1**,[17] which contains two sets of fixed *cis*-1,2-diol units on the same face of a nearly planar indacene framework. 1,4-Benzenedi(boronic acid) **2** was chosen as the boronic component because of its rigid and planar structure. When equimolar amounts of tetrol **1** and di(boronic acid) **2** were mixed in methanol, both components dissolved instantaneously and then precipitation of products followed immediately. After the mixture was further stirred for 3 h at room temperature, the precipitates were filtered to give a white powder in high yield (Scheme 1). Their solubility in various organic solvents was examined to find that they are insoluble in common organic



Scheme 1. Reaction of **1** and **2** in methanol.

solvents such as chloroform, ethyl acetate, toluene, DMSO, and tetrahydrofuran. Although the average and the distribution of molecular weight could not be determined due to their insolubility, the precipitates were thought to be linear polymeric boronic esters made up of tetrol **1** and di(boronic acid) **2** in a 1:1 ratio, which was supported by elemental analysis.

We investigated next the templating effect of different guest molecules on the formation of macrocyclic boronic esters. We first examined several common solvents as guest molecules in a 2:1 solution in methanol under the same reaction conditions as described above (Table 1). Reaction mixtures were stirred for one day and products were mostly recovered as precipitates by filtration. When *n*-hexane, diethyl ether, tetrahydrofuran, acetonitrile, ethyl acetate, or dimethylsulfoxide were used as additives, only insoluble polymeric materials were recovered, as in the reaction carried out in methanol, thereby suggesting that these additives were not suitable guest molecules for the formation of a host macrocycle. On the other hand, a new, discrete boronic ester was obtained when using DMF or chloroform as an additive, although the insoluble polymeric products were also obtained in large amounts. This new boronic ester was soluble in several organic solvents such as chloroform, toluene, DMSO, and tetrahydrofuran. This product could be separated from the polymeric boronic ester by dissolution in CH_2Cl_2 and filtration, and isolated in a pure form by evaporating solvents from the filtrate. Furthermore, when the reaction was carried out in methanol/toluene (2:1), the reaction mixture again turned heterogeneous but the formation of insoluble materials was completely suppressed and the same soluble boronic ester was obtained in high yield. FAB-MS data for the newly formed compound suggested that it is a 2:2 complex of the di(boronic acid) and the tetrol (abbreviated as

Table 1. Reaction of **1** and **2** in the presence of several additives.

rac-**1** + 1.0 equiv **2** → boronic esters (precipitates)
MeOH/additive (2:1), RT, 1 d

Entry	Additive	Precipitate
1	*n*-hexane	polymer quant.
2	Et_2O	polymer quant.
3	THF	polymer quant.
4	CH_3CN	polymer quant.
5	AcOEt	polymer quant.
6	DMSO	polymer quant.
7	DMF	polymer 42%, homo-[**2+2**][a] 52%
8	$CHCl_3$	polymer 73%, homo-[**2+2**][a] 25%
9[b]	toluene	homo-[**2+2**]·toluene 90%

[a] Exact amounts of the guest molecule included in homo-[**2+2**] could not be determined because the polymeric products were present in the precipitates. [b] Reaction was carried out for 30 min.

[**2+2**]). ^{1}H and ^{13}C NMR spectra revealed the highly symmetric nature of the product, and the presence of an equimolar amount of toluene along [**2+2**] was confirmed by integration of ^{1}H NMR spectroscopy and elemental analysis, thereby indicating that toluene is neatly acting as a template in the formation of [**2+2**]. The chemical shifts of toluene in the ^{1}H NMR spectra were identical with those measured in the absence of the host, thus suggesting a rapid exchange of toluene with the solvent ($CDCl_3$) and that the interaction between the toluene molecule and the host was not very strong (Figure 2).

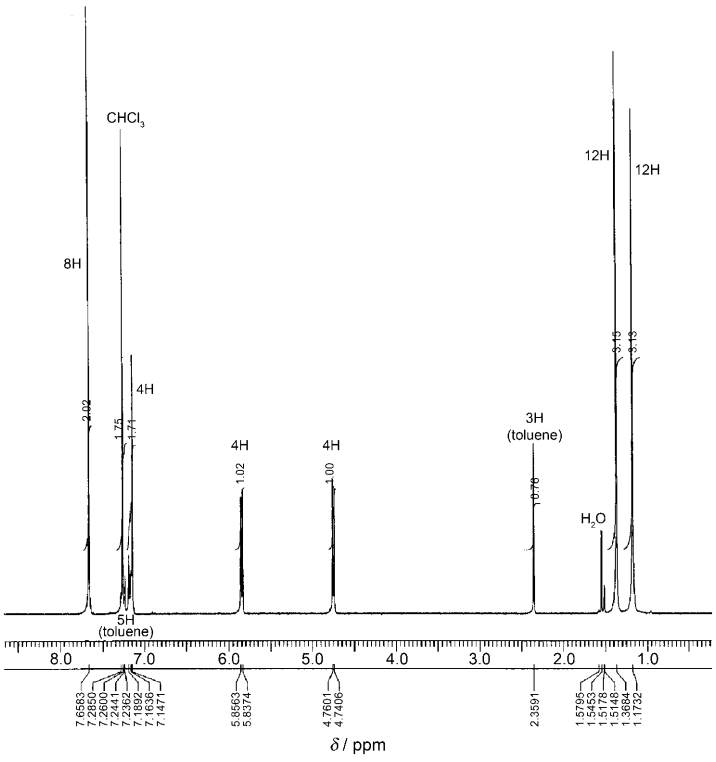


Figure 2. ^{1}H NMR spectrum of homo-[**2+2**]·toluene (300 MHz, $CDCl_3$, 25 °C).

