Molecular recognition using β-cyclodextrin-modified dendrimers: novel building blocks for convergent self-assembly

George R. Newkome,*† Luis A. Godínez, and Charles N. Moorefield

Center for Molecular Design and Recognition, University of South Florida, Tampa, FL, 33620, USA

The synthesis of β-cyclodextrin-based dendrimers 3 and 5 is described; using phenolphthalein as a UV–VIS active probe, it is shown that the binding cavities of these modified receptors retain their molecular recognition properties and can be employed as polyfunctional monomers in self-assembly.

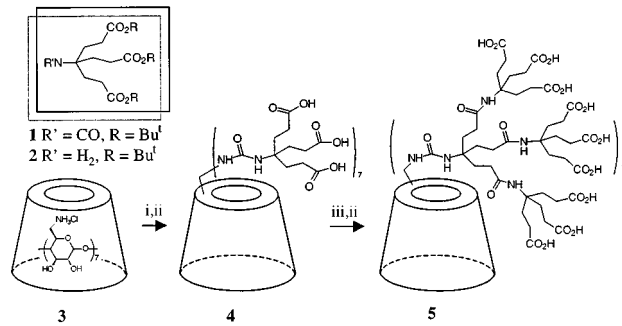
Cyclodextrins (CDs) constitute a popular family of cyclic oligosaccharides whose molecular structures resemble truncated cones.[1] These polyhydroxylated materials have been the subject of numerous investigations in the area of molecular recognition due to their combined solubility in aqueous media and their ability to embrace a wide variety of molecular guests in a well-defined cavity.[2] Also, the *n* primary hydroxy groups at the narrow side of the receptor's cavity exhibit greater reactivity with sterically demanding electrophiles than the *2n* secondary OH groups on the wider, bottom side of the molecule.[1] Therefore, using the appropriate reagents, CDs can be selectively modified to incorporate specific functional groups on the narrow side of the receptor's hydrophobic cavity. Many researchers have capitalized on this property and have subsequently reported the synthesis of modified CDs that have been successfully used as catalysts,[3] receptors for nucleotides[4] and ions,[5] molecular tube precursors,[6] modified electrodes[7] and chemical sensors,[8] to mention but a few applications.[9] Recently, a single CD has been attached to a dendritic surface and investigated with respect to ester hydrolysis activity.[10] β-CDs have also been coordinated to ferrocenyl-terminated dendrimers to study redox characteristics.[11]

As a complementary part of our research program, we are exploring the use of non-covalent interactions and molecular recognition concepts[12] to promote the ordered self-assembly of dendritic structures. These concepts have been eloquently employed by Zimmerman and co-workers.[13]

We herein report the synthesis of two water-soluble dendritic β-CD monomers that retain their molecular recognition properties. These materials therefore belong to a new family of modified receptors that can be envisioned as synthons for convergent, molecular recognition-based assembly of more complex structures and, ultimately, dendritic networks.

Recently, we reported the synthesis of isocyanate[14] **1** and its use in the synthesis of combinatorial-based dendrimers.[15] Attempted treatment of β-CD with triester **1**, under different reaction conditions, afforded no addition products, presumably due to combined steric hinderance. To circumvent this inertness, we prepared 6-heptaamino-β-CD heptahydrochloride[16] **3**‡ (Scheme 1) since isocyanate **1** was known to react with amines under mild conditions.[14] Thus, treatment of heptaamine **3** with 7 equiv. of isocyanate **1** (Pr^i_2EtN, DMF, 25 °C, 5 h) afforded (85%) the first tier polyester dendritic CD monomer. Formic acid hydrolysis (12 h) and dialysis afforded (40%) the polycarboxylic acid **4**, as supported by the ^{13}C NMR spectral data [$\delta(D_2O)$ 158.9 (NH*C*ONH), 178.0 (CO_2).

