ChemComm

Dendritic hydrogen bonding receptors: enantiomerically pure dendroclefts for the selective recognition of monosaccharides

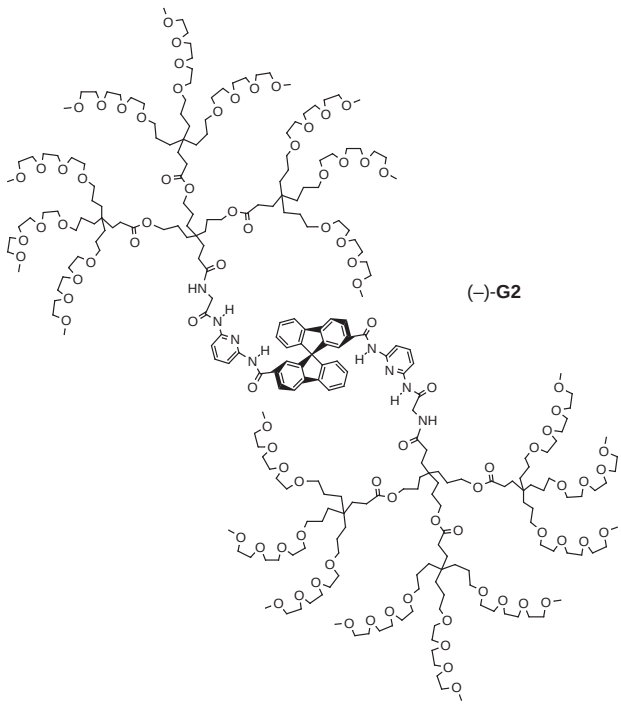
David K. Smith and François Diederich*

Laboratorium für Organische Chemie, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland. E-mail: diederich@org.chem.ethz.ch

Received (in Cambridge, UK) 21st August 1998, Accepted 2nd October 1998

Enantiomerically pure dendritic cleft receptors (dendroclefts) with a 9,9′-spirobi[9*H*-fluorene] core are prepared for the recognition of glucopyranosides by H-bonding in $CDCl_3$; the enantio- and diastereo-selectivities in the complexation processes are modulated by the presence of the dendritic shell.

The development of functional dendrimers is of great current interest.[1] In particular, the dendritic shell can alter the properties of a functional core.[2] Hydrogen-bonding dendritic hosts have been reported, but the branching does not appear to play an active role in modulating guest recognition.[3] In addition chiral recognition inside a dendrimer is as yet unknown, but possesses great scientific and technological potential.[4] Here we report enantiomerically pure dendritic cleft-type receptors (dendroclefts) of first [(−)-**G1**] and second [(−)-**G2**] generation for the chiral recognition of monosaccharide guests *via* H-bonding.



Dendrocleft (−)-**G2** was targeted by the attachment of flexible branches to a rigid, optically pure 9,9′-spirobi[9*H*-fluorene] initiator core bearing 2,6-di(carboxamido)pyridine moieties in the 2,2′-positions.[5] The resulting dendrimer possesses a buried H-bonding cleft suitable for complexing carbohydrate guests.[5,6] Its periphery is functionalised with neutral polyether groups, which provide excellent solubility in a wide range of solvents, including H_2O.

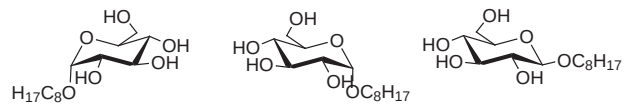
For the synthesis of (−)-**G1** and (−)-**G2** by the convergent approach,[7] the optically active core (−)-**3** was prepared from dicarboxylic acid (−)-(*R*)-**1**[5,8] *via* (−)-**2** and (−)-**G0** (Scheme 1). Attachment of the new dendritic branches **4** or **5**[9] to (−)-**3** provided the optically pure dendroclefts (−)-**G1** and (−)-**G2**, respectively, which were isolated in good yield by preparative gel permeation chromatography {GPC; Biobeads SX-1, CH_2Cl_2 [(−)-**G1**] and THF [(−)-**G2**]}.

