Regioselective introduction of two boronic acid groups into [60]fullerene using saccharides as imprinting templates

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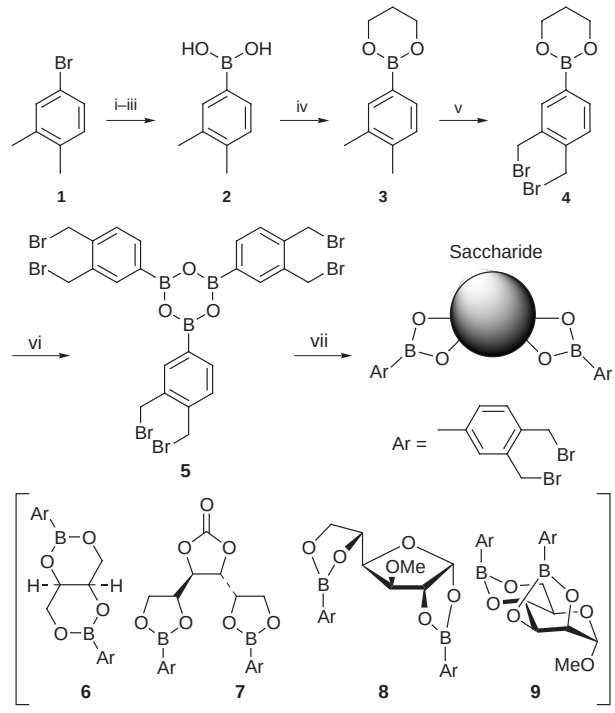
Two boronic acid groups were introduced into [60]fullerene using saccharides as template molecules: it was found that the regioselectivity changes depending on the saccharide structure.

The molecular imprinting technique attracted considerable attention in the 1970s, but recently has been revived as an active research area.[1–3] The principle involves copolymerisation of vinyl monomers with divinyl monomers in the presence of guest metals or molecules to produce three-dimensional network polymers.[1–3] Although this technique has achieved some degree of success, two complex problems have been left unresolved, *i.e.* the evaluation of the imprinting effect is difficult because it can be performed only in a heterogeneous system, and the storage capacity is small because only the particle surface is useful for the re-binding of guests. Is there an alternate method in which both the imprinting process and the estimation process can be carried out in a more reliable homogeneous system? [60]Fullerene and its homologues are moderately soluble in organic solvents and have plenty of reactive C=C double bonds which are useful for the immobilisation of functional groups. It thus occurred to us that they would be useful as a base for the imprinting of functional groups and for use in a homogeneous system. There are a limited number of precedents for regioselective introduction of substituents into [60]fullerene.[4–6] In order to apply [60]fullerene to the memory storage, we here chose saccharides as the template and guest molecules and boronic acids as the functional groups. Saccharides have several specific advantages for the present purpose which other template molecules do not have, *i.e.* (i) they can arrange two boronic acid groups in a variety of spatial positions, (ii) removal and re-binding can occur reversibly, and (iii) because of their inherent chirality, chiroselective introduction of two boronic acid groups is possible.[7] We here report the fact that, using saccharides as template molecules, two boronic acid groups can be regioselectively introduced into [60]fullerene; the regiospectrum is closely related to the structure of saccharides used as template molecules.

