A New Ditopic Receptor Molecule for Ionic Guest Molecules

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A new ditopic host molecule (**3**), composed of the macromonocyclic 1,4,7,10,13,16-hexa-azacyclo-octadecane (**1**) and the macrocyclic polyether benzo-15-crown-5 (**2**) covalently linked, forms stable 1 : 1 complexes with zwitterionic molecules such as amino acids, peptides, and dopamine in aqueous solution at neutral pH.

Macrocyclic polyethers (crown ethers) bind with cationic guests (*e.g.* primary ammonium cations),[1] whereas anionic substrates (*e.g.* carboxylates) or electron-donor substrates (*e.g.* catechols) are recognized by macrocyclic polyamine cations.[2] However, receptor molecules that can simultaneously recognize both cations and anions are very rare. Such ditopic hosts would offer efficient and selective recognition sites for ionic molecules by concerted binding action. So far only one such receptor has been synthesized, in a laborious procedure from a macrotricyclic quaternary ammonium molecule and an aza-crown ether.[3]

Herein we report the first example of a ditopic receptor molecule (**3**) composed of macromonocyclic polyamine and crown ether units, which indeed forms 1 : 1 complexes with ionic substrates such as the amino acids (**4**)—(**7**), the peptide (**8**), or catecholamine (**9**) in neutral aqueous solutions. The synthesis of (**3**) is simple and is as follows: the polyamine (**1**) (2.7 g) and 4′-chloromethylbenzo-15-crown-5 (**2b**) (680 mg) in $CHCl_3$ (100 ml) were stirred for 24 h at room temperature. The resulting solution was washed with H_2O (100 ml) to remove excess of (**1**) and its HCl salts. Silica gel chromatography of the $CHCl_3$ layer ($CHCl_3$–MeOH–28% aq. NH_3, 100 : 3 : 1) gave the purified product (**3**) as an oil; the 6HCl salt was isolated from HCl–saturated MeOH [yield 45% based on (**2b**)]: m.p. 243—245 °C; *m/z* 538 (M^+), 281 ($M^+ - 257$), and 257 (polyamine moiety); ^{1}H n.m.r. (as free base form, in $CDCl_3$) δ 2.27 (s, 5H, NH), 2.68 (m, 24H, NCH_2), 3.34 (s, 2H, benzyl H), 3.73—4.25 (m, 16H, OCH_2), and 6.72 (s, 3H, Ar-H); satisfactory elemental analyses were obtained.

The extent of host–guest interaction was estimated using anodic wave polarography as described for the complexation of polycarboxylates[3] and catechols with the polyamine (**1**).[5] The half-wave potentials, $\Delta E_{1/2}$, of the anodic dissolution waves at a dropping mercury electrode (DME) due to (**3**) shifted to more positive values upon addition of the substrates (**4**)—(**10**) in Tris buffer. The potential shift values increased with increase in the concentration of the added substrates. The wave heights decreased as the substrate concentration increased. This and all other polarographic behaviour was similar to that observed for the polyamine (**1**)–substrate systems,[4—6] leading us to conclude that complex formation had occurred between (**3**) and the substrates (**4**)—(**10**). The stoicheiometries and stability constants of the complexes were determined from the $\Delta E_{1/2}$ values.

If it is assumed that 1 : 1 complexes H_iL^{i+}–S^{j+} are formed from a protonated polyamine H_iL^{i+} and an organic ion S^{j+}, one can express the $\Delta E_{1/2}$ value at a given pH by equation (1),

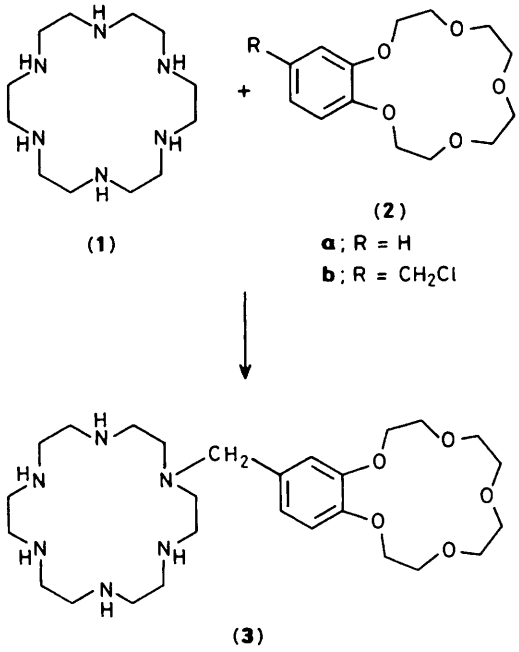
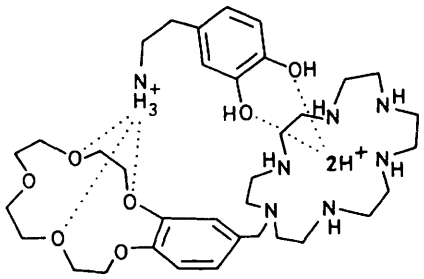


Table 1. 1 : 1 Association constants β_L for (**3**)[a] with ionic substrates at 25 °C and I = 0.20 M ($NaClO_4$).