Attempts to obtain single crystals of [**2+2**]·toluene suitable for X-ray analysis succeeded when recrystallization was performed from toluene.[18] As shown in Figure 3, the complex is composed, as expected, of two molecules of di(boronic acid) and two of tetrol, whereas one molecule of toluene lies in the center of the macrocycle, thus suggesting the presence of π–π interactions with the phenyl rings of the di(boronic acid). The distance between the phenyl rings of the cage and the toluene molecule is 3.5 Å, an optimal distance for this type of interaction.[19] It should be emphasized that the two tetrol units in this 2:2 complex are derived from the same enantiomer of the starting material (homo-[**2+2**]), thereby showing that matching between enantiomers occurs during complex formation.[20] In addition, the single crystal is a racemic compound, that is, equal amounts of both enantiomers of homo-[**2+2**]·toluene were present in the unit cell (Figure 3, right).

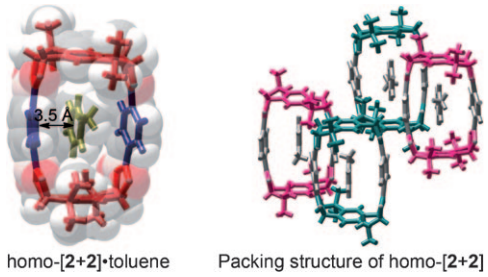


Figure 3. Crystal structure of homo-[**2+2**]·toluene. Left: tetrol units (red), di(boronic acid) units (blue), toluene (yellow). Right: two enantiomers of tetrol in different colors.

Since π–π interactions appeared to play an important role in the formation of the supramolecular structure, we decided to study the influence of different aromatic compounds on the reaction (Table 2). Xylenes acted as an appropriate guest for the formation of homo-[**2+2**] irrespective of its substitution pattern. On the contrary, addition of cumene, which has one bulky substituent, resulted in the formation of polymeric boronic esters along with homo-[**2+2**]. Furthermore, only polymeric boronic esters were obtained when

Table 2. Reaction of **1** and **2** in the presence of several aromatic additives.

rac-**1** + 1.0 equiv **2** → boronic esters (precipitates)
MeOH/additive (2:1), RT, 1 d

Entry	Additive	Precipitate
1	*o*-xylene	homo-[**2+2**]·*o*-xylene 96%, polymer 3%
2	*m*-xylene	homo-[**2+2**]·*m*-xylene 92%, polymer trace
3	*p*-xylene	homo-[**2+2**]·*p*-xylene 91%, polymer 9%
4	cumene	homo-[**2+2**]·cumene 46%, polymer 36%
5	mesitylene	polymer quant.
6[a]	benzene	hetero-[**3+3**]·2benzene[b] 94%

[a] Reaction was carried out for 3 h. [b] Trace amount of homo-[**3+3**] was included.

mesitylene, a 1,3,5-trisubstituted benzene, was added. These results suggest that bulky additives hinder the formation of homo-[**2**+**2**].

Interestingly, when benzene was employed instead of toluene (methanol/benzene 2:1), the mixture here again became instantaneously heterogeneous and precipitates were obtained that were soluble in several organic solvents but their ^{1}H NMR spectra were obviously different from those of homo-[**2**+**2**]. FAB-MS data for this precipitate clearly supported the formation of a 3:3 complex, whereas elemental analysis and integration of ^{1}H NMR spectra demonstrated the inclusion of two molecules of benzene in a host molecule composed of three molecules of 1,4-benzenedi(boronic acid) and three of tetrol. More specifically, careful analysis of the ^{1}H and ^{13}C NMR spectra showed that this precipitate contained both diastereomers of the 3:3 complex in more than 95:5 ratio. The major product showed three sets of signals for each proton and carbon (Figure 4 and S4 in the Supporting Information), thereby suggesting it was composed of two molecules of one tetrol enantiomer and one molecule of the other (abbreviated as hetero-[**3**+**3**]). Enlargements of the NMR spectroscopic signals of aromatic protons and methyl group of the tetrol units are shown in Figure 5. Along with hetero-[**3**+**3**], a trace amount of a minor product is observed, which is thought to be homo-[**3**+**3**] composed