Construction of the second tier was accomplished by treatment of **4** with 21 equiv. of Behera's amine[17] **2** [DCC, HOBT, DMF–DMSO, 2 d, 25 °C]. Formic acid hydrolysis subsequently afforded (25%) the desired dendritic CD polyacid



Scheme 1 *Reagents and conditions*: i, **1** (7 equiv.), base, DMF; ii, HCO_2H; iii, **4** (21 equiv.), DCC, HOBT, DMF–DMSO

5, whose spectral data supported the conversion [$\delta(D_2O)$158.6 (NH*C*ONH), 179.6 (CO_2).

An important requirement for the synthesis of 'dendrimerized' CDs, that are to be subsequently used as monomers of more complex structures, is that the complexation site, *i.e.* the hydrophobic cavity of the receptor, must remain basically unchanged. In order to verify that CDs **4** and **5** had retained the critical binding locus, displacement experiments, exploiting the well-known association properties of β-CD, were performed.

In moderately basic aqueous medium, phenolphthalein solutions are characterized by a deep purple color that essentially turns colorless upon addition of β-CD.[2b] This dramatic decrease in the UV absorption of the indicator is not

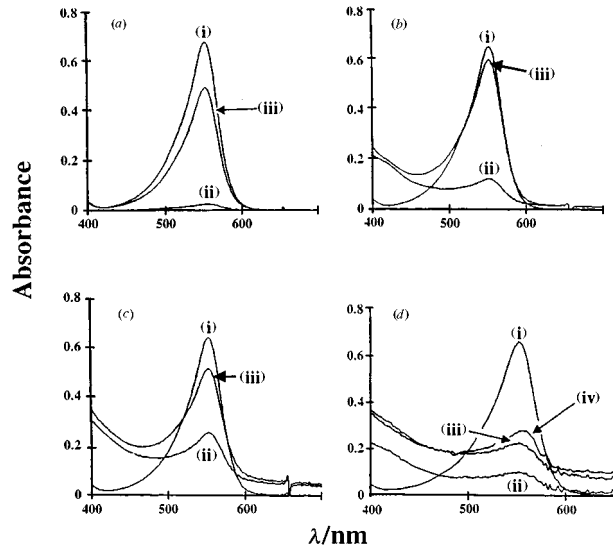
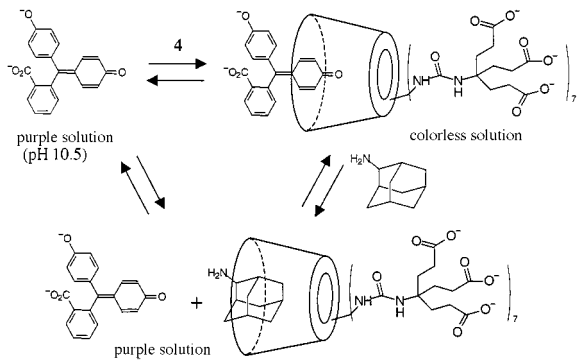


Fig. 1 The effect of CD addition to a 30 μM solution of phenolphthalein pH 10.5 buffer solution (I = 0.6) on the UV spectra for (*a*) β-CD, (*b*) **4** and (*c*) **5**: (i) dye only, (ii) dye and CD (2 mM) and (iii) dye, CD and adamantan-2-amine hydrochloride (5 mM). (*d*) UV spectra of (i) dye, (ii) dye and **4**, (iii) dye, **4** and the bis(adamantane ester) of tetraethylene glycol and (iv) dye, **4**, bis(adamantane ester)and 18-crown-6.