Molecular recognition studies were performed by ^{1}H NMR titrations in dry $CDCl_3$ at 298 K using 1-*O*-octyl glucopyranosides (**6–8**) as guests.† Association constants K_a (M^{-1}) and binding free enthalpies $\Delta G°$ (kJ mol^{-1}) for the formed 1:1 complexes are summarized in Table 1. The following conclusions can be drawn.

(i) The complexes formed by the dendroclefts (−)-**G1** and (−)-**G2**, and core (−)-**G0** are of similar strength (K_a between 100 and 600 M^{-1}). Hydrogen bonds between the O-atoms of the sugars and the NH groups of the receptors represent major host–guest interactions in all complexes as evidenced by the large complexation-induced downfield shifts (up to 1.2 ppm at saturation binding) of the NH resonances in the di(carboxamido)pyridine moieties. Apparently, the bulky dendritic shell in (−)-**G1** and (−)-**G2** does not prevent the sugar molecules from penetrating the receptor and interacting with the core H-bonding sites. It is actually quite remarkable that the binding by (−)-**G1** and (−)-**G2** is not weakened by the dendritic shell, which contains a relatively high density of potentially competitive donor oxygen atoms.

(ii) The degree of enantioselectivity in the complexation of the enantiomeric α-glucosides **6** and **7** is reduced upon attachment of the dendritic shells. The difference in stability between diastereoisomeric complexes $\Delta\Delta G°$ decreases from 3.6 kJ mol^{-1} [(−)-**G0**], to 0.8 kJ mol^{-1} [(−)-**G1**], and to 0.5 kJ mol^{-1} [(−)-**G2**].

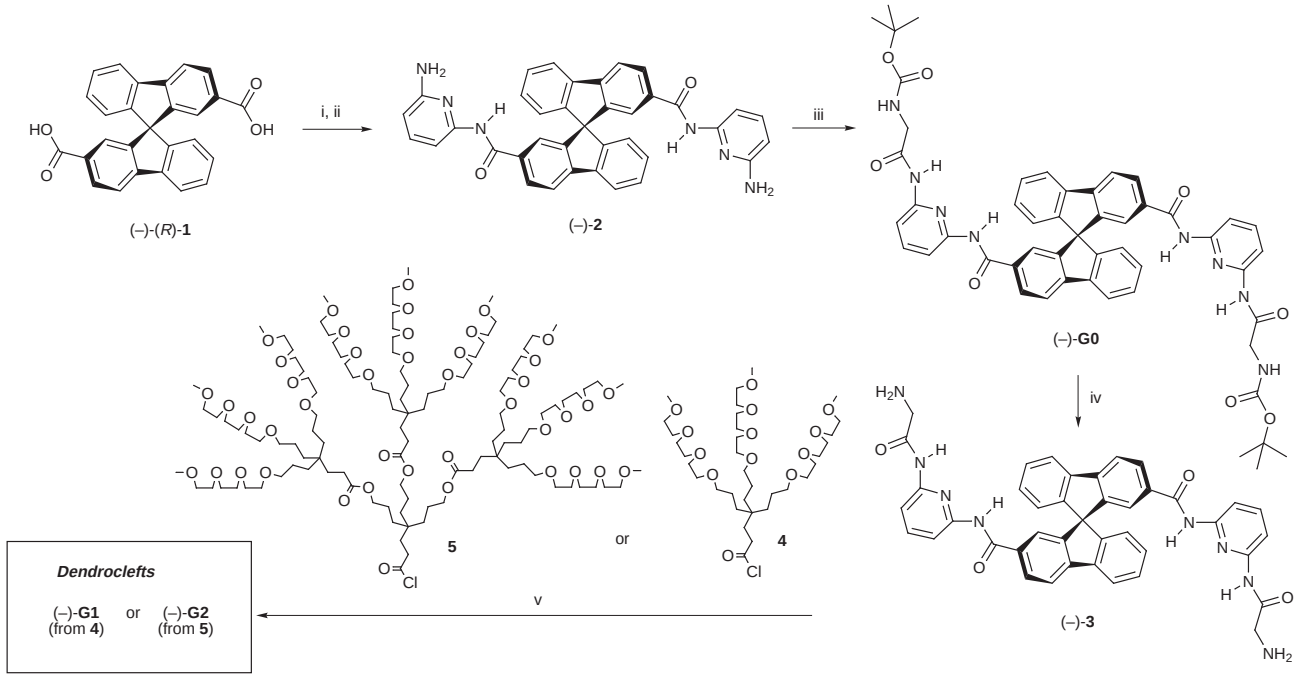
(iii) On the other hand, the diastereoselectivities of complexation are remarkably enhanced by the presence of the dendritic branches. Thus, the difference in stability between the complexes of the diastereoisomeric guests **7** and **8** increases from 0.7 kJ mol^{-1} [(−)-**G0**], to 1.4 kJ mol^{-1} [(−)-**G1**], and to 2.3 kJ mol^{-1} [(−)-**G2**].



