Efficient Complexation of Quaternary Ammonium Compounds by a New Water-soluble Macrobicyclic Receptor Molecule

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The hexacarboxylic macrobicycle **1** is a readily accessible water-soluble receptor molecule which binds strongly quaternary ammonium cations.

Macropolycyclic molecules constructed from rigid non-polar subunits and bearing polar functional groups may function as water-soluble molecular receptors capable of complexing substrate species by inclusion into their hydrophobic cavity.[1,2] Their binding properties result from the synergistic operation of electrostatic interactions and of hydrophobic effects, as defined for the class of receptors termed speleands, that form inclusion complexes, speleates, with molecular substrates of various geometries.[3,4] Since the rigid groups are usually aromatic residues these receptors belong in most cases to the cyclophane family and related structures. In particular, the binding of cationic molecular substrates by macrocyclic receptors bearing negatively charged groups has been a subject of much activity in recent years.[4–12]

We report here the synthesis and the remarkable binding properties of the new water-soluble macrobicyclic receptor molecule **1** that is easily prepared in a single step from readily available simple starting materials. The macrocyclic analogue **4** was also prepared for comparison purposes.

Our attention was primarily directed towards the binding of quaternary ammonium cations, in view of our early interest in the complexation of the neurotransmitter acetylcholine[4] and of the neuropharmacological properties of numerous quaternary ammonium compounds.[13]

Dropwise addition of an equimolecular solution of 1,3,5-tris(bromomethyl)benzene and dimethyl methylenedisalicylate **3**[14] to a suspension of an excess of caesium carbonate in refluxing acetone gave, after twelve hours heating and usual work-up **2** in 23% yield.‡ This yield is remarkable since six bonds are formed in a single synthetic step without using high dilution conditions. Hydrolysis of the hexaester **2** with NaOH in a tetrahydrofuran (THF)–methanol mixture (*ca.* 50/50; v/v) gave, after work-up and recrystallisation from a methanol–water mixture by diffusion of THF [**1**–Na] (70% yield) which is readily soluble in water.§

The macrocyclic analogue **4** was prepared by a similar condensation reaction of **3** with 1,3-bis(bromomethyl)benzene followed by basic hydrolysis of the tetraester **5** obtained.¶

Considering the mesitylene groups simply as bridgehead elements, molecule **1** may be considered as a cyclophane of macrobicyclic type, a bicyclophane, which in its fully extended form has average C_3 symmetry and delineates a large spheroidal cavity. The structure of **1** has been confirmed by X-ray radiocrystallographic analysis of the hydrated sodium salt [**1**–Na].[15] Its binding properties were obtained from ^{1}H NMR spectroscopic studies.

When various ammonium cations were added to [**1**–Na] in aqueous solution their ^{1}H NMR spectra displayed large upfield shifts $\Delta\delta$, which reached a limiting value at high proportion of macrocycle. The curves $\Delta\delta = f[C]/[S]$, ([C] and [S] being the macrobicycle and substrate concentrations, respectively) indicated the formation of a 1 : 1 complex and the association constants K_S (K_S = [complex]/[ligand][substrate]) were determined by a non-linear least-squares method (Table 1).[16]

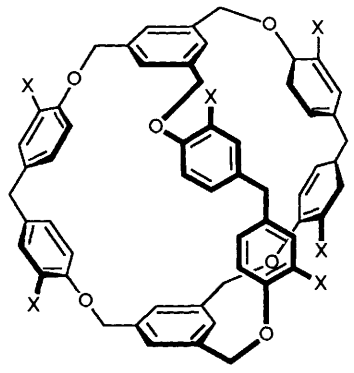
The hexacarboxylate macrobicycle functions as a receptor molecule forming remarkably *stable 1 : 1 complexes* with a variety of cationic molecular substrates in aqueous solution. Both electrostatic and hydrophobic effects contribute to the stability of the complexes of receptor **1**. Electrostatic effects are illustrated by the increase in stability from monoammonium to diammonium cations (Table 1, entries 5 and 7, 9 or 13 and 15 for instance). The participation of lipophilic effects is indicated by the increase of stability for cations containing

† UPR 285 of the CNRS.

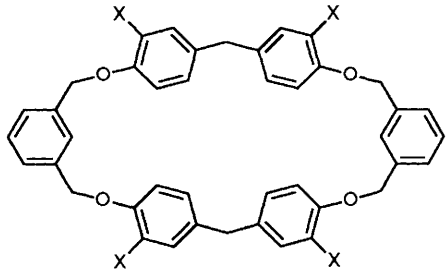
‡ *^{1}H NMR spectroscopic data* for **2** [200 MHz, $CDCl_3$, δ in ppm relative to $SiMe_4$ (= 0 ppm)]: δ 3.86 (18H, s); 3.83 (6H, s); 5.18 (12H, s); 6.65 (6H, d); 6.89 (6H, dd); 7.30 (6H, s).

§ *^{1}H NMR spectroscopic data* for [**1**–Na]: [200 MHz, D_2O, δ in ppm relative to Bu^{t}OH (= 0 ppm)]; δ 2.37 (6H, s); 3.80 (12H, s); 4.69 (6H, d); 5.13 (6H, dd); 5.91 (6H, s); 6.06 (6H, d).

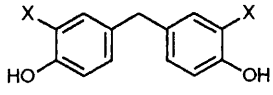
¶ The compounds gave satisfactory elemental analyses.



