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Switching the selectivity of a polyglycerol dendrimer monomolecularly imprinted with D-(−)-fructose

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ABSTRACT

A polyglycerol dendrimer monomolecularly imprinted with D-(−)-fructose (Fru) was synthesized. The dendrimer formed adducts with several monosaccharides, Fru, D-(+)-galactose, D-(+)-glucose, D-(+)-mannose, and methyl-α-D-mannopyranoside (MMan), by removal of four water molecules. The dendrimer preferred Fru in the absence of *N*,*N*,*N*′,*N*′-tetramethyldiaminomethane (TMDAM), whereas it preferred MMan in the presence of TMDAM.

Developing synthetic receptors for carbohydrates is an important challenge with potential applications in sensing, catalysis, and targeting.[1] Altering the selectivity of a carbohydrate receptor in a controllable way would further expand the types of applications available. We recently reported that monomolecularly imprinted dendrimers (MIDs) can act as selective receptors for porphyrins and amines.[2] With partial success, these previous studies sought dendrimers with a high cross-linking density to fix recognition sites rigidly for high selectivity. This article reports the synthesis of MIDs with lower cross-link densities whose recognition sites can be repositioned, thus switching the carbohydrate selectivity. The aryl boronic acid group was chosen as the recognition unit because of its well-documented ability to form covalent adducts with monosaccharides[3] and its Lewis acidic nature allowing it to be further manipulated.

We have chosen D-(−)-fructose (Fru) as a monosaccharide template because preliminary studies showed that Fru underwent a clean reaction with 2 equiv of phenylboronic acid in methanol, as reported previously.[4,5] The Fru MID was prepared as shown in Scheme 1. Thus, polyglycerol dendron **1** was prepared by a slight modification of the procedure described elsewhere.[6] Two equivalents of the dendron **1** were coupled with dibromide **2**, which was prepared according to the procedures of Wong[7] and Singaram,[8,9] in the presence of sodium hydride and tetrabutylammonium iodide (TBAI) in tetrahydrofuran (THF) to give boronic acid-carrying dendron **3** in 83% yield. Two equivalents of **3** were mixed with Fru in methanol. After 12 h, the solvent was evaporated, and the dendrimer **4** bearing Fru at the core was purified by preparative size exclusion chromatography (SEC) using toluene as eluent (94% yield after purification). The ring closing metathesis (RCM)-mediated cross-linking of **4** was carried out under high dilution (36 μM) using Hoveyda–Grubbs 2nd generation catalyst (6.3 mol % for alkene) in refluxing dichloromethane for 26 h. After quenching the catalyst with ethyl vinyl ether, the cross-linked dendrimer **5** was purified by preparative toluene SEC followed by lyophilization from a benzene solution (86% yield). The extent of RCM cross-linking can be quantified using ^{1}H NMR spectroscopy by comparing the alkene methine signals in **4** and **5** (Fig. S2 in ESM). Likewise, the MALDI-TOF-MS indicated that the major product was the cross-linked dendrimer **5** of 16 cross-links (Fig. S5 in ESM). The SEC of **5** indicated that the RCM reaction of **4** occurred in an intramolecular fashion predominantly (Fig. S7 in ESM). The cross-linked dendrimer **5** was cored by treatment with aqueous acidic THF for 20 h.[10] The cored dendrimer (MID) **6** was extracted with dichloromethane and recovered by lyophilization from a benzene solution. The coring was confirmed by ^{1}H NMR and MALDI-TOF-MS as can be seen in Figures S3 and S6 in ESM. The yield of the coring step was 78% and the SEC showed minimal fragmentation suggesting that the RCM reaction occurred between the dendrons. Work with the Fréchet-type dendrimers showed that longer range RCM cross-links are preferred.[11]

Because MID **6** was insoluble in water and methanol it was not possible to carry out quantitative binding studies with monosaccharides in these solvents. Binding studies were carried out in various mixed aqueous organic solvents, but under conditions where the components were soluble only weak binding was detected. Thus, we examined the preparation of adducts of the cored dendrimer **6** with several monosaccharides, that is, Fru, D-(+)-galactose, D-(+)-glucose, D-(+)-mannose, and methyl-α-D-mannopyranoside (MMan). A solution of the cored dendrimer **6** in dichloromethane and a solution of a monosaccharide in methanol were mixed (see ESM for concentrations and other details). After ca. 30 min, the mixed solvent was evaporated under reduced pressure. The

