6-HYDROXYALKYLAMINO-6-DEOXY-CYCLODEXTRINS: TOWARDS DENDRIMERIC HOST-MOLECULES

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ABSTRACT

6-Perhydroxyalkylamino-6-perdeoxy-β–cyclodextrins have been synthesised by treating 6-perbromo-6-perdeoxy-cyclodextrins with hydroxyalkylamines. The products (**1**, **2**) are precursors of dendrimeric cyclodextrins in which the cavity provides access for the guest to interact with the branches. A fluorescence study has demonstrated the effects of the branches on binding of anilinonaphthalene sulfonate probes. The hosts show selectivity towards guests, and pH-dependence of binding, consistent with polar interaction between guest sulfonate anions and the protonated amino groups of the dendrimeric structure.

1. INTRODUCTION

Dendrimers [1] are highly-branched macromolecules which have potential as hosts because of the spaces between the branch stems. Such structures, if grafted onto cyclodextrins, might be expected to modulate the cyclodextrin's host properties, and in turn, the cyclodextrin might act as a channel to the dendrimer core. As a development of our studies on branched cyclodextrins [2], we have synthesised the heptakis(6-hydroxyalkylamino-6-deoxy)-β-cyclodextrins **1** and **2**, and evaluated the effects of the branched structures on their ability to bind naphthalene sulfonate probes.

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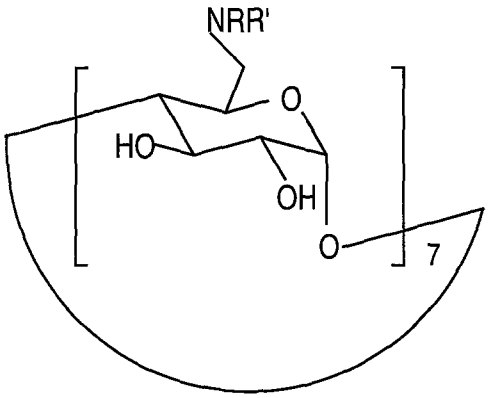

1 R = H, R' = CH_2CH_2OH

2 R = R' = CH_2CH_2OH

2. MATERIALS AND METHODS

2.1 Syntheses

The heptakis(6-hydroxyethylamino-6-deoxy)-β-cyclodextrins **1** and **2** were prepared from heptakis(6-bromo-6-deoxy)-β-cyclodextrin [3] by dissolving the latter at 65° in ethanolamine (15 molar equivalents)(for **1**), or in diethanolamine (for **2**), and heating at the same temperature for 48 hours. The reagent/solvent was removed under vacuum, and the residue was dissolved in hot methanol and precipitated by addition of this solution to stirred acetone. The precipitate was collected by gravity filtration, then dissolved in water, and the solution was treated with basic ion-exchange resin. Lyophilisation yielded **1**, $[\alpha]_D$+110°(*c* 0.1, water), or **2**, $[\alpha]_D$+109°(*c* 0.1, water)(60-65%).

Persubstitution was confirmed by elemental analysis and by the simple NMR spectra, although the ^{1}H-spectrum of the more highly branched **2** showed fluxional broadening: (**1**) δ^1H (500 MHz, D_2O) 5.10 (d, 1H, $J_{1,2}$ 4Hz, H-1), 3.98-3.93 (m, 2H, H-3, H-5), 3.73-3.63 (m, 3H, CH_2O, H-2), 3.51 (t, 1H, $J_{3,4}$=$J_{4,5}$=9Hz, H-4), 3.02 (dd, 1H, $J_{5,6a}$ = 2Hz, $J_{6a,6b}$ 13Hz, H-6a), 2.88 (dd, 1H, $J_{5,6b}$ = 7.5 Hz, H-6b), 2.7 (m, 2H, NCH_2); δ^{13}C (68 MHz, D_2O) 101.5 (C-1), 82.7 (C-4), 72.6 (C-3), 71.8 (C-2), 70.1 (C-5), 59.7 (CH_2O), 50.0 (NCH_2), 48.8 (C-6); (**2**) δ^1H (270 MHz, D_2O) 5.25 (d, 1H, $J_{1,2}$ 2Hz, H-1), 3.98-3.94 (m, 2H, H-3, H-5), 3.6-3.52 (m, 4H, CH_2O, H-2, H-4), 2.97-2.73 (m, H-6a, H-6b, NCH_2); δ^{13}C (68 MHz, $CHCl_3$) 99.2 (C-1), 79.7 (C-4), 72.9 (C-3), 71.8 (C-2), 70.4 (C-5), 59.0 (CH_2O), 56.4 (NCH_2), 55.7 (C-6).

2.2 Fluorescence measurements

Fluorescent probes were obtained from Molecular Probes Europe BV. Solutions were buffered with HCl-carbonate. Binding constants were calculated from double reciprocal plots of variations in fluorescence intensity with host concentrations [4].

3. RESULTS AND DISCUSSION

3.1 Fluorescence measurements

Binding of these probes is complicated by the possibility of inclusion of either the naphthalene or anilino systems [5], however it is probable that both are at least partially included, and there may not be a clear kinetic distinction between complexes of different configuration. From a double reciprocal plot there is evidence for a 2:1 (CD: probe) complex at high host concentrations in the case of the methylanilino probe but only at pH 10. This indicates non-inclusion of the (protonated) methylanilino group by a second CD molecule at low pH. It also favours the view that those probes which show the stronger binding at lower pH, do so because of favourable interaction between the protonated cyclodextrin amino branches and probe sulfonate group. This effect is evident also for the simple naphthalene sulfonate probe. It is consistent with results for nucleoside phosphate binding [6] where the polar interaction is between protonated methylamino groups and phosphate ion.

TABLE 1. Association constants of hydroxyalkylamino-CD's with naphthalene sulfonate probes

CD	probe	K_a (M^{-1})		
		pH 2	6	10
1	2,6-anilino (ANS)	2300	700	1200
1	2,6-tolylamino (TNS)	200	170	300
1	2,6-methylanilino (MANS)	1000		5300
1	1,8-anilino	200		
1	naphthalene sulfonate	9000		3000
2	2,6-methylanilino (MANS)			2500

Strong binding (ANS and MANS) (Table) is accompanied by blue shifts in fluorescence emission wavelengths of 30-45nm, compared with 20nm for β-cyclodextrin, which confirm inclusion in the hydrophobic cavity [7]; while weak binding is associated with red shifts of 20-40nm.

The electrostatic binding by the branches also prevents the guests from threading through the cavity, and this results in shallower and weaker binding of MANS at lower pH. Polar binding by the amino branches does not always therefore result in higher K_a values, but there is very selective modulation of these values compared with unmodified cyclodextrin [5]. The similar ANS and TNS structures are undifferentiated by β-cyclodextrin, but with **1** they show binding constants differing by a factor of ten at pH2 (Table). Also, large variations in K_a with pH are observed here for some guests, which are not observed with β-cyclodextrin until it itself is deprotonated above pH10 [5]. An obvious design improvement however would be to have binding groups further removed from the cavity.

4. CONCLUSION

The concept of extending the hydrophobic cavity of cyclodextrins by means of dendritic structures has been realised with increased solubility in spite of the extended structures. Access to the core groups of the branches is provided, and these modulate binding, although the ultimate advantages of dendrimeric cyclodextrins have yet to be realised.

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