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Synthesis of Novel C₂ Symmetric Receptors Containing a Diaza-Crown Macrocycle

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Recently, the cation-π interaction has been recognized as an important noncovalent intermolecular force.[1] The scope and importance of this interaction have been established by theoretical calculations[2] and by studies of organic model systems[3] and biological recognition systems.[1b,1c,2d,4] Dougherty et al proposed that in most aromatic systems, electrostatic interactions between the positive charge and the permanent quadrupole moment of an aromatic make major contributions to the cation-π interaction.[2a] However, there remains much need to experimentally verify the origin and magnitude of the cation-π interaction.

In the present work, we describe design and synthesis of chiral model receptors (**1a** and **1b**) which might provide a quantitative measurement for the cation-π interaction in a nonpolar organic solvent.

1a X = H, Y = O
1b X = OMe, Y = H₂
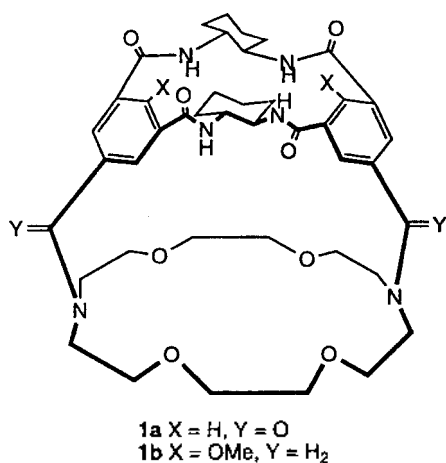
Since the cation-π interaction is relatively weak binding force in a nonpolar organic solvent compared to the other noncovalent interactions such as hydrogen bonding, ion-dipole interaction, and electrostatic interaction, the azacrown ether was used as a primary binding site for cations. Our strategy is to compare an azacrown ether derived acyclic precursor (**3a** or **3b**) with an azacrown ether based receptor (**1a** or **1b**)[5] for the cation binding which might show enhanced binding by an additional cation-π interaction. In order to provide a potent binding site for cations in a nonpolar organic solvent, we designed chiral, C₂ symmetric, and macrocyclic host molecules (**1a** and **1b**)[6] possessing a rigidly defined cavity consisting of an azacrown ether moiety, amide functionalities, and aromatic rings used to define the "walls" of the host. CPK models of the designed receptors indicated that alkali metal cations can be embedded within the cavity through the combination of the ion-dipole interaction between the cation and azacrown ether moiety, the hydrogen bonding interaction between the cation and amide carbonyls, and the cation-π interaction between the cation and the aromatic rings. The binding cavity of **1a** and **1b** with a rigid framework is expected to show size-selectivities in the binding of alkali metal cations and an ammonium ion.

The synthesis of the receptor **1a** starts from the amide bond formation between the pentafluorophenyl active ester
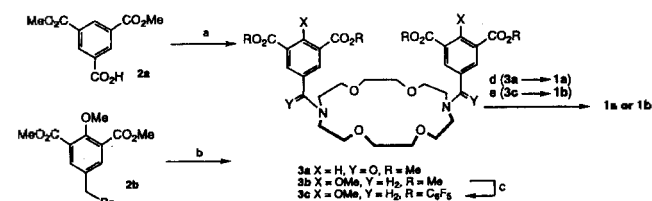
Scheme 1. (a) C₆F₅OH, EDC, THF; 4,13-diaza-18-crown-6, THF (b) 4,13-diaza-18-crown-6, Cs₂CO₃, CH₃CN, reflux (c) LiOH, THF-MeOH-H₂O; C₆F₅OH, EDC, THF (d) LiOH, THF-MeOH-H₂O; C₆F₅OH, EDC, THF; (1*R*,2*R*)-1,2-diaminocyclohexane, THF. (e) (1*R*,2*R*)-1,2-diaminocyclohexane, THF.