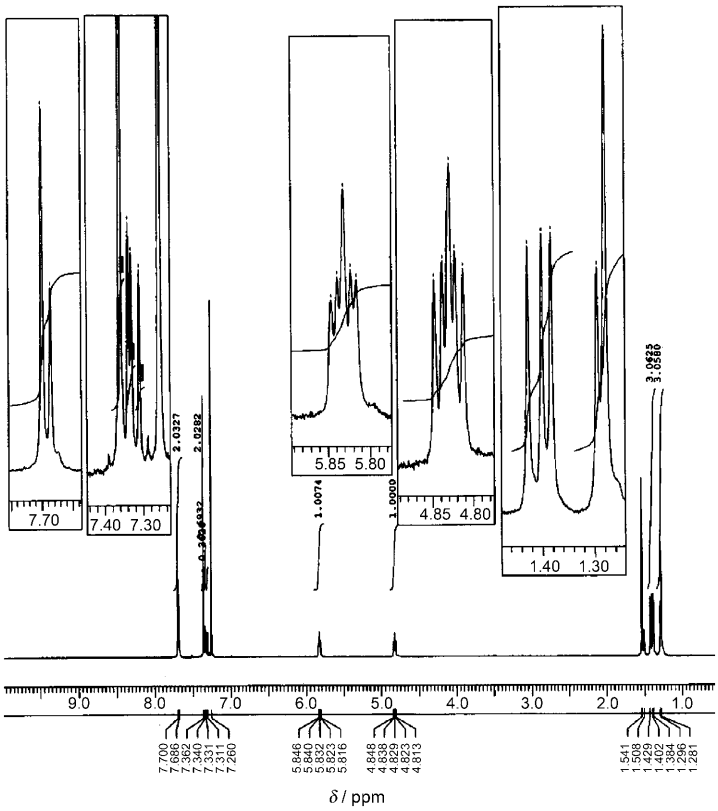


Figure 4. ^{1}H NMR spectrum of hetero-[**3**+**3**]·2benzene (400 MHz, $CDCl_3$, 25 °C).

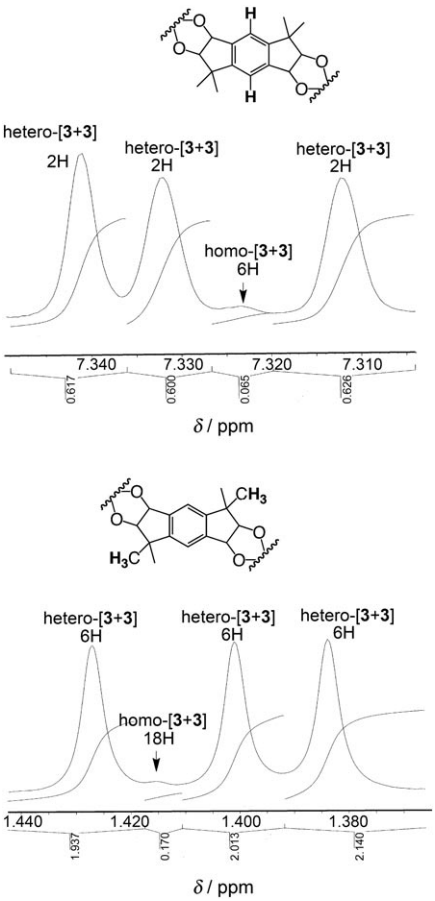


Figure 5. Extended figure of the signals of aromatic protons and methyl group of the tetrol units in the ^{1}H NMR spectrum of hetero-[**3**+**3**]·2benzene (500 MHz, $CDCl_3$, 25 °C).

of the same three enantiomers of the tetrol, since the reaction using optically pure tetrol also gave this product (described in a later section). These results suggested that the self-assembly that leads to the formation of hetero-[**3**+**3**] proceeded in a highly diastereoselective manner. The chemical shift of benzene in ^{1}H NMR spectra was also identical to that measured in the absence of the host, thus suggesting that exchange with the solvent ($CDCl_3$) took place rapidly. However, attempts to grow single crystals of this complex were unsuccessful, and we have no information about the arrangement of the two benzene molecules inside the host structure.

Effect of the amount of guest molecules: As described in the prior section, homo-[**2**+**2**] and hetero-[**3**+**3**] were obtained as precipitates in high yield with almost perfect selectivity by carrying out the reaction in MeOH/toluene (2:1) or MeOH/benzene (2:1), respectively. Since toluene and benzene were used as co-solvent in the experiments described above, we wished to determine the minimal amount of guest molecules required for selective precipitation of the host–guest complex (Table 3). When tetrol **1** and di(boronic acid) **2** were mixed in methanol in the presence of 10 molar amounts of toluene based on tetrol **1** for one day, homo-

Table 3. Requisite amount of guest molecules for selective self-assembly of homo-[**2+2**] or hetero-[**3+3**].

rac-**1** + 1.0 equiv **2** —(*X* equiv additive; MeOH; RT, 1 d)→ boronic esters (precipitates)

Entry	Additive	*X*	Precipitate
1	toluene	10	homo-[**2+2**]·toluene 87%
2	toluene	1	polymer quant.
3	benzene	10	polymer 85%, hetero-[**3+3**] trace
4[a]	naphthalene	0.5	homo-[**2+2**]·naphthalene 87%, polymer trace
5	triphenylene	0.33	polymer 46%, hetero-[**3+3**]·triphenylene[c] 24%
6[b]	triphenylene	0.67	hetero-[**3+3**]·triphenylene[c] 88%

[a] Reaction was carried out for 10 h. [b] Reaction was carried out for 8 h. [c] Trace amount of homo-[**3+3**] was included.