Ionic substrate [pK_a value]	Experimental (i + j) value[b]	β_L/dm^3 mol^{-1}	Measured pH in Tris buffer
Glycine (**4**) [9.68]	4.1_5	1.50×10^2	6.5—8
β-Alanine (**5**) [10.44]	4.1_8	1.10×10^2	7—8
$H_2N[CH_2]_3CO_2H$ (**6**) [10.67][c]	3.8_6	1.02×10^2	7—8
$H_2N[CH_2]_5CO_2H$ (**7**) [10.89][c]	4.1_7	1.05×10^2	7—8
Diglycine (**8**) [8.10]	3.8_0	6.87×10^1	7—8.5
Dopamine (**9**) [12.20, 10.61, 9.06]	5.0_5	2.92×10^4	7—8
Catechol (**10**) [12.49, 9.31]	5.0	1.50×10^2	7—8

[a] pK_a = 9.66, 9.13, 7.75, 4, ~2, ~1. [b] Number of protons involved in complexation. [c] Conditional association constants of (**6**) and (**7**) with Schmidtchen's host molecule in 10% aq. MeOH are reported to be 250 and 233, respectively.[3]



(A)

where $\beta_L = [H_iL^{i+}\text{–}S^{j+}]/[H_iL^{i+}][S^{j+}]$. Equation (1) may be rearranged to equation (2). Logarithmic plots of the left hand of equation (2) *vs.* pH at constant $[S^{j+}]$ are all linear with slopes corresponding to $-(i + j)$. The β_L values were determined from plots of log (left-hand side of equation 2) *vs.* [substrate] at constant pH. The final results along with the K_i values used for calculation are summarized in Table 1.

$$\Delta E_{1/2} = 0.0296\,[\log\{(\alpha_H)_L + \beta_L K_1K_2 \cdots K_i\,[H^+]^i \cdot K_1'K_2' \cdots K_j'\,[H^+]^j[S^{j+}]\} - \log(\alpha_H)_L] \quad (1)$$

$$[\text{antilog}(\Delta E_{1/2}/0.0296) - 1]\,(\alpha_H)_L \cdot (\alpha_H)_S = \beta_L \cdot K_1K_2 \cdots K_i[H^+]^i \cdot K_1'K_2' \cdots K_j'\,[H^+]^j[S^{j+}] \quad (2)$$

The involvement of $(i + j) = 4$ protons in 1 : 1 association between (**3**) and amino acids (**4**)—(**7**) permits us to formulate the complexes as H_3L^{3+} (triprotonated form of L)–HS (monoprotonated amino acid $+H_3\overset{\frown}{N}CO_2^-$ form), taking into account the protonation constants of L and S (see Table 1). Until now no interaction of glycine (**4**) with any synthetic host molecules has been reported. Crown ethers are known to interact only with protonated amino acid esters $+NH_3CHR^1CO_2R^2$.[1] We have confirmed that neither (**1**) alone nor benzo-15-crown-5 (**2a**) alone interacts with amino acids (**4**)—(**7**) in neutral pH solution. It is most reasonable to conclude that the concerted binding action makes (**3**) a ditopic receptor; the terminal anionic carboxylate is taken care of by the (protonated) macrocyclic polyamine moiety and the primary ammonium cation segment by the crown ether part. A molecular model indicates that the ditopic receptor (**3**) is flexibile so as effectively to sandwich the zwitterions. Glycylglycine (**8**) shows a weaker interaction with (**3**).

The strong interaction of (**3**) with dopamine (**9**) is noteworthy. (**1**)·$3H^+$ alone binds with the catechol moiety of dopamine (**9**) with a β_L value of 1.1×10^3 dm^3 mol^{-1}.[5] Addition of 10 equiv. of benzo-15-crown-5 (**2a**) does not affect its polarographic behaviour at all. However, by covalent attachment as in (**3**), the crown ether moiety interacts in a complementary manner with the primary ammonium cation part of dopamine (**9**), as depicted in structure (A), resulting in a β_L value greater by a factor of ten. Since the experiment indicates involvement of $(i + j) = 5$ protons in this complexation, we assign $2H^+$ to the polyamine part and $3H^+$ to the dopamine part. On the other hand, for catechol (**10**), a monotopic guest of (**1**)·$3H^+$,[5] an affinity enhancement is not observed on attachment of the crown ether moiety: the β_L value of 1.5×10^2 with (**3**) is almost the same as that (1.6×10^2) with (**1**).[5]

In view of the versatility and simplicity of the present synthetic method, the macromonocyclic polyamine linked with a crown ether provides a promising prototype for design of a variety of polytopic recognition receptors that should find a number of applications.

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