JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

Number 24
1983

Diaza-crown Ether Capped Cyclodextrin. A Receptor with Two Recognition Sites

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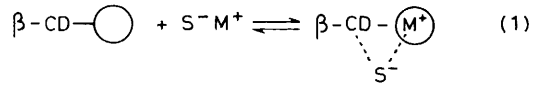
The tetraoxadiazacyclo-octadecanyl-β-cyclodextrin (**1**) provides a molecular assembly with two recognition receptor sites, which co-operate in the association of alkali-metal *p*-nitrophenolates as substrates.

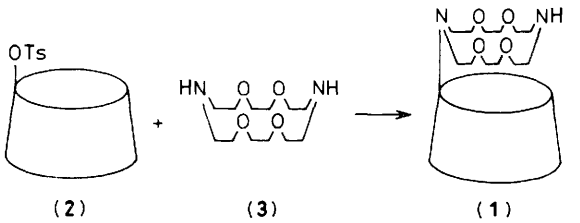
The modelling of the receptor sites of enzymes has attracted great interest in recent years.[1–5] Crown-ethers[1,2] and cryptates[3] have been extensively studied as specific receptors for cationic substrates. Cyclodextrins[4,5] (cycloamyloses) and cyclophanes[6] have been widely used as artificial hosts for neutral and charged organic guest molecules. The binding of organic substrates to cyclodextrins (CD) is usually characterized by low association constants as compared to the binding properties of natural enzymes.

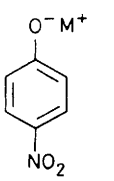
Several approaches to increase the binding properties of cyclodextrins by appropriate functionalization with additional recognition sites for the substrate have been reported,[4,5] including organometallic capped cyclodextrins that involve the co-ordination of the substrate as an additional anchoring site, and double cyclodextrin receptors with two hydrophobic binding cavities. Here we report the preparation of the diaza-crown ether capped β-CD (**1**). The molecular assembly of (**1**) includes two recognition sites for the binding of specific substrates, *i.e.* a hydrophobic cavity of β-CD, and a crown ether moiety as a cation receptor site, which should lead to enhanced binding of anionic substrates, as shown in equation (1). Remarkable enhancements in the association constants of alkali-metal *p*-nitrophenolates to the modified crown-β-CD (**1**) have indeed been observed as compared with the binding of these substrates to unmodified β-CD.

The capped cyclodextrin (**1**) was prepared as in Scheme 1. Reaction of 6-*O*-tosyl-β-CD (**2**) (0.8 mmol)[7] with 1,4,10,13-tetraoxa-7,16-diazacyclo-octadecane (**3**) (10 mmol) in dry dimethylformamide (DMF) at 80 °C for 48 h afforded pure (**1**) (37% yield) after repeated gel filtration over Sephadex G-10 and Sephadex G-25.† Binding of the Li^+, Na^+, and K^+ *p*-nitrophenolates (**4a—c**) to the crown-β-CD was examined spectroscopically in DMF by measuring the absorption changes of the substrate at 400 nm upon addition of (**1**). The binding properties of (**4a—c**) to (**1**) were compared with their binding properties to unmodified β-CD.‡ In all the complexation studies two isosbestic points were observed implying the presence of a 1 : 1 substrate–receptor complex. The association constants of the substrates (**4a—c**) to the different receptors



(1)





(4)

a; $M^+ = Li^+$
b; $M^+ = Na^+$
c; $M^+ = K^+$

Scheme 1

† Characterized by ^1H n.m.r. spectroscopy; satisfactory elemental analyses were obtained, m.p. 255 °C (decomp.).

‡ No association of (**4a—c**) with the diaza-crown ether in DMF could be determined in accordance with the low association constants observed in methanol.

Table 1. Association constants, $K/(dm^3\ mol^{-1})$, for the alkali-metal *p*-nitrophenolates and the different receptors.

	Crown-β-CD (**1**)[a]	β-CD	Diaza-crown (**3**)[b]	K(**1**)/K(β-CD)
(**4a**)	7500	1170	—[c]	6.4
(**4b**)	28 000	400	10	70
(**4c**)	9000	720	109	12.5

[a] Error estimates ±5—8%. No association of the substrates (**4a**—**c**) with (**1**) was observed in water. [b] Association of alkali metals measured in methanol.[8,9] [c] No association of Li^+ with the diaza-crown ether is observed.

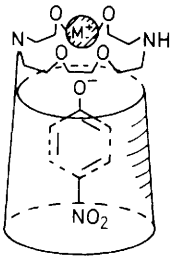


Figure 1

were determined from the respective Benesi–Hildebrand plots (equation 2), and are summarized in Table 1.§

$$\Delta A/(S^\circ R^\circ) = 1/(K\Delta\epsilon) + (S^\circ + R^\circ)/\Delta\epsilon \qquad (2)$$

It is evident that the binding of the alkali-metal *p*-nitrophenolates (**4a**—**c**) to the modified receptor (**1**) is substantially improved compared with their association to the separate host components (β-CD and diaza-crown-ether). The association constant of (**4b**) is increased by a factor of 70 relative to its association constant to the non-functionalized cyclodextrin. Association of the anionic unit with the hydrophobic cavity of β-CD assists the binding of the cation to the crown component and association of the cation with the crown receptor provides an electrostatic anchoring site for the anion in the β-CD cavity (Figure 1).

It should be noted that the maximum effect of the bireceptor (**1**) is observed for the association of (**4b**) as substrate, which contrasts with the binding properties of alkali-metal ions to the diaza-crown ether (**3**), where Na^+ is bound 10-fold less efficiently than K^+. We believe that the effectiveness of the bireceptor (**1**) for the binding of the substrates (**4a**—**c**) might be affected by steric constraints involved with the association of the cation in the proximity of the phenolate anion. Thus, the most favourable balance between association of the cation to the crown component and effective electrostatic interactions is obtained with Na^+ (ionic radii 1.90 Å).

The strong association of substrates to natural enzymes is attributed to the participation of remote functional groups of the protein backbone in anchoring the substrate to the hydrophobic receptor site. The two recognition sites of the bifunctional receptor (**1**) mimic such co-operative functions in the association of the substrates.

This study was supported by the E. D. Bergmann Foundation Fund.

Received, 5th September 1983; Com. 1186

§ S° and R° are the initial concentration of the substrate and receptor respectively. ΔA is the change in absorbance upon addition of the receptor. $\Delta\epsilon$ is the difference in the molar extinction coefficient of the associated and free substrates at the specific wavelength of absorption changes.

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