[**2+2**]·toluene was still obtained as a precipitate selectively. However, an equimolar amount of toluene no longer worked so effectively, and only insoluble polymeric boronic esters were obtained. In the case of benzene as guest molecule, even 10 molar amounts did not work effectively. These results indicate that excess amounts of guest molecules are required for the selective formation of homo-[**2+2**] and hetero-[**3+3**] in the cases of toluene and benzene. We next looked for a guest molecule that could induce the formation of the host–guest complex even at lower concentrations, and found that both naphthalene and triphenylene worked very effectively, thus leading to the precipitation of homo-[**2+2**]·naphthalene and hetero-[**3+3**]·triphenylene, respectively, in high yield. Thus, the reaction of equimolar amounts of di(boronic acid) and tetrol in the presence of only a half-molar amount of naphthalene (the theoretical minimum amount) in methanol gave homo-[**2+2**]·naphthalene as precipitate in 87% yield. In a similar manner, use of only 0.67 molar amounts of triphenylene (twice the theoretical minimum amount) gave hetero-[**3+3**]·triphenylene in 88% yield, although 0.33 molar amounts of triphenylene (the theoretical minimum amount) resulted in the formation of insoluble polymeric materials along with hetero-[**3+3**]. The X-ray structure of homo-[**2+2**]·naphthalene is shown in Figure 6a.[18] One molecule of naphthalene is trapped within homo-[**2+2**], and here again π–π interactions between naphthalene and the phenyl rings of the di(boronic acid) seem to play a decisive role. It is assumed that the stronger π–π interaction due to the wider π face of naphthalene compared to toluene enabled the selective formation of homo-[**2+2**] even with the minimum required amount of naphthalene. More importantly, the detailed structure of hetero-[**3+3**] was successfully determined by X-ray analysis of a single crystal of hetero-[**3+3**]·triphenylene, composed of two molecules of one tetrol and one molecule of the other. As shown in Figure 6b, triphenylene fits perfectly inside hetero-[**3+3**].[18] In this case, there is no π–π interaction but probably CH–π interaction between the hydrogen atoms of triphenylene and the π faces of the host molecule as seen from the X-ray structure.

Influence of the reaction time and NMR spectroscopic study: As already described in the previous section, homo-[**2+2**]·toluene or hetero-[**3+3**]·2benzene were selectively produced within one day by carrying out the boronic ester formation in the presence of toluene or benzene. We wished to understand more precisely what was happening in the early stage of the reaction and investigated the yield evolution of homo-[**2+2**] and hetero-[**3+3**] in methanol/toluene (2:1) and methanol/benzene (2:1) with the reaction time (Table 4). At the indicated time after tetrol **1** and di(boronic acid) **2** were mixed, the reaction mixture was filtrated and both precipitates and filtrate were analyzed by ^{1}H NMR spectroscopy. When toluene was used as a guest molecule, homo-[**2+2**]·toluene (41%) was obtained in moderate yield as precipitates after 3 min of mixing. Concerning the filtrate, about 40% of the components were recovered and its ^{1}H NMR spectra suggested that homo-[**2+2**] was obtained as the major product along with a trace amount of hetero-[**3+3**] (Table 4, entry 1).[21] On the contrary, when the mixture was filtered after 30 min, homo-[**2+2**]·toluene was selectively precipitated in high yield and no significant amounts of boronic esters were observed in the filtrate (entry 2). The same tendency was observed in the case of benzene except that the rate of precipitation was slower than in toluene and a significant amount of homo-[**2+2**] was observed in the filtrate after a shorter reaction time (entries 4–6). It should be emphasized that, in all entries, precipitates were composed of homo-[**2+2**]·toluene or hetero-[**3+3**]·2benzene selectively depending on the co-solvent, whereas the filtrate was often a mixture of both. These results indicate that, although all homo-[**2+2**], hetero-[**3+3**], and a small amount of homo-[**3+3**] were present in solution, only one of those macrocyclic boronic esters could precipitate selectively, depending on the nature of the host molecule.[22]

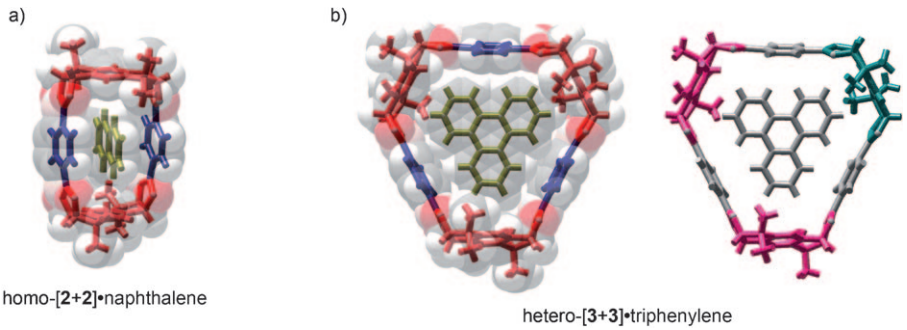
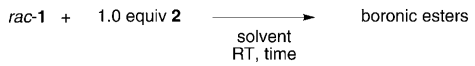