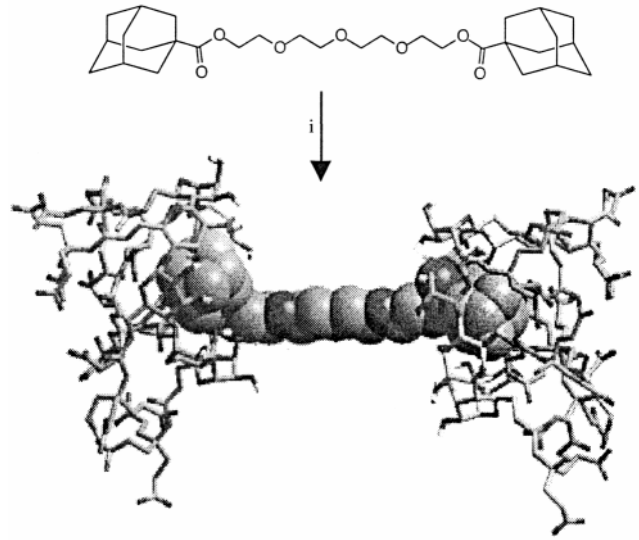
due to a change on the protonation state of the molecule but rather to a specific host–guest inclusion interaction involving hydrogen-bonding, van der Waals forces, and the hydrophobic effect.[18] Complexation of the indicator by inclusion into the β-CD hydrophobic cavity can be thus conveniently followed by UV–VIS spectroscopy. It can be seen in Fig. 1, by comparing spectra (*a*)(i) and (*a*)(ii), that the absorbance at λ = 552 nm of a 30 μM solution of phenolphthalein in a pH 10.5 buffer solution[19] drops dramatically upon the addition of 60 equiv. of β-CD. Consistent with the complexation properties of the unmodified β-CD, spectra (*b*), (*c*) and (*d*) showed similar changes in the absorbance of basic phenolphthalein solutions [spectra (i)] after addition of either CDs **4** or **5** [spectra (iii)]. This decrease in the absorbance of phenolphthalein in the presence of the modified receptors suggests that the indicator is either included in the hydrophobic cavity of the CD or interacting in a similar way with the hyperbranched structure of either **4** or **5**. To rule out the later possibility, we added non-UV-active adamantane derivatives which are known[20] to bind very strongly to β-CD molecules by forming 1:1 inclusion complexes with stability constants on the order of 10^4 M^{-1}.

As observed in Scheme 2, the addition and subsequent inclusion of an adamantane in the CD cavity should promote, if in fact the phenolphthalein is included in the CD cavity, the displacement of the indicator into the bulk of the basic aqueous medium. As a consequence, the solution should become purple



Scheme 2

and the absorbance at λ = 552 nm should increase. Figs. 1(a)(iii), (b)(iii) and (c)(iii), indicate that addition of 2.5 mol of 2-adamantanamine hydrochloride per mol of CD increases the absorption of light of the three aqueous solutions; therefore, as with simple β-CD, the dendritic CDs **4** and **5** retain their binding sites and can incorporate, on the basis of molecular recognition, hydrophobic guests in basic aqueous media. Reappearance of the solution color and absorbance observed in Fig. 1(*d*)(iii), while not as dramatic, was promoted by the addition (0.5 equiv.) of a bis(adamantane ester) of tetraethylene glycol (prepared by the addition of 2 equiv. of adamantanecarbonyl chloride to tetraethylene glycol in the presence of Et_3N). The smaller shift in equilibrium [as compared to Figs. 1(*a*)–(*c*)] to uncomplexed dye in the bulk solution was postulated to arise, at least in part, from Na^+ binding of the polyethylene glycol chain promoting a compact, non-linear structure and thus inhibiting chain elongation and bis-dendrimer assembly. Saturating the solution with 18-crown-6 [Fig. 1(*d*)(iv)] supports this conjecture by further slightly shifting the equilibrium toward displaced absorbing dye and increasing the concentration of the bis-complex (Scheme 3). Another explanation for diminished absorption using the bis(adamantane) could center on other aggregation phenomena as suggested by a heightened spectral baseline. For all cases the percent displacement of dye *via* the addition of adamantane was determined: Fig. 1(*a*), 71.5%; 1(*b*), 89.5%; 1(*c*), 69.5%; 1(*d*), 23%; 1(*d*) with 18-crown-6, 33%.