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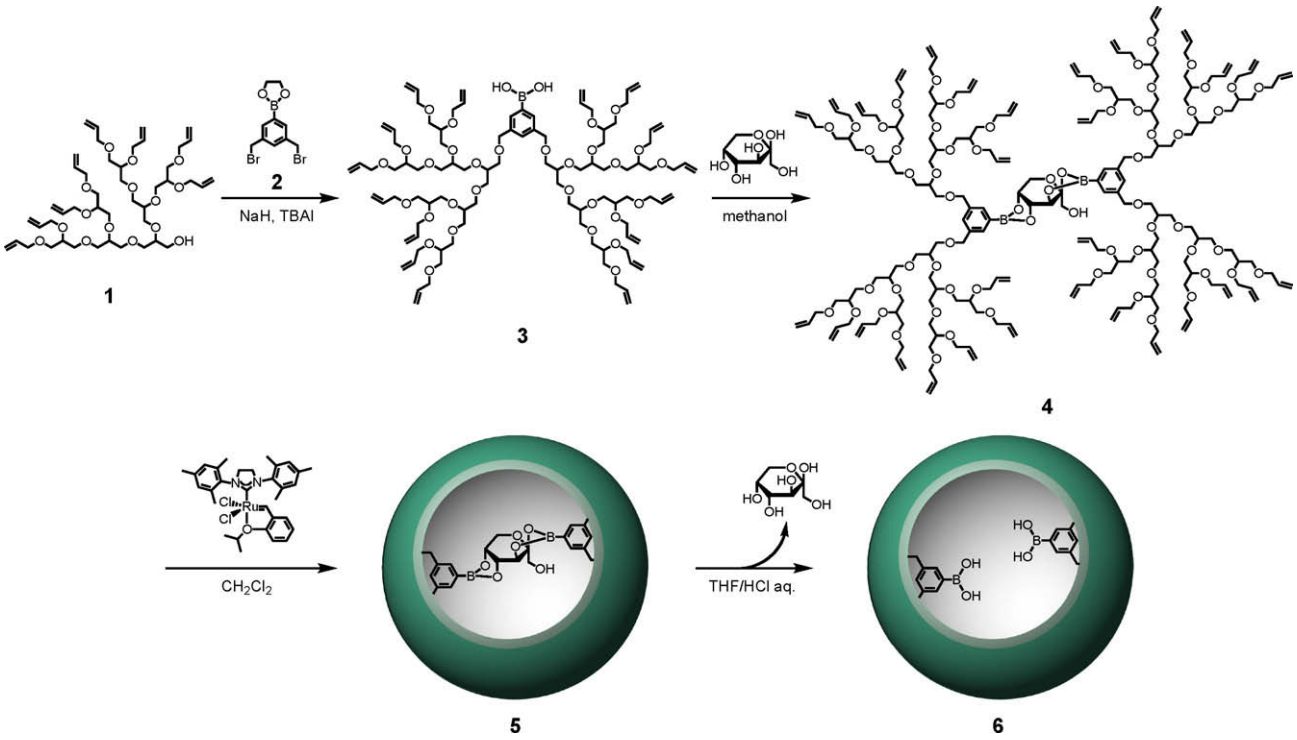

Scheme 1.

dendrimer was recovered by lyophilization from a benzene solution.[†] MALDI-TOF-MS data (not shown) indicated that MID **6** formed adducts with all the monosaccharides examined by removal of four water molecules.

It is known that Fru and MMan form well-defined adducts with 2 equiv of phenylboronic acid derivatives: in the adduct of Fru, the two boronic acid residues are located in the opposite sides,[5] whereas, in the adduct of MMan, the two boronic acid residues are close to each other.[12] ^{1}H NMR for the adducts with Fru and MMan showed broad but clear resonance bands ascribable to the saccharide in the region of 4.6–5.2 ppm, corresponding well to those for model compounds, that is, adducts of these monosaccharides with phenylboronic acid (Fig. S9 in ESM).[‡] This observation indicates that the cored dendrimer **6** forms adducts of a well-defined structure with Fru and MMan and that the configurations of the core are the same as those of the model compounds. Based on these data, it was concluded that the relative location of the two boronic acid residues is adjustable presumably because MID **6** contains a comparatively small number (i.e., $\leqslant$16) of cross-links providing flexibility.

In an attempt to control the relative position of the two boronic acid residues in **6**, advantage was taken of their ability to coordinate to Lewis bases.[13] In particular, we examined whether an appropriate diamine added to MID **6** would simultaneously coordinate the two boronic acid residues and preorganize them for binding a specific monosaccharide. *N*,*N*,*N*′,*N*′-Tetramethyldiaminomethane (TMDAM) was chosen for its potential to place the boronic acid groups in close proximity, which, in turn might favor the binding of MMan. A solution of MID **6**, Fru, and MMan in a 1:1:1 ratio (solvent mixture: CH_2Cl_2, MeOH, and THF) and in the