Figure 6. a) Crystal structure of homo-[**2+2**]·naphthalene: tetrol units (red), di(boronic acid) units (blue), naphthalene (yellow). b) Crystal structure of hetero-[**3+3**]·triphenylene. Left: tetrol units (red), di(boronic acid) units: (blue), triphenylene (yellow). Right: two enantiomers of tetrol in different colors.

Table 4. Effect of the reaction time.

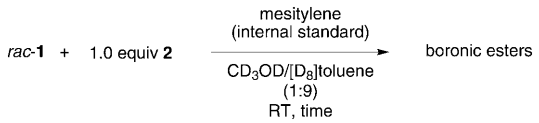


Entry	Solvent	Time	Precipitate	Filtrate[a]
1	MeOH/toluene (2:1)	3 min	homo-[**2+2**]·toluene 41 %	homo-[**2+2**] 38 %, hetero-[**3+3**] trace
2		30 min	homo-[**2+2**]·toluene 90 %	not detected
3		1 d	homo-[**2+2**]·toluene 81 %	homo-[**2+2**] trace
4	MeOH/benzene (2:1)	3 min	hetero-[**3+3**]·benzene[b] 24 %	[**3+3**][c] 20 %, homo-[**2+2**] 20 %
5		30 min	hetero-[**3+3**]·benzene[b] 60 %	[**3+3**][c] 31 %, homo-[**2+2**] 5 %
6		3 h	hetero-[**3+3**]·benzene[b] 94 %	hetero-[**3+3**] trace, homo-[**2+2**] trace

[a] NMR spectroscopic yield. [b] A trace amount of homo-[**3+3**] was included. [c] Ratio of homo- and hetero-[**3+3**] was approximately 1:17.

Then we monitored by NMR spectroscopy the reaction mixture to further confirm the presence of homo-[**2+2**] and hetero-[**3+3**] in solution. Because a large amount of products precipitated within a few minutes, the NMR spectroscopic study of the reaction in CD_3OD/[D_8]toluene (2:1) could not provide us with any significant information. We then monitored the reaction in CD_3OD/[D_8]toluene (1:9) in which a higher solubility of the products was expected. Table 5 shows changes in the yields of soluble components by using mesitylene as internal standard.

Table 5. NMR spectroscopic observation in CD_3OD/[D_8]toluene (1:9).



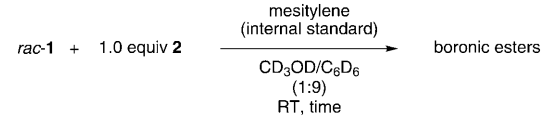
Time	% homo-[**2+2**]	[**3+3**] % homo	[**3+3**] % hetero	[**3+3**] homo/hetero	[**2+2**]/[**3+3**]	Oligomers [%]	Total yield (in solution) [%]
10 min	10	2	8	1:4.0	1:1.0	16	36
30 min	20	4	19	1:4.8	1:1.2	16	59
2.5 h	38	10	36	1:3.6	1:1.2	8	92
11 h	34	9	29	1:3.2	1:1.1	7	79
24 h	31	9	25	1:2.8	1:1.1	7	72
52 h	31	7	20	1:2.9	1:0.9	7	65
6 d	23	5	16	1:3.2	1:0.9	7	51

In this case, the total yield of soluble products at the early stage of the reaction was rather low because the starting materials did not fully dissolve. After mixing tetrol **1** and di(-boronic acid) **2** for about 2.5 h, a clear solution was obtained, followed by the progressive precipitation of homo-[**2+2**], which led to a yield for the soluble products of 51 % after six days. During this examination, homo-[**2+2**], homo-[**3+3**], and hetero-[**3+3**] were all observed in solution. The ratio of homo-[**2+2**] and [**3+3**] was nearly 1:1 throughout the observation. This result indicates that the selective formation of homo-[**2+2**] in the presence of toluene does not occur in solution and is induced by the precipitation process.