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of **2a** and 4,13-diaza-18-crown-6 to give rise to the tetraester **3a** as shown in Scheme 1. Ester hydrolysis and subsequent EDC coupling with pentafluorophenol furnished the cyclization precursor. The final step is an intermolecular macrocyclization between a tetrakis(pentafluorophenyl)ester and (1*R*,2*R*)-1,2-diaminocyclohexane.[7] A solution of the active ester in dry THF and a solution of chiral 1,2-diamine in dry THF was simultaneously added via syringe pumps over 12 hr to a large amount of THF (final concentration=1 mM). Purification by flash chromatography furnished the macrotricycle **1a** in overall 9% yield from **3a**.

The best evidence for the successful macrocyclization was provided by several informative differences between the ^{1}H NMR spectrum of **1a** and that of its acyclic precursor **3a**. Mass spectrum showed an M+1 signal at m/z 803, and the 500 MHz ^{1}H NMR in CDCl$_3$ displayed three proton moieties-cyclohexyl, azacrown methylene and aromatic. Three different aromatic proton peaks, two different methine proton signals in a cyclohexane part, and five different azacrown methylene proton signals presumably result from the partial asymmetric structure of overall C$_2$ symmetric receptor (see the Experimental section). In particular, ^{1}H NMR and HH-COSY showed that the azacrown ether methylene protons (-NC*H$_2$CH$_2$O- and -OC*H$_2$CH$_2$O-) were completely splitted. The complex pattern seemed to be derived from two rigid amide linkages of ArC(=O)N (CH$_2$CH$_2$)$_2$- which might reduce the number of accessible low energy conformations and thus break the symmetry of the azacrown ether part.

Molecular modeling[8] *via* molecular dynamics followed by energy minimization finds the structure in Figure 1(a) as the lowest energy conformation, which is C$_2$ symmetric and has an open cavity for appropriately sized cations.

In order to test for the presence of the cation-π interaction in binding of **1a** to cations, we performed binding studies with the acyclic precursor **3a** and the C$_2$ receptor **1a** by the picrate extraction method.[9] However, binding affinities of **1a** for various cations are weaker than **3a** indicating that the cation-π interaction is not operative in **1a**.[10] Probably the presence of two amide bonds that connect the aromatic part and the azacrown ether moiety made **1a** too rigid for the resulting conformation to establish a suitable cav-
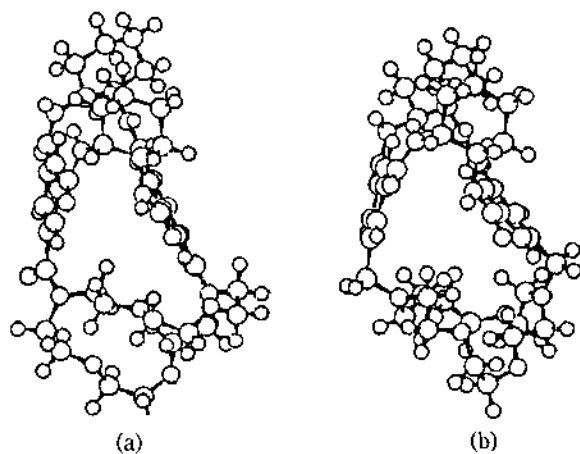
ity for the cation binding.

Therefore we thought that replacing Y=O (**1a**) by Y=H$_2$ (**1b**) would presumably increase conformational flexibility and provide a productive cavity for the cation-π interaction.

Synthesis of **1b** is described in Scheme 1. In ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C) of **1b**, the phenyl, methylene, and methine proton signals appear as broad multiplets.[11] HPLC analysis shows that **1b** may be composed of at least 2 conformers. Broad ^{1}H NMR signals of **1b** reflect several discrete low energy conformations in solution. Lowest energy structure of **1b** by calculation is depicted in Figure 1(b), showing an open cavity for the cation binding. However, binding affinities of **1b** for various cations are not stronger than **3b** indicating that the cation binding does not occur inside the aromatic cavity and/or suitable cation binding conformation is not available even in slightly more flexible **1b**.[10]

The rationale for the absence of the cation-π interaction in spite of the open cavity of **1a** and **1b** can be envisaged from the computational modeling, in which cations (K$^+$ and Cs$^+$) are not found inside the aromatic cavity in the the lowest energy structures of the **1a**-K$^+$ (Figure 2(a)), **1a**-Cs$^+$, **1b**-K$^+$ (Figure 2(b)), and **1b**-Cs$^+$ complexes,[8] due to unfavorable cation binding conformation of the azacrown part resulting from the overall conformational rigidity.