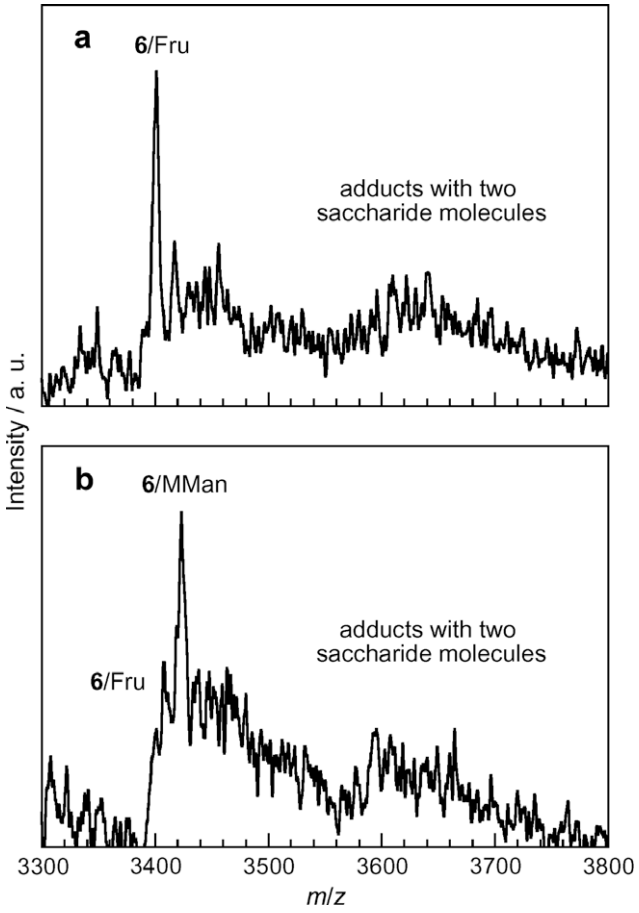

Figure 1. MALDI-TOF-MS for the adducts of the dendrimer **6** with Fru and MMan obtained in the absence (a) and presence (b) of TMDAM. Dithranol was used as a matrix.

[†] When the residue was dissolved in benzene for lyophilization there was no precipitate, indicating of no free monosaccharide.

[‡] Other than Fru and MMan, the adducts of MID 6 with monosaccharides exhibited no clear resonance bands because these adducts were mixtures of several isomers.

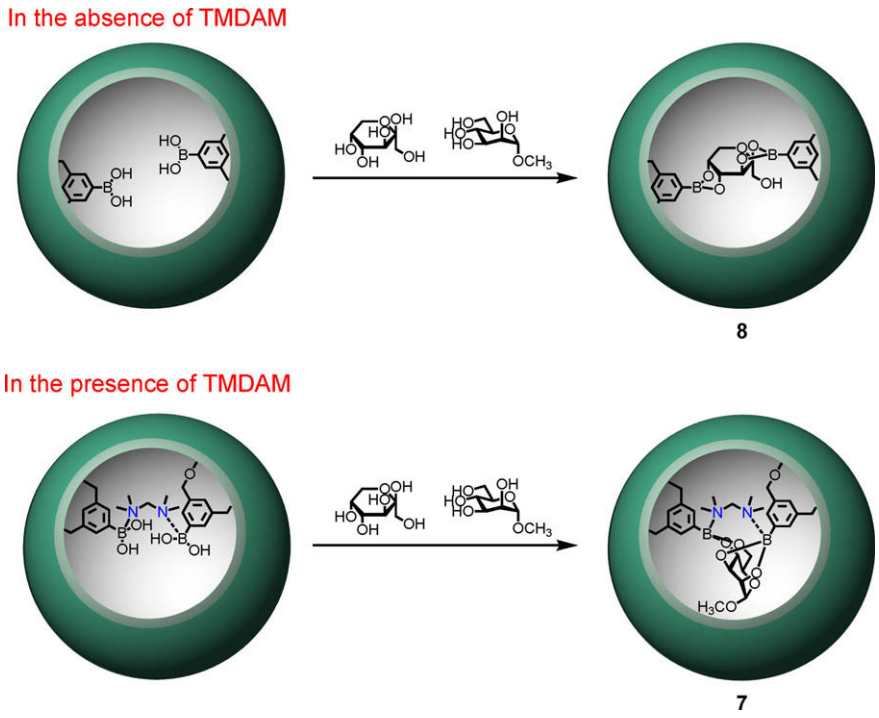

Figure 2. Conceptual illustration of saccharide recognition of the dendrimer **6** in the absence and presence of TMDAM.

presence and absence of 1 equiv of TMDAM was equilibrated for 2 h and the solvent was removed to prepare adducts. As can be seen in Figure 1a, in the absence of TMDAM, the MALDI-TOF-MS indicates that the main product was the one-to-one adduct of Fru and MID **6**. In the presence of TMDAM, however, the MALDI-TOF-MS indicates the predominant formation of the one-to-one adduct of MID **6** with MMan (Fig. 1b).[§] Thus, the selectivity of MID **6** was switched by adding TMDAM (Fig. 2). It is hypothesized that the basis for the switching is the added stability of complex **7**, containing two B···N interactions from single TMDAM molecule, whereas complex **8** with Fru requires two TMDAM molecules and, thus, an additional entropic price.