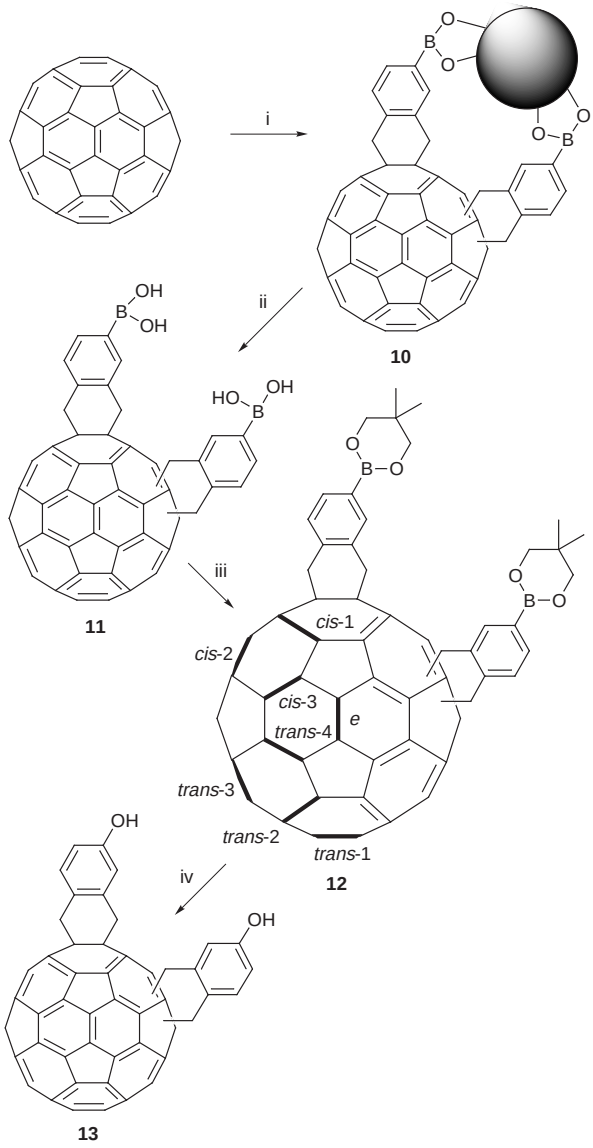
In order to access saccharide–boronic acid 1 : 2 complexes **6**–**9**, we first synthesised **5** from 4-bromo-*o*-xylene **1** (Scheme 1). Compound **5**, which was isolated as a cyclic trimer,[7,8] was identified by ^{1}H NMR, IR (KBr) and mass (negative SIMS) spectral evidence and elemental analysis. Complexes **6**–**9** were synthesised from **5** and the corresponding saccharides in refluxing toluene with azeotropic removal of water under a nitrogen atmosphere. The products were identified by ^{1}H and ^{11}B NMR and IR (KBr) spectral evidence and elemental analyses.[9] The reaction of **6**–**9** with [60]fullerene was carried out in refluxing toluene for 40 h in the presence of 18-crown-6 and KI under a nitrogen atmosphere. To simplify the product analysis, the saccharides were removed by the treatment with aqueous 1.2 mol dm^{-3} HCl solution and then the boronic acid groups in the product **11** were protected using 2,2-dimethylpropane-1,3-diol[10] (Scheme 2). The product was purified by column chromatography. We thus isolated a regioisomeric mixture of **12** in 49–58% yield. This mixture was subjected to HPLC analysis [COSMOSIL 5 PBB, *n*-hexane–toluene (3 : 7 v/v)]. The results are summarised in Table 1.

In the HPLC analysis, 7–8 peaks were always observable and the relative intensity changed depending on the saccharide used as the template molecule. Compounds **6**, **7** and **8** with D-threitol, D-mannito 3,4-carbonate and 3-*O*-methyl-D-glucofuranose as template molecules, respectively, afforded major peaks for Peak 7 (47.3%), Peak 8 (55.7%) and Peak 6 (72.5%), respectively, whereas compound **9** with 1-*O*-methyl-α-D-mannopyranoside as a template molecule featured a rather nonselective product distribution. The results imply that the saccharide changes the distance between two *o*-xylenyl dibromide groups in **6**–**9** and the addition reaction occurs at different C=C double bonds on the [60]fullerene surface.

It is difficult to isolate the eight different isomers of disubstituted **12** and thus identify the structure of each isomer. We decided to attempt the isolation of Peak 6 [with the highest (72.5%) yield] in the mixture obtained from **8** and [60]fullerene. Through trial and error it was found that Peak 6 can be isolated by recrystallisation from *n*-hexane–CH_2Cl_2: the HPLC analysis showed a single peak for Peak 6. In the ^{1}H NMR spectrum (300 MHz, [$^2H_8$]toluene, 90 °C) of this compound (**12a**) one could observe one CH_3 proton peak (δ 0.71, 12 H) and one CH_2 proton peak (δ 3.50, 8 H) for the protective groups and four CH_2 proton peaks (δ 4.04, 4.04, 4.12 and 4.19, 2 H each) and three ArH proton peaks (δ 7.42, 8.13 and 8.17, 2 H each) for the *o*-xylenyl groups. This splitting pattern is commensurate with either C_2 symmetry (*cis*-3, *trans*-2 or *trans*-3) or C_s symmetry (*cis*-1, *cis*-2,