In summary, we prepared chiral, C$_2$ symmetric, and macrocyclic host molecules (**1a** and **1b**) possessing a rigidly defined cavity consisting of an azacrown ether moiety, amide functionalities, and aromatic rings. Modification of the upper part for making more flexible conformation could lead to capturing proper cations inside the aromatic cavity.

Experimental

N,N'-Bis(3,5-methoxycarbonylbenzoyl)-4,13-diaza-18-crown-6 (**3a**). To a solution of 3,5-dimethoxycarbonylbenzoic acid (**2a**)[12] (0.423 g, 1.78 mmol) in 15 mL of THF were added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) (0.510 g, 2.66 mmol) and pentafluorophenol (PFP) (0.453 g, 2.46 mmol). After stirring at rt for 12 h, the solvent was evaporated and CH$_2$Cl$_2$ was added. The organic layer was washed with aqueous saturated NaHCO$_3$, dried over MgSO$_4$ and concentrated. The resulting pentafluorophenyl active ester was directly used in the next step.

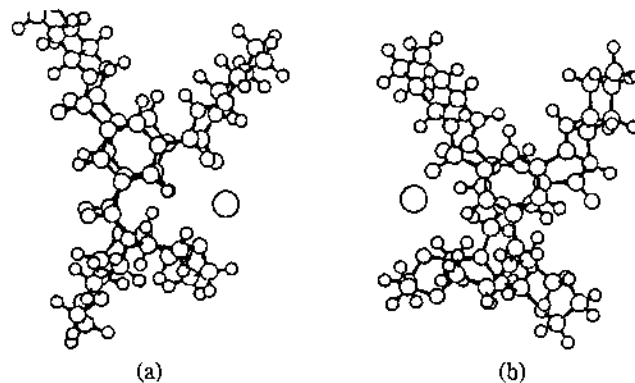To a solution of 4,13-diaza-18-crown-6[13] (0.207 g, 0.79

(a)   (b)

Figure 1.

(a)   (b)

Figure 2.

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mmol) in 10 mL of THF was added a solution of the active ester in 10 mL of THF. After stirring at rt for 1 day, the solvent was evaporated and 50 mL of water was added. The mixture was extracted three times with $CHCl_3$. The combined organic extracts were washed with 1 N HCl and 1 N NaOH and dried over $MgSO_4$. Concentration and purification of the residue by column chromatography (silica gel, 5% $MeOH/CH_2Cl_2$) gave 0.25 g of **3a** as a white solid (48% yield).

IR (neat) 2880, 1728, 1635, 1510, 1440, 1248, 1123, 995 cm^{-1}; ^{1}H NMR (80 MHz, CDCl$_3$) δ 3.60-3.80 (br, 24H, NCH_2CH_2O and OCH_2CH_2O) 3.90 (s, 6H, ArCO$_2$CH_3) 8.2 (s, 4H, ArH) 8.65 (s, 2H, ArH).

Receptor 1a. To a solution of **3a** (0.25 g, 0.39 mmol) in 40 mL of methanol-water (v/v, 3:1) was added LiOH· H$_2$O (0.13 g, 3.1 mmol). The solution was stirred at rt for 1 day and concentrated to 1/4 of the original volume. The residue was carefully acidified with 1 N HCl (pH 2-3). Water insoluble white precipitation was observed. Water was completely evaporated *in vacuo*. The resulting tetrakisacid and inorganic salt mixture was directly used in the next step without separation.

