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SYNTHESIS OF A MOLECULAR RECEPTOR CONTAINING TWO RECOGNITION SITES[1]

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Summary: We report the synthesis and preliminary binding properties of a molecular receptor containing two distinct binding sites; a cyclophane and a crown ether.

A receptor molecule can be defined as one that contains a cavity capable of complexing a substrate species. The specificity of the complexation will depend on the degree of complementarity between receptor and substrate. This takes two forms: a) steric complementarity-the compatability of substrate shape and size to the receptor cavity, b) binding site complementarity-the presence of binding sites within the cavity which complement in number, spatial arrangement and nature chemical features on the substrate. In recent years there has been much interest in the design of synthetic molecules capable of recognizing and complexing organic substrates.[2] In general, these have been based on a single recognition feature. For example, crown ethers[3] and cryptands[4] have been used as hosts for cationic substrates, cyclic polyammonium[5] and polyguanidinium[6] species as hosts for anionic substrates, and cyclodextrins[7] and cyclophanes[8] as receptors for hydrophobic guests. In order to increase the substate specificity of these hosts additional binding or recognition sites must be added. A number of ditopic receptors have been prepared, based primarily on cyclodextrins with loosely-attached binding sites.[9,10]

As part of a program aimed at the design and preparation of receptors for the phenethylamine series of neurotransmitters, we required flexible synthetic routes to multitopic hosts incorporating phenyl and ammonium ion binding sites. Our strategy was to covalently attach a crown ether to a cyclophane,

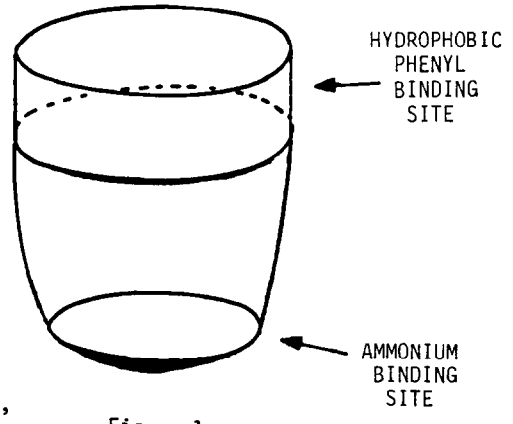
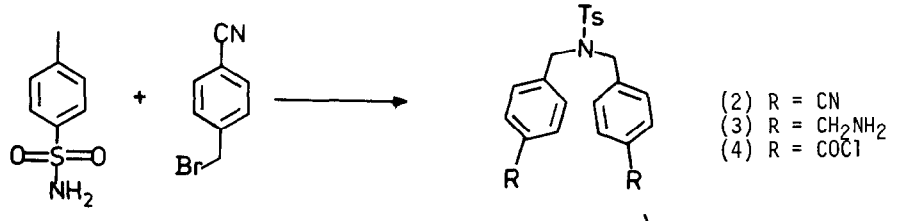


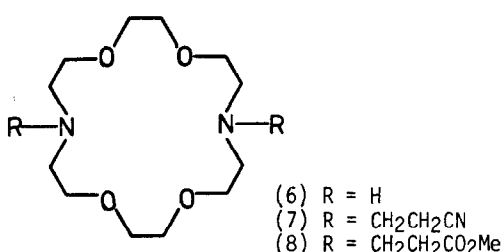
Figure 1

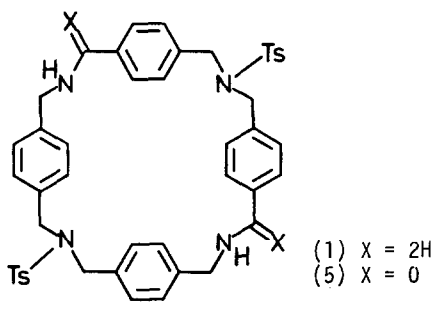
as shown in figure 1. We chose 1,10-diaza-4,7,13,16-tetraoxocyclooctadecane as the crown component and a tetraazatetra-p-xylyl macrocycle as the cyclophane component.[11] These are known to form hydrogen-bonded complexes with primary ammonium ions[2] and hydrophobic complexes with phenyl derivatives,[11] respectively.

The required diagonally diprotected tetraazacyclophane(1) was prepared by the route outlined in scheme 1. Dialkylation of tosylamide with α-bromo-p-tolunitrile (aqueous NaOH) gave dinitrile (2)[12] in 67% yield. This could be either catalytically hydrogenated (Pd-C) in 98% yield to diamine (3)[12] or hydrolysed (10N NaOH) and reacted with thionyl chloride to produce a 76% yield of diacid chloride (4).[12] Reaction of (3) and (4) under high dilution conditions (CH_2Cl_2, Et_3N) afforded the macrocyclic ditosylamide (5)[12] in 60% yield. Diborane reduction (BH_3·THF) followed by acidic methanolysis (MeOH, HCl) converted (5) quantitatively into (1).[12,13]



Scheme 1





Inspection of CPK models suggests that the optimum distance between ammonium and phenyl binding sites in a phenethylamine receptor (figure 1) is provided by $(CH_2)_3$ linkages.[14] Reaction of diamine (6) with acrylonitrile (reflux, 24 hrs) gave dinitrile (7)[15] which was converted to diester (8) (HCl, MeOH). Diacid chloride (10) was formed by hydrolysis of (8) (6N HCl) to amino acid (9) followed by oxalyl chloride treatment (CH_2Cl_2, Et_3N). High dilution coupling of the two components was achieved by simultaneously adding solutions of (10) ($4.3x10^{-3}$M in CH_2Cl_2) and (1)($4.3x10^{-3}$M in CH_2Cl_2 plus two equivalents of Et_3N) to CH_2Cl_2. Preparative layer chromatography (alumina, CH_2Cl_2: MeOH 20:1) gave diamide (11)[12,15a] in 27% yield. Diborane reduction (BH_3·THF) and acidification (MeOH, HCl) provided cylindrical tetramine (12)[12,16] in 92% yield as an oil.