Octyl α-L-glucoside **6** | Octyl α-D-glucoside **7** | Octyl β-D-glucoside **8**

These results indicate that the dendritic shell is controlling the selectivity of complexation at the core, an unprecedented result. There are two plausible reasons for this dendritic modulation of binding selectivity which are currently under investigation. Firstly, the steric demands of the dendritic branching may disfavour certain complexes. Secondly, the oxygen donor atoms in the dendritic shell could participate in the formation of a hydrogen bonding network with the guest, changing the binding selectivity.‡

The use of such dendroclefts as chiroptical sensors[11] is currently under active investigation. Profound changes in the circular dichroism (CD) spectra are observed on addition of the glucopyranoside guests, the response being selective for



Scheme 1 Synthesis of (−)-**G1** and (−)-**G2**. *Reagents and conditions*: i, $SOCl_2$; ii, 2,6-diaminopyridine, NEt_3, THF, 85%; iii, *N*-Boc-glycine, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), NEt_3, THF, 81%; iv, TFA, CH_2Cl_2, 87%; v, NEt_3, DMAP, THF, 40–80%.

Table 1 Association constants K_a and binding free enthalpies $\Delta G°$ for complexes of dendrocleft with glucopyranosides in $CDCl_3$ at 298 K

Host	Guest	K_a/M^{-1}	$\Delta G°$/kJ mol^{-1}
(−)-**G0**	6	100	−11.4
(−)-**G0**	7	425	−15.0
(−)-**G0**	8	570	−15.7
(−)-**G1**	6	160	−12.6
(−)-**G1**	7	225	−13.4
(−)-**G1**	8	390	−14.8
(−)-**G2**	6	170	−12.7
(−)-**G2**	7	205	−13.2
(−)-**G2**	8	520	−15.5

different sugars and different for (−)-**G0** and (−)-**G2**. In addition, the dendritic receptor is readily recycled owing to the very large size difference between host and guest. Gel permeation filtration through a plug of Sephadex gel LH-20 with MeOH as eluent provides quantitative recovery of pure (−)-**G2** from host–guest solutions.

Efforts are now in progress to synthesise dendritic receptors with even more deeply embedded optically active cores. This general approach to dendritic molecular recognition has great potential, both for modelling the buried active sites of sugar binding proteins[12] and for the development of tunable, recyclable receptors and sensors for various analytes.

Support from the ETH Research Council and the Royal Society (E.S.E.P. fellowship to D. K. S) is gratefully acknowledged.