To a solution of the crude tetrakisacid in 5 mL DMA was added EDC (0.447 g, 2.33 mmol) and PFP (0.50 g, 2.7 mmol). The solution was stirred at rt for 12 h. CH$_2$Cl$_2$ was added and washed with 1 N HCl, saturated Na$_2$CO$_3$ and dried over MgSO$_4$. Concentration and purification of the residue by column chromatography (silica gel, 1:1 EtOAc/hexane) gave 0.17 g of the tetrakis(pentafluorophenyl) ester. This product was directly used in the next cyclization.

A solution of the active ester in 25 mL of dry THF and a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (0.035 g, 0.30 mmol) in 25 mL of dry THF were separately added with stirring to 100 mL of dry THF at rt over 12 h *via* syringe pumps. After the solution was stirred for an additional 1 day, the solvent was evaporated and water was added. The mixture was extracted three times with 30 mL of CH$_2$Cl$_2$. The combined organic extracts were washed with 1 N HCl, saturated Na$_2$CO$_3$ and brine and dried over MgSO$_4$. Concentration and purification of the residue by column chromatography (silica gel, 5% MeOH/CH$_2$Cl$_2$) gave 28 mg of macrocycle **1a** as a white solid (9% yield).

IR (neat) 3328, 2912, 1644, 1532, 1472, 1440, 1283, 1129, 915, 742 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.41-2.02 (m, 16H, aliphatic CH$_2$'s), 2.44 (ddd, *J*=5.09, 9.60, 19.3 Hz, 2H, XCH_2CH_2Y), 3.03 (ddd, *J*=2.68, 10.5, 14.1 Hz, 2H, XCH_2CH_2Y), 3.41-3.46 (m, 2H, XCH_2CH_2Y), 3.53-3.69 (m, 16H, XCH_2CH_2Y), 4.05 (br, 2H, XCH_2CH_2Y), 3.98 (ddd, *J*= 3.1, 10.7, 21.2 Hz, 2H, CH_aNH), 4.27 (ddd, *J*=3.3, 10.7, 21.0 Hz, 2H, CH_bN), 6.83 (d, *J*=10 Hz, 4H, CONH), 7.74 (s, 2H, ArH), 7.91 (s, 2H, ArH), 8.25 (s, 2H, ArH), X=O and Y=(N or O); ^{13}C NMR (125 MHz, CDCl$_3$) δ 25.1, 25.2, 31.8, 32.4, 45.9, 50.7, 54.1, 56.3, 68.0, 70.1, 70.7, 71.1, 128.1, 128.5, 128.8, 132.9, 133.5, 135.7, 166.0, 170.3; MS (FAB, Glycerol) m/z 803 (M$^+$+1).

N,N'-Bis(3,5-dimethoxycarbonyl-4-methoxybenzyl)-4,13-diaza-18-crown-6 (3b). To a solution of 4, 13-diaza-18-crown-6 (0.26 g, 0.99 mmol) in 30 mL of CH$_3$CN were added 1-methoxy-2,6-dimethoxycarbonyl-4-bromomethylbenzene (**2b**)^{14} (0.63 g, 2.0 mmol) and Cs$_2$CO$_3$

(0.97 g, 3.0 mmol). The mixture was heated at reflux temperature for 8 h, cooled, and concentrated. Water was added and extracted three times with CHCl$_3$. The combined extracts were washed with brine and dried over Na$_2$SO$_4$. Concentration and purification of the residue by column chromatography (silica gel, 5% MeOH/CH$_2$Cl$_2$) gave 0.23 g of **3b** as a white solid (28% yield).

IR (neat) 3340, 2960, 1728, 1500, 1257, 1206, 1107, 995 cm^{-1}; ^{1}H NMR (80 MHz, CDCl$_3$): δ 2.83 (t, *J*=5.66 Hz, 8H, NCH_2CH$_2$O) 3.49-3.68 (m, 16H, NCH$_2$CH_2O & OCH_2-CH$_2$O) 3.70 (s, 18H, ArOCH_3 & ArCO$_2$CH_3) 7.88 (s, 4H, ArH).