1; X = CO_2^-
[**1**-Na]; X = CO_2Na
2; X = CO_2Me



4; X = CO_2^-
[**4**-Na]; X = CO_2Na
5; X = CO_2Me



3; X = CO_2Me

bulkier organic groups (Table 1, entries 3 and 4 and 13–15). This enhancement is particularly important with aromatic compounds which bind to **1** with moderate to very strong affinities (Table 1, entries 10–20).

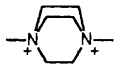
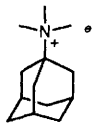
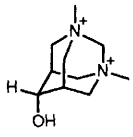
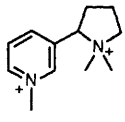
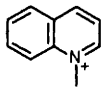
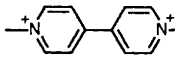
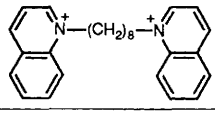
As already pointed out in a similar case,[6] strong π-stacking donor–acceptor interactions may operate between the electron rich receptor and the electron deficient pyridinium groups (Table 1, entries 18, 19 and 20). The very strong binding of the bis(quinolinium) compound (Table 1, entry 20) is remarkble, the $\Delta\delta = f[C]/[S]$ curve indicating a 1:1 complex. Since the cavity should be able to encapsulate only one quinolinium subunit, the second subunit may be externally folded over the macrobicycle giving additional electrostatic interactions with the carboxylate groups. The difference between the binding constant of methylviologen (entry 19) and that of the 'half-molecule' *N*-methylpyridinium (entry 16) is exceptionally strong and may be attributed to combined electrostatic, hydrophobic and π-stacking effects.

Entries 7–9 reveal good affinities for more or less globular cations; indeed Corey–Pauling–Koltun (CPK) models show that the cavity of **1** is well suited for the binding of such compounds.

For the macrocycle analogue **4** one observes a significant decrease in stability constants with respect to **1** (Table 1, entries 7, 10, 18 and 20), revealing a *macrobicyclic effect* on complex stability, a feature already found for the macrobicyclic cryptates of metal ions.[17]

The binding of acetylcholine by **1** (Table 1, entry 3) is larger than found earlier for a tetracarboxylate receptor,[4a] but lower than with another tetracarboxylate macrocyclic

Table 1 Stability constants $\log K_S$ and limiting ^1H NMR upfield shifts Δν calculated for the complexes of macrobicyclic **1** and macrocyclic **4**[a] receptor molecules with cationic molecular substrates[b]

Entry	Substrate	$\Delta\nu_c$[c]	$\log K_S$[d]
1	NMe_4^+	39	3.0
2	NEt_4^+	180.5	3.2
3	$MeCO_2CH_2CH_2NMe_3^+$	70.5	3.1
4	$PhCO_2CH_2CH_2NMe_3^+$	126	3.8
5		186	3.3
6		213	3.3
7		141 (90)	4.1 (3.4)
8		193	4.2
9		94.5	4.2
10	$PhCH_2NMe_3^+$	241.5 (114.5)	4.1 (3.0)
11	$PhCH_2NEt_3^+$	152.5	4.0
12	$PhCH(Me)NMe_3^+$	220.5	4.1
13	$PhNMe_3^+$	320	4.0
14	Me_2N–pC_6H_4–NMe_3^+	214	4.7
15	$^+Me_3N$–pC_6H_4–NMe_3^+	197	4.6
16	*N*-methylpyridinium	290	3.5
17		217.5	4.4
18		361 (266)	5.5 (4.4)
19		271	6.6
20		209.5 (151)	6.9 (5.1)

[a] $\Delta\nu_c$ and $\log K_S$ values given in parentheses are for the complexes of receptor **4**. [b] $\log K_S$ and $\Delta\nu_c$ are calculated from the plots of substrate chemical shift as a function of macrocycle : substrate ratio, obtained by addition of an aqueous solution of the ammonium salt to an aqueous solution of [**1**-Na] (2 mmol dm^{-3}) adjusted to pH *ca.* 7 at *ca.* 23 °C. Competition experiments 1, between $PhCO_2CH_2CH_2NMe_3^+$ taken as reference substrate and $PhCH_2NMe_3^+$, $PhNMe_3^+$, $MeCO_2CH_2CH_2NMe_3^+$; 2, between $PhNMe_3^+$ as reference and $PhCH(Me)NMe_3^+$, Me_2N–pC_6H_4–NMe_3^+; 3, between $^+Me_3N$–pC_6H_4–NMe_3^+ as reference and $PhCH_2NMe_3^+$; 4, between substrates of entry 18 and 20, gave results (ratios of stability constants) consistent with the direct method. All substrates were used as halide salts. [c] Shifts of Me signals given in Hz at 200 MHz. [d] $\log K_S \pm 0.2$; K_S in 1 mol^{-1}; determination of the largest stability constants is difficult owing to limitations of the method at high values. [e] We are grateful to M.-J. Fernandez for the gift of this compound.[19]

receptor,[6c] the latter, however, binds larger organic substrates more strongly than acetylcholine. In the case of **1**, it is remarkable that there is no significant increase in stability when NMe_3^+ groups are replaced by NEt^+ (Table 1, entries 1, 2 and 10, 11) indicating that the macrobicyclic receptor **1** is apparently able to balance the effect of lipophilicity increase by structural discrimination. Acetylcholine binding by a biological receptor involves interaction with both lipophilic and anionic residues.[18] Artificial molecules such as **1** also make use of both factors; in addition its closed structure allows for improved size selection. Studies are underway in order to explore further, by means of artificial receptor molecules, the factors that determine the binding of molecular cationic substrates, especially of neuropharmacologically active ones; an extension to neutral substrates is also being pursued.

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