When a similar examination was carried out in CD_3OD/C_6D_6 (1:9) (Table 6), the products in solution were again a mixture of homo-[**2+2**], homo- and hetero-[**3+3**], and of unidentified oligomers. However, several differences should be pointed out here, the first one being the ratio of homo-[**2+2**] to [**3+3**]. In CD_3OD/[D_8]toluene, this ratio was about 1:1 throughout the reaction, whereas in CD_3OD/C_6D_6, the ratio decreased from about 1:1 in the beginning to a minimum of 1:4 at equilibrium. Thus, formation of [**3+3**] is more favorable in CD_3OD/C_6D_6 than in CD_3OD/[D_8]toluene at equilibrium in solution. The second difference is the solubility of the products. In CD_3OD/[D_8]toluene, the amount of the soluble boronic esters increased in the beginning and reached its maximum in 2.5 h, but gradually decreased thereafter. On the contrary, in CD_3OD/C_6D_6, the soluble components gradually increased throughout the reaction to reach a maximum of 75 % yield after about 20 h. It should also be pointed out that a significant amount of homo-[**3+3**] was also observed, thereby suggesting that the diastereoselectivity in the formation of [**3+3**] as well as the selectivity between [**2+2**] and [**3+3**] are induced by the precipitation process.

Reaction using optically active tetrol 1: All the examinations so far have been carried out using racemic tetrol **1**. We next investigated the same reaction using optically active tetrol,

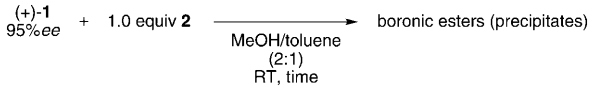
Table 6. NMR spectroscopic observation in CD_3OD/C_6D_6 (1:9).



Time	% homo-[**2+2**]	[**3+3**] % homo	[**3+3**] % hetero	[**3+3**] homo/hetero	[**2+2**]/[**3+3**]	Oligomers [%]	Total yield (in solution) [%]
10 min	14	3	11	1:3.7	1:1.0	3	31
30 min	12	5	17	1:3.4	1:1.8	7	41
2.5 h	18	7	27	1:3.9	1:1.3	5	57
7 h	14	10	30	1:3.0	1:2.9	4	58
20 h	12	13	33	1:2.5	1:3.8	3	61
45 h	15	18	42	1:2.3	1:4.0	0	75
6 d	15	18	41	1:2.3	1:3.9	0	74

which was obtained by chiral preparative HPLC. The results for the reaction in methanol/toluene (2:1) are shown in Table 7. In contradiction to the results obtained using racemic tetrol, insoluble polymeric materials were the major products regardless of the reaction time, and homo-[**2+2**] was scarcely obtained. It should be noted that a small amount of homo-[**3+3**] was obtained when the reaction was carried out for 30 min, as supported by FAB-MS analysis. As the homo-[**2+2**] produced using racemic tetrol consisted of two tetrol units of the same enantiomer, homo-[**2+2**] could be theoretically produced as the major product even when optically active tetrol is used. This unexpected result can be understood if one considers the crystal packing of the product in the solid state. It is thought that an appropriate pair of enantiomers of homo-[**2+2**], the pair of *R*,*R*–*S*,*S* in Scheme 2, is required for the selective precipitation of homo-[**2+2**] from the solution. The result of X-ray analysis of racemic homo-[**2+2**]·toluene, in which equal amounts of both enantiomers are present in a unit cell, supports this assumption. In the case of optically active tetrol, the equilibrium could be driven toward the formation of polymeric boronic esters due to unfavorable packing at the unit-cell level in the solid state.

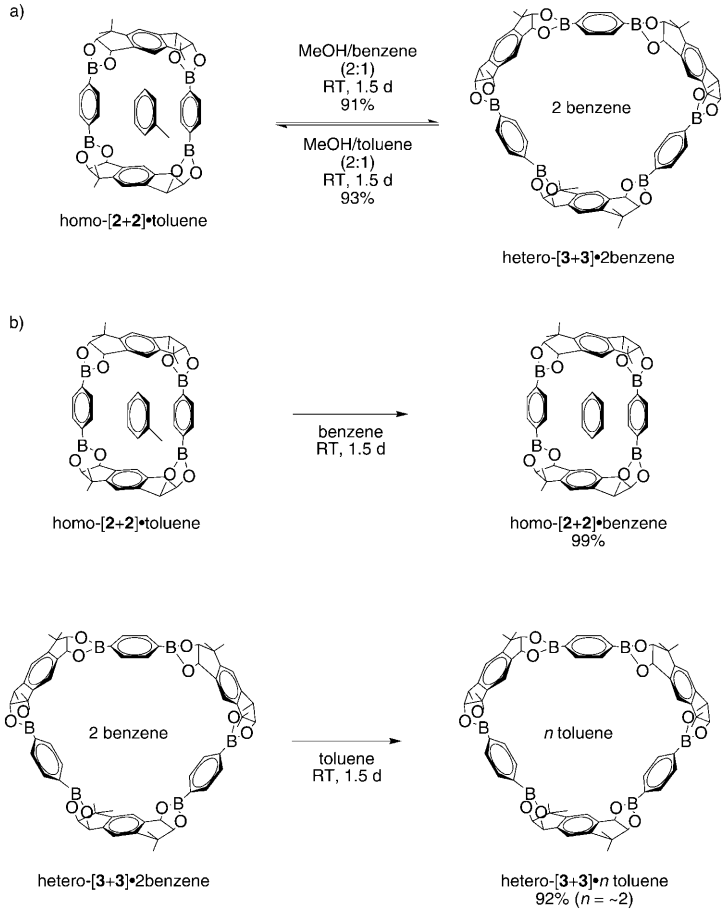
Table 7. Reaction using optically active tetrol.