Tetrakis(pentafluorophenyl)ester of 3b (3c). To a solution of **3b** (0.40 g, 0.54 mmol) in 60 mL of THF-MeOH-water (v/v/v, 4:1:1) was added LiOH·H$_2$O (0.18 g, 4.4 mmol). The mixture was stirred at rt for 12 h and treated with CF$_3$CO$_2$H (0.45 mL, 5.8 mmol). After the mixture was stirred for 30 min, all volatiles were removed under reduced pressure. The resulting tetrakisacid and inorganic salt mixture were directly used in the next step without separation.

To a solution of the tetrakisacid in 40 mL of THF were added EDC (0.48 g, 2.5 mmol) and PFP (0.48 g, 2.6 mmol). The mixture was stirred at rt for 10 h, filtered, and the filtrate was concentrated. The residue was treated with 2% aqueous NaHCO$_3$ (15 mL) and extracted three times with CH$_2$Cl$_2$. The combined extracts were washed with brine and dried over Na$_2$SO$_4$. Concentration and purification of the residue by column chromatography (silica gel, 5% MeOH/CH$_2$Cl$_2$) gave 0.13 g of **3c** as an oily solid (18% yield).

IR (neat) 2944, 1769, 1705, 1513, 1468, 1358, 1254, 1107, 995 cm^{-1}; ^{1}H NMR (80 MHz, CDCl$_3$): δ 2.80 (br, 8H, NCH_2CH$_2$O) 3.49-3.68 (m, 16H, NCH$_2$CH_2O & OCH_2-CH$_2$O) 3.70 (s, 4H, ArCH_2N) 3.95 (s, 6H, ArOCH_3) 7.88 (s, 4H, ArH).

Receptor 1b. A solution of **3c** (0.13 g, 0.097 mmol) in 25 mL of dry THF and a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (0.023 g, 0.020 mmol) in 25 mL of dry THF were separately added with stirring to 200 mL of dry THF at rt over 12 h *via* syringe pumps. After the solution was stirred for an additional 1 day, the solvent was evaporated and water was added. The mixture was extracted three times with 30 mL of CH$_2$Cl$_2$. The combined organic extracts were washed with 1 N Na$_2$CO$_3$ and brine and dried over Na$_2$SO$_4$. Concentration and purification of the residue by column chromatography (silica gel, 1:10:50 NH$_4$OH/MeOH/CH$_2$Cl$_2$) gave 10 mg of macrocycle **1b**^{11} as a transparent solid (13%).

IR (neat) 3360, 2944, 1468, 1528, 1459, 1254, 1113 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.18-1.85 (m, 16H, aliphatic CH$_2$'s), 2.50-2.95 (m, 8H, NCH_2CH$_2$O), 3.25-4.30 (m, 30H, NCH$_2$CH_2O, OCH_2CH_2O, CHNH, ArCH_2N, & ArOCH_3), 6.34 (d, *J*=8 Hz, CONH), 6.87 (br, CONH), 7.41-7. 52 (m, ArH) 7.59-7.65 (m, ArH), 7.78-7.81 (m, ArH), 8.05 (d, *J*=8 Hz, H, CONH), 8.21 (br, CONH), 8.38-8.43 (m, ArH); MS (FAB, Glycerol) m/z 836 (M$^+$+1).

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10. Complexation Data (logK_a) of Complexes of Hosts with Alkali and Ammonium Picrates in $CHCl_3$ Saturated with H_2O[9]

Guest	3a	1a	3b	1b
K^+	4.8	4.0	7.5	5.8
Cs^+	4.1	3.9	6.8	6.9
NH_4^+	4.4	3.9	6.7	6.7

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12. 3,5-dimethoxycarbonylbenzoic acid was prepared from 1,3,5-benzenetricarboxylic acid as follows; esterification and monohydrolysis by H_2NNMe_2 (40% overall yield).

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14. 1-Methoxy-2,6-dimethoxycarbonyl-4-bromomethylbenzene was prepared from 2,6-bis(hydroxymethyl)-*p*-cresol as follows; phenol protection, oxidation, esterification, and bromination (26% overall yield).