Scheme 1 *Reagent and conditions*: i, Mg, THF; ii, $B(OMe)_3$, −60 °C; iii, H_2SO_4, 69% from **1**; iv, propane-1,3-diol, toluene, reflux, 71%; v, NBS, CCl_4, reflux, 50%; vi, HCl, THF, 90%; vii, saccharide, toluene, reflux, 82% for **6**, 95% for **7**, 76% for **8** and 60% for **9**



Scheme 2 *Reagent and conditions*: i, **6**–**9**, KI, 18-crown-6, toluene, reflux; ii, HCl, THF: iii, 2,2-dimethylpropane-1,3-diol, toluene, reflux, 49% from **6**, 53% from **7**, 58% from **8** and 52% from **9**; iv, 30% H_2O_2, AcOH, THF, 56%

Table 1 Results of HPLC analysis of **12**

Peak number	Retention time/min	Product (%)[a]			
		6	**7**	**8**	**9**
1	39.6	1.5	4.2	0.2	5.6
2	41.5	2.3	4.3	1.5	7.5
3	43.0	5.4	3.4	3.0	11.4
4	46.5	7.8	10.5	3.7	15.2
5	49.7	12.3	7.7	3.6	23.7
6	51.2	11.3	14.2	72.5	15.6
7	52.9	47.3	0	0	0
8	54.1	12.1	55.7	15.5	21.0

[a] Computed from the peak area obtained by the chromatogram followed at 350 nm.

trans-1 or *trans*-4).[4–6,11] Among them, the size of the saccharide used as the template molecule is too small or too large to give *cis*-1, *trans*-1, *trans*-2 and *trans*-3: therefore, these isomers can be excluded. The residual, possible isomers are *cis*-2, *cis*-3 and *trans*-4.

In absorption spectroscopy (CH_2Cl_2, 25 °C) compound **12a** gave two absorption maxima at 643 and 708 nm. Since these absorption maxima are observable only for *cis*-3 and *trans*-4,[11,12] *cis*-2 can be excluded. The solubility of **12a** into deuterated NMR solvents was not high enough to obtain a satisfactory ^{13}C NMR spectrum, so we converted **12a** to **13a** (Nishimura's phenol adduct[6]) *via* treatment with H_2O_2 (56% yield). Compound **13a** did not coincide either with *cis*-2 or with *cis*-3, as reported by Nishimura.[6] Furthermore, the ^{13}C NMR spectrum (75.5 MHz, [$^2H_6$]DMSO, 120 °C) gave 30 sp^2 carbon peaks and 2 sp^3 carbon peaks for the [60]fullerene moiety. This splitting pattern is commensurate with C_s-symmetrical *cis*-2 and *trans*-4.[11,12] Thus **12a** can be identified as *trans*-4.[13]

As a preliminary study to test whether **11a** retains the memory for 3-*O*-methyl-D-glucose, we carried out solid (excess 3-*O*-methyl-D-glucose)–liquid ([$^2H_8$]THF) extraction with **11a**. Judging from the fact that the ratio of the integral intensity between 1-H in the complexed 3-*O*-methyl-D-glucose and ArH in the complexed **11a** is 1 : 6, one can conclude that **11a** can quantitatively bind the templated saccharide.

In conclusion, the present study has demonstrated that saccharides are useful as potential templates to regioselectively introduce two boronic acid groups into [60]fullerene.

Notes and References

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13 In **12a**, three isomers (in–in, out–in and out–out) are available, in principle, owing to the direction of the $B(OCH_2CMe_2CH_2O)$ group in the benzene ring. Judging from the size of the template saccharide and the splitting pattern of the ^1H NMR spectrum, the out–in and out–out isomers can be excluded. Thus, **12a** isolated here is the in–in isomer. For an explanation of the concept of in–in, out–in and out–out isomers, see refs. 4–6.

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