Notes and references

† ^{1}H NMR titrations (300 MHz) were performed at [dendrocleft] = 0.5 mM and [sugar] = 1.25–12.5 mM in $CDCl_3$ de-acidified with K_2CO_3 and dried over 4 Å molecular sieves. The complexation-induced downfield shifts (up to 1.2 ppm at saturation binding) of the resonances of the NH-protons in the dendroclefts were evaluated by nonlinear least-squares curve fitting. Job plot analyses were in agreement with the exclusive formation of 1:1 host–guest complexes. All titrations were repeated with good reproducibility, and the uncertainty in K_a is estimated as ±10%.

‡ The oxygen atoms in the dendritic shell may control the strength and selectivity of binding, as polar additives are well-known to modify sugar recognition in $CDCl_3$ (ref. 10). The core receptor (−)-**G0** was investigated in $CDCl_3$–THF (99:1) to test the effect of intermolecularly added ether (with oxygen donor atoms) on complexation. The association constants for the complexes with **7** and **8** were K_a = 320 and 390 M^{-1}, respectively. Thus, the binding strength was reduced compared to pure $CDCl_3$, as a result of competitive solvation of host and guest by THF molecules. The diastereoselectivity, however, remained low ($\Delta\Delta G°$ = 0.5 kJ mol^{-1}), and it is evident that addition of THF does not induce the same increase in diastereoselectivity as that caused by the dendritic shell.

1 J. Issberner, R. Moors and F. Vögtle, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2413.
2 D. K. Smith and F. Diederich, *Chem. Eur. J.*, 1998, **4**, 1353.
3 G. R. Newkome, B. D. Woosley, E. He, C. N. Moorefield, R. Güther, G. R. Baker, G. H. Escamilla, J. Merrill and H. Luftmann, *Chem. Commun.*, 1996, 2737; S. C. Zimmerman, Y. Wang, P. Bharathi and J. S. Moore, *J. Am. Chem. Soc.*, 1998, **120**, 2172.
4 H. W. I. Peerlings and E. W. Meijer, *Chem. Eur. J.*, 1997, **3**, 1563.
5 (*a*) V. Alcázar and F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1521; (*b*) J. Cuntze, L. Owens, V. Alcázar, P. Seiler and F. Diederich, *Helv. Chim. Acta*, 1995, **78**, 367.
6 (*a*) K. M. Bhattarai, R. P. Bonar-Law, A. P. Davis and B. A. Murray, *J. Chem. Soc., Chem. Commun.*, 1992, 752; (*b*) Y. Kikuchi, Y. Tanaka, S. Sutarto, K. Kobayashi, H. Toi and Y. Aoyama, *J. Am. Chem. Soc.*, 1992, **114**, 10 302; (*c*) M. Inouye, T. Miyake, M. Furusyo and H. Nakazumi, *J. Am. Chem. Soc.*, 1995, **117**, 12 416; (*d*) For a dendrimer which forms covalent boronic esters with monosaccharides in the dendritic branches, see: T. D. James, H. Shinmori, M. Takeuchi and S. Shinkai, *Chem. Commun.*, 1996, 705.
7 C. Hawker and J. M. J. Fréchet, *J. Chem. Soc., Chem. Commun.*, 1990, 1010.
8 The spirobifluorene cleft is *R*-configured in all compounds reported here: P. Lustenberger, E. Martinborough, T. Mordasini Denti and F. Diederich, *J. Chem. Soc., Perkin Trans. 2*, 1998, 747.
9 D. K. Smith, A. Zingg and F. Diederich, in *Supramolecular Science*: *Where it is and where it is going*, ed. R. Ungaro, NATO ASI Series Book, Kluwer, Dordrecht, in the press.
10 R. P. Bonar-Law and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1995, **117**, 259; T. Mizutani, T. Kurahashi, T. Murakami, N. Matsumi and H. Ogoshi, *J. Am. Chem. Soc.*, 1997, **119**, 8991.
11 T. D. James, K. R. A. S. Sandanayake and S. Shinkai, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1911.
12 F. A. Quiocho, *Pure. Appl. Chem.*, 1989, **61**, 1293.

Communication 8/06596I