The competitive binding studies were also carried out in the presence of amines of different carbon numbers between the two amine groups, that is, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (TMPDA), and *N*,*N*,*N*′,*N*′-tetramethyl-1,4-butanediamine (TMBDA). MALDI-TOF-MS for a mixtures of MID **6**, Fru, MMan, and TMEDA also exhibited a main peak ascribable to the adduct of MID **6** with MMan with a lower signal-to-noise ratio, indicating that TMEDA can switch the selectivity of MID **6**. On the other hand, MALDI-TOF-MS for mixtures of MID **6**, Fru, MMan, and TMPDA or TMBDA exhibited only weak signals ascribable to adducts of MID with Fru and MMan, indicative of arrangements of the boronic acid residues in MID **6** unfavorable for Fru and MMan in the presence of TMPDA or TMBDA. These observations confirmed that TMDAM is the most useful diamine to switch the selectivity of MID **6** toward MMan.

In summary, we have synthesized a polyglycerol dendrimer monomolecularly imprinted with Fru and have switched its binding selectivity by adding TMDAM. More broadly, the combination of loosely connected boronic acids and appropriately designed diamines may provide a more versatile recognition approach for polyols, including chiral or stimuli-responsive recognition.

[§] We did not observe any peaks ascribable to the adducts containing TMDAM in MALDI-TOF-MS experiments. It is likely that volatile TMDAM was removed in high vacuum in the instrument, or was eliminated in MALDI event.

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Supplementary data

Supplementary data (experimental details, characterization data for the dendrimers, and ^{1}H NMR spectra for the adducts of MID **6** and phenylboronic acid) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.168.

References and notes

1. For lead references: (a) James, T. D.; Shinkai, S. *Top. Curr. Chem.* **2002**, *218*, 159–200; (b) Davis, A. P.; James, T. D. In *Functional Synthetic Receptors*; Schrader, T., Hamilton, A. D., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005; pp 45–109.
2. (a) Zimmerman, S. C.; Wendland, M. S.; Rakow, N. A.; Zharov, I.; Suslick, K. S. *Nature (London, UK)* **2002**, *418*, 399–403; (b) Mertz, E.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2003**, *125*, 3424–3425; (c) Zimmerman, S. C.; Zharov, I.; Wendland, M. S.; Rakow, N. A.; Suslick, K. S. *J. Am. Chem. Soc.* **2003**, *125*, 13504–13518; (d) Zimmerman, S. C.; Lemcoff, N. G. *Chem. Commun.* **2004**, 5–14.
3. James, T. D.; Phillips, M. D.; Shinkai, S. In *Boronic Acids in Saccharide Recognition*; Stoddard, J. F., Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry: Cambridge, UK, 2006.
4. Wulff, G.; Schauhoff, S. *J. Org. Chem.* **1991**, *56*, 395–400.
5. Draffin, S. P.; Duggan, P. J.; Fallon, G. D. *Acta Crystallogr., Sect. E* **2004**, *60*, o1520–o1522.
6. Elmer, S. L.; Man, S.; Zimmerman, S. C. *Eur. J. Org. Chem.* **2008**, *2008*, 3845–3851.
7. Wong, K.-T.; Chien, Y.-Y.; Liao, Y.-L.; Lin, C.-C.; Chou, M.-Y.; Leung, M.-k. *J. Org. Chem.* **2002**, *67*, 1041–1044.

8. Suri, J. T.; Cordes, D. B.; Cappuccio, F. E.; Wessling, R. A.; Singaram, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5857–5859.
9. Cordes, D. B.; Gamsey, S.; Sharrett, Z.; Miller, A.; Thoniyot, P.; Wessling, R. A.; Singaram, B. *Langmuir* **2005**, *21*, 6540–6547.
10. Ishi-i, T.; Shinkai, S. *Chem. Commun.* **1998**, 1047–1048.
11. Beil, J. B.; Lemcoff, N. G.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2004**, *126*, 13576–13577.
12. Ishi-i, T.; Nakashima, K.; Shinkai, S.; Ikeda, A. *J. Org. Chem.* **1999**, *64*, 984–990.
13. Koumoto, K.; Takeuchi, M.; Shinkai, S. *Supramol. Chem.* **1998**, *9*, 203–210.