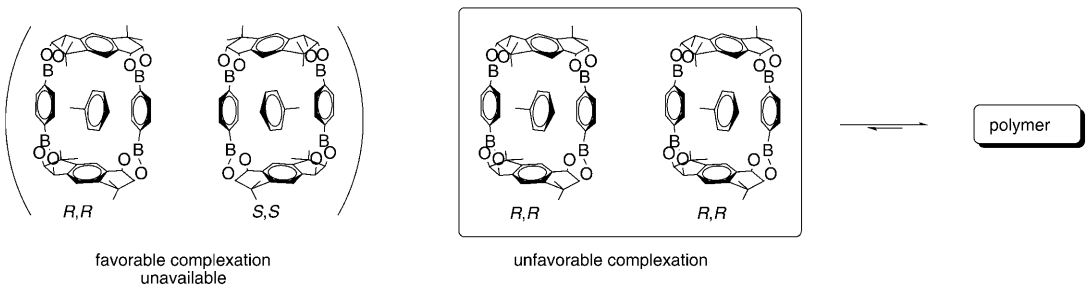
Entry	Time	Precipitate
1	30 min	polymer ca. 85%, homo-[**2+2**] 8%[a], homo-[**3+3**] 4%[a]
2	1 d	polymer quant.

[a] NMR spectroscopic yield.

Switch on/off equilibration between two host molecules: We next examined the interconversion between homo-[**2+2**] and hetero-[**3+3**] (Scheme 3a). When isolated homo-[**2+2**]·toluene was suspended in methanol/benzene (2:1), perfect conversion to hetero-[**3+3**]·2benzene occurred within 36 h. The opposite conversion could also be carried out by treatment of hetero-[**3+3**]·2benzene with methanol/toluene (2:1) for 36 h. Thus, homo-[**2+2**] and hetero-[**3+3**] can be interconverted in the presence of methanol and an appropriate guest molecule. Even the polymeric boronic esters were converted to homo-[**2+2**] (62% yield) by stirring the suspension in MeOH/toluene (2:1) for five days. Unfortunately, the conversion of the polymer into hetero-[**3+3**] in MeOH/benzene (2:1) did not proceed even by heating, possibly due to the lower host-inducing ability of benzene. In contrast to the reactions in the presence of methanol, when homo-[**2+2**]·toluene was dissolved in pure benzene, and after the solvent was removed under reduced pressure, homo-[**2+2**]·benzene was obtained in quantitative yield without the formation of hetero-[**3+3**] (Scheme 3b). Evi-



Scheme 3. On/off switch for equilibration. a) Interconversion between homo-[**2+2**] and hetero-[**3+3**] in the presence of methanol. b) Kinetic stability of homo-[**2+2**] and hetero-[**3+3**] in the absence of methanol.



Scheme 2. Two enantiomer pairs of homo-[**2+2**].

dence for this structure was supported by elemental analysis and ^{1}H NMR spectrum. It should be emphasized that this host–guest complex cannot be prepared under thermodynamically controlled, equilibrating conditions. In a similar manner, treatment of hetero-[**3+3**]·2benzene in toluene only gave hetero-[**3+3**]·*n*toluene ($n \approx 2$) almost quantitatively. This ability to switch on/off the conversion between [**2+2**] and [**3+3**] depending on the presence or absence of a protic solvent—in this case, methanol—is a very attractive feature of this system.[23] It is likely that methanol coordinates with the boron atom of the host molecule, and then transesterification occurs by means of the borate intermediate generated by the coordination.

Conclusion

In conclusion, we have demonstrated that, from the same starting boronic acid and alcohol, it was possible to obtain, in the presence of specific guest molecules and by means of dynamic self-assembling boronic ester formation, two types of supramolecular structures, homo-[**2+2**] and hetero-[**3+3**] in nearly quantitative yield under neutral conditions. Advancement of the reaction in methanol/toluene (2:1) and methanol/benzene (2:1) suggests that both the selectivity of formation of homo-[**2+2**] and hetero-[**3+3**] and the diastereoselectivity of hetero-[**3+3**] are induced by the precipitation process. That is, although homo-[**2+2**], homo-[**3+3**], and hetero-[**3+3**] are all present in solution, only one of these macrocycles will precipitate, depending on the nature of the guest molecule that drives the system. This interpretation is also supported by the NMR spectroscopic observations in CD_3OD/[D_8]toluene (1:9) and CD_3OD/C_6D_6 (1:9). Additionally, the reaction in methanol/toluene (2:1) using optically active tetrol resulted in the formation of polymeric boronic ester instead of the homo-[**2+2**]·toluene complex, thereby suggesting the necessity to form the appropriate pair of enantiomers of homo-[**2+2**] to achieve selective precipitation. Furthermore, homo-[**2+2**] and hetero-[**3+3**] could be interconverted in the presence of methanol and of appropriate guest molecules, whereas they are kinetically stable in the absence of methanol. Thus, in addition to the supramolecular structures directly available by crystallization-controlled dynamic self-assembly, the possibility to switch on/off the interconversion between the different forms of the host structure and to exchange guest molecules leads to the formation of new supramolecular assemblies.