Scheme 3 *Reagents and conditions*: i, **4**, aq. NaOH–$NaHCO_3$ buffer (I = 0.6) (ref. 19).

The National Science Foundation (DMR-96-22609) is gratefully acknowledged for partial financial support of this work.

Notes and References

† E-mail: gnewkome@research.usf.edu

‡ All new compounds exhibited satisfactory spectral and elemental analysis.

1 G. Wenz, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 803.
2 (*a*) M. L. Bender and M. Komiyama, *Cyclodextrin Chemistry*, Springer, Berlin, 1978; (*b*) J. Szejtli, *Cyclodextrins and their Inclusion Complexes*, Akadémiai Kiadó, Budapest, 1982.
3 M. T. Reetz and S. R. Waldvogel, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 865.
4 A. V. Eliseev and H. J. Schneider, *J. Am. Chem. Soc.*, 1994, **116**, 6081.
5 L. A. Godínez, J. Lin, M. Muñoz, A. W. Coleman and A. E. Kaifer, *Electroanalysis*, 1996, **8**, 1072.
6 A. Harada, J. Li and M. Kamachi, *Nature*, 1993, **364**, 516.
7 M. T. Rojas, R. Königer, J. F. Stoddart and A. E. Kaifer, *J. Am. Chem. Soc.*, 1995, **117**, 336; C. Henke, C. Steinem, A. Janshoff, G. Steffan, H. Luftmann, M. Sieber and H. J. Galla, *Anal. Chem.*, 1996, **68**, 3158.
8 R. Corradini, A. Dossena, G. Galaverna, R. Marchelli, A. Panagia and G. Sartor, *J. Org. Chem.*, 1997, **62**, 6283.
9 H. Asanuma, M. Kakazu, M. Shibata, T. Hishiya and M. Komiyama, *Chem. Commun.*, 1997, 1971.
10 J. Suh, S. S. Hah, and S. H. Lee, *Bioorg. Chem.* 1997, **25**, 63.
11 R. Castro, I. Cusdrado, B. Alonso, C. M. Casado, M. Morán and A. E. Kaifer, *J. Am. Chem. Soc.*, 1997, **119**, 5760.
12 G. R. Newkome, B. D. Woosley, E. He, C. N. Moorefield, R. Güther, G. R. Baker, J. Merrill, G. H. Escamilla and H. Luftmann, *Chem. Commun.* 1996, 2737.
13 F. Zeng and S. C. Zimmerman, *Chem. Rev.*, 1997, **97**, 1681.
14 G. R. Newkome, C. D. Weis, C. N. Moorefield and F. R. Fronczek, *Tetrahedron Lett.*, 1997, **38**, 7053; G. R. Newkome and C. D. Weis, *US Pat.*, 5,703,271 (Dec. 30, 1997).
15 G. R. Newkome, C. D. Weis, C. N. Moorefield, G. R. Baker, B. J. Childs and J. Epperson, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 307; *Angew. Chem.*, 1998, **110**, 318.
16 Syntheses of the peraminated CD derivative **3** was accomplished *via* the following procedure: J. Boger, R. J. Corcoran and J.-M. Lehn, *Helv. Chim. Acta*, 1978, **61**, 2190.
17 G. R. Newkome and C. D. Weis, *Org. Prep. Proced. Int.*, 1996, **28**, 485.
18 Á. Buvári and L. Barcza *J. Chem. Soc., Perkin Trans. 2*, 1988, 1687.
19 (HCO_3^-/CO_3^{2-}, I = 0.6). Prepared according to *CRC Handbook of Chemistry and Physics*, 72nd edn., ed. D. R. Lide, CRC Press, Boca Raton, 1991.
20 L. A. Godínez, L. Schwartz, C. M. Criss and A. E. Kaifer, *J. Phys. Chem. B*, 1997, **101**, 3376.

Received in Corvallis, OR, USA, 11th May 1998; 8/03536I