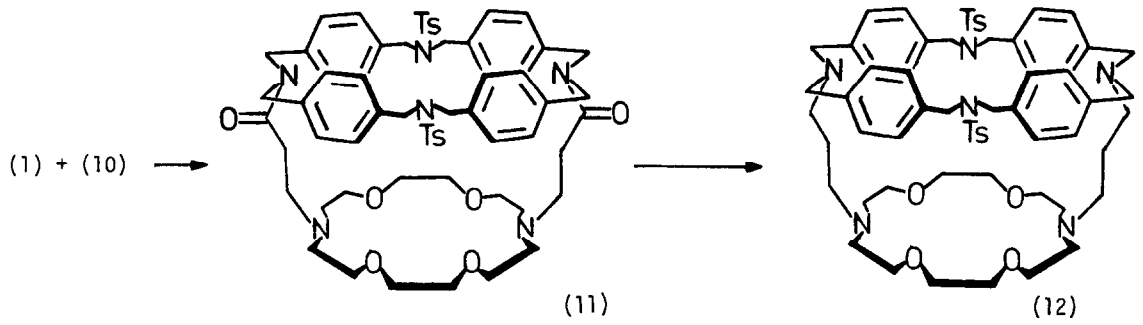


Table 1

Peak	CH_2O	OCH_2CH_2N	OCH_2CH_2N	$(CE)NCH_2(CH_2)_2$	CH_2NTS	Cycloph.ArH
δppm(free)	3.60	3.25	2.69	2.40	4.23(s)	6.91(s)
δppm (complexed)	3.50 (+0.1)	3.50 (-0.25)	2.73 (-0.04)	2.09 (+0.31)	4.21,4.33 (2xd,J=12Hz)	6.88,7.02 (2xd,J=7Hz)

Tetramine (12) is a hollow cyclindrical molecule and should be capable of binding primary alkylammonium ions both inside and outside the cavity.[17,18] Indeed, in $CDCl_3$ solution (12) will solubilize just one equivalent of normally insoluble alkylammonium picrate salts. We have investigated the changes in the ^1H NMR spectrum of (12) in the presence of various alkylammonium picrates (1 equiv.) and these results, for key protons in the representative propylammonium picrate case, are summarized in Table 1. That complexation is occurring can be seen in the upfield or small downfield shifts of several protons (e.g.$(CE)NCH_2CH_2CH_2$ and NCH_2CH_2O) near to the crown ether portion of the receptor; simple proton transfer from guest to host would result in large downfield shifts (>0.5 ppm) of these peaks. In addition, there are marked changes in some of the cyclophane proton signals. The singlets at 6.91 and 4.23, due to cyclop.aromatic H and $TsNCH_2$ respectively, each collapse to two doublets, suggesting an interaction between cyclophane and guest[19] and probable internal binding.

We are continuing our spectroscopic investigation of (12) to determine more precisely the structure of the complex. We are also investigating other binding possibilities in ditopic receptors of type (12). These include; removing the tosyl groups of (12) and studying neutral and anionic molecule binding in aqueous environments; blocking the open face of the crown ether to ensure internal binding; adding additional recognition sites to the cyclophane.

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12. All new compounds gave satisfactory NMR, ir, uv-vis and microanalytical and/or mass spectral data.
13. Purified by alumina chromatography followed by recrystallization from CH_2Cl_2/hexane ^1H NMR ($CDCl_3$) 2.48 (s, 6H, CH_3), 3.34 (s, 8H, CH_2NH), 4.24 (s, 8H, CH_2NT_s), 6.87 and 6.98 (2d, J = 8Hz, 16H, ring ArH), 7.40 and 7.81 (2d, J = 8Hz, 8H, tosyl ArH).
14. This distance is readily varied by using a bromo nitrile (e.g. α-bromo-p-tolunitrile) in place of acrylonitrile in the synthesis, to provide a differently shaped ditopic receptor
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15a. Mass spec. (M^+) 1155.5404 $C_{64}H_{78}N_6O_{10}S_2$ requires 1155.5299.

16. $^1H(CDCl_3)$ 250 MHz 1.67 (m, 4H, $CH_2CH_2CH_2$), 2.40 (m, 4H, $CH_2CH_2CH_2N$ crown), 2.46 (s, 6H, CH_3), 2.51 (m, 4H, $CH_2CH_2CH_2N$ cycloph.), 2.69 (m, 8H, OCH_2CH_2N), 3.35 (m, 8H, OCH_2-CH_2N), 3.60 (bs, 8H, OCH_2), 3.67 (s, 8H, CH_2N cycloph.), 4.23 (s, 8H, CH_2NTs), 6.91 (s, 16H, cycloph. ArH), 7.37 and 7.79 (2d, J = 8Hz, 8H, TsH). Mass Spec (M+H) 1127.5562 $C_{64}H_{83}N_6O_8S_2$ requires 127.5713.
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19. Similar changes are seen with (12) and methyl and phenethylammonium picrates.

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