Experimental Section

Self-assembly of homo-[**2+2**]**·toluene in MeOH/toluene (2:1)**: 1,4-Benzenedi(boronic acid) **2** (19.0 mg, 0.11 mmol) was added to a solution of tetrol **1** (31.0 mg, 0.11 mmol) in methanol/toluene (2:1; 9.0 mL). The reaction mixture rapidly became homogeneous, and in a few seconds precipitation started to appear. After the mixture was stirred at room temperature for 30 min, homo-[**2+2**]·toluene was obtained in more than 95% purity as a white powder by filtration followed by drying under air (41.8 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, $CHCl_3$): $\delta = 7.66$ (s, 8H; CH), 7.29–7.15 (m, 9H; CH and toluene), 5.85 (d, $J = 5.9$ Hz, 4H; CH), 4.75 (d, $J = 5.9$ Hz, 4H; CH), 2.36 (s, 3H; toluene), 1.37 (s, 12H; CH_3), 1.17 ppm (s, 12H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, $CDCl_3$): $\delta = 149.5$ (C_{ar} of tetrol), 141.6 (C_{ar} of tetrol), 137.9 (C_{ar} of toluene), 134.4 (C_{ar} of boronate), 129.0 (C_{ar} of toluene), 128.2 (C_{ar} of toluene), 125.3 (C_{ar} of toluene), 119.8 (C_{ar} of tetrol), 90.0 (CH of tetrol), 82.9 (CH of tetrol), 47.0 (C of tetrol), 31.6 (CH_3 of tetrol), 21.9 (CH_3 of tetrol), 21.5 ppm (CH_3 of toluene); IR (KBr): $\tilde{\nu} = 2951$, 1355, 1102 cm^{-1}; elemental analysis calcd (%) for $C_{51}H_{52}B_4O_8$: C 73.25, H 6.27; found: C 73.03, H 6.27.

Self-assembly of hetero-[**3+3**]**·2benzene in MeOH/benzene (2:1)**: 1,4-Benzenedi(boronic acid) **2** (28.6 mg, 0.17 mmol) was added to a solution of tetrol **1** (47.8 mg, 0.17 mmol) in methanol/benzene (2:1; 13.8 mL). The reaction mixture rapidly became homogeneous, and in a few seconds precipitation started to appear. After the mixture was stirred at room temperature for 3 h, hetero-[**3+3**]·2benzene was obtained in more than 95% purity as a white powder by filtration followed by drying under air (68.4 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, $CHCl_3$): $\delta = 7.70$ (s, 8H; CH), 7.69 (s, 4H; CH), 7.36 (s, 12H; benzene), 7.34 (s, 2H; CH), 7.33 (s, 2H; CH), 7.31 (s, 2H; CH), 5.84 (d, $J = 5.6$ Hz, 2H; CH), 5.83 (d, $J = 6.8$ Hz, 2H; CH), 5.82 (d, $J = 6.4$ Hz, 2H; CH), 4.84 (d, $J = 7.6$ Hz, 2H; CH), 4.82 (d, $J = 6.0$ Hz, 2H; CH), 4.82 (d, $J = 6.4$ Hz, 2H; CH), 1.43 (s, 6H; CH_3), 1.40 (s, 6H; CH_3), 1.38 (s, 6H; CH_3), 1.30 (s, 6H; CH_3), 1.28 ppm (s, 12H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, $CDCl_3$): $\delta =$ 150.3 (C_{ar} of tetrol), 150.2 (C_{ar} of tetrol), 141.00 (C_{ar} of tetrol), 140.98 (C_{ar} of tetrol), 140.9 (C_{ar} of tetrol), 133.8 (C_{ar} of boronate), 128.3 (C_{ar} of benzene), 120.7 (C_{ar} of tetrol), 120.54 (C_{ar} of tetrol), 120.49 (C_{ar} of tetrol), 90.35 (CH of tetrol), 90.28 (CH of tetrol), 90.2 (CH of tetrol), 83.3 (CH of tetrol), 83.2 (CH of tetrol), 83.1 (CH of tetrol), 46.82 (C of tetrol), 46.78 (C of tetrol), 46.7 (C of tetrol), 31.4 (CH_3 of tetrol), 23.7 (CH_3 of tetrol), 23.5 (CH_3 of tetrol), 23.4 ppm (CH_3 of tetrol); IR (KBr): $\tilde{\nu} = 2959$, 1351, 1101 cm^{-1}; HRMS (FAB$^+$, NBA): *m*/*z*: calcd for $C_{66}H_{66}B_6O_{12}$ [*M*−2benzene]$^+$: 1116.5113; found: 1116.5092; elemental analysis calcd (%) for $C_{78}H_{78}B_6O_{12}$: C 73.63, H 6.18; found: C 73.50, H 6.11.

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