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Synthesis of a Bowl-Shaped, C_3 Symmetric Receptor with a Phosphate Functionality at the Cavity Bottom

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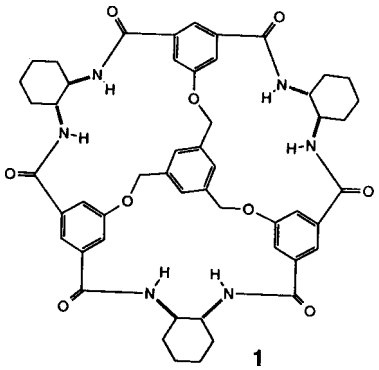
Construction of host molecules possessing a rigidly defined cavity with a concave functionality is of current interest.[1,2] Incorporation of an inwardly pointing functionality into the cavity of a bowl-shaped receptor[3] is reminiscent of the active site of enzymes. If a functional group is embedded in an appropriately sized molecular bowl with a rigid framework, the cavity will function as a reaction site or binding site with unique properties.

Previous C_3 symmetric receptor (**1**) synthesized in our group has a hydrophobic binding cavity with a preference for binding lipophilic residues.[4] We expected that introduction of a hydrogen-bonding functionality within the binding cavity would alter binding selectivity to hydrogen-bonding guests.[5]



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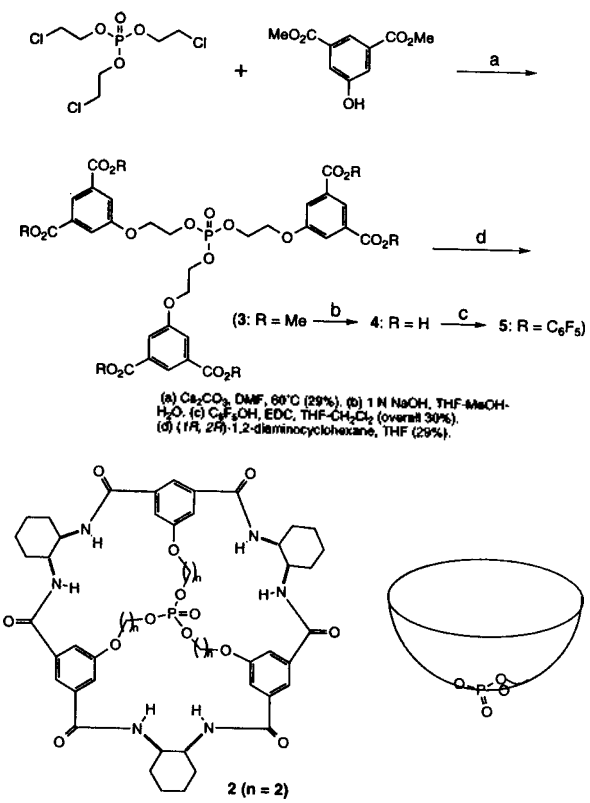
In order to introduce a concave functionality into the cavity, we designed C_3 symmetric receptor (**2**) with a phosphate functionality at the bottom of the bowl (Scheme 1). CPK model of the designed receptor indicates that P=O of the phosphate is directed either inside the cavity or outside the cavity. Composed of a binding cavity with a hydrogen-bonding functionality, and hydrogen bond donor and acceptor functionalities on the periphery of the surrounding wall of the bowl-shaped host, **2** is expected to show enantio- and residue-selectivities in the binding of amino acids and small peptides.



Scheme 1. A Bowl-Shaped, C_3 Symmetric Receptor with a Phosphate Functionality at the Cavity Bottom.
(1)

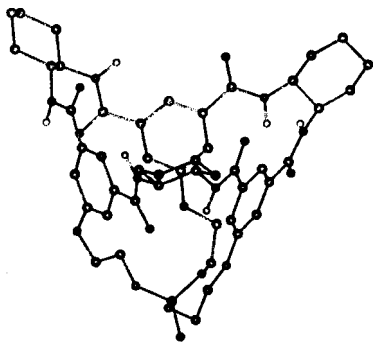
The synthesis of the receptor **2** starts from the trialkylation of dimethyl 5-hydroxyisophthalate with tris(chloroethyl) phosphate as shown in Scheme 1. Ester hydrolysis and subsequent EDC coupling with pentafluorophenol furnished the cyclization precursor **5**. The final step is an intermolecular macrolactamization between a hexakis(pentafluorophenyl)ester **5** and (1*R*,2*R*)-1,2-diaminocyclohexane.[6] A solution of the active ester **5** in THF was added *via* syringe pumps over 15 h to a solution of chiral 1,2-diamine in THF (final concentration = 0.35 mM). Purification by flash chromatography furnished the macrotricycle **2** in 29% yield as a white solid.

The best evidence for the successful macrocyclization was provided by several informative differences between the ^1H NMR spectrum of **2** and that of its acyclic precursor **5**. The 500 MHz ^1H NMR in DMSO-d_6 displayed a simple spectrum as would be expected for the symmetrical structure. Three different aromatic proton peaks, two different methine proton signals in a cyclohexane part, two different amide proton signals of the ^1H NMR spectrum, and two different carbonyl carbon signals of the ^{13}C NMR spectrum presumably result from the partial asymmetric structure of overall C_3 symmetric receptor (see the Experimental section). Furthermore, mass spectrum showed an M+1 signal at m/z 958.

It is expected from the CPK models that the 3-dimensional structure of the receptor **2** is similar to that of the previously synthesized C_3 receptor **1**.[4] However, it has more rotatable bonds between meta-substituted aromatics of the cavity wall and the phosphorus atom at the cavity bottom. Therefore, **2** should be conformationally more flexible than **1**. Viewed

from two widely separated amide proton signals, **2**, as in our previous receptor **1**, also seems to have three 7-membered intramolecular hydrogen bonds between three sets of two amide groups around the periphery of a binding cavity which may limit the number of accessible low energy conformations.[4]

Molecular modeling[7] *via* molecular dynamics followed by energy minimization finds the structure below as the lowest conformation, which is C_3 symmetric and has a large open cavity with P=O at the cavity bottom pointing outward. If indeed the structure found reflects the real situation, **2** would show a similar binding tendency, however, relatively reduced binding affinity and selectivity compared to **1** considering its increased conformational flexibility.



In summary, we synthesized a chiral, C_3 symmetric receptor having a phosphate functionality at the cavity bottom, deep bowl-shaped three-dimensional binding cavity and appropriately positioned hydrogen bond donor and acceptor functionalities. Computational modeling suggests that P=O of the phosphate at the cavity bottom is pointing outside the cavity. We are currently working on the design and synthesis of a bowl-shaped receptor with an inwardly pointing functionality.

Experimental

Hexakis(methyl)ester (3). To a solution of tris(chloroethyl)phosphate (2.25 g, 7.88 mmol) and dimethyl 5-hydroxyisophtalate (5 g, 23.8 mmol) in 50 mL of DMF was added Cs_2CO_3 (8 g, 24.6 mmol). The reaction mixture was stirred at 60 ℃ for 5 h. H_2O was added, and solvent was distilled off *in vacuo*, The residue was dissolved with EtOAc, and filtered. After removing EtOAc *in vacuo*, the residue was chromatogaphed on silica gel eluting with EtOAc/*n*-hexane (3 : 1, v/v) to give 1.89 g (29%) of **3** as a white solid.

mp 109-111 ℃; IR (KBr) 2944, 1718, 1590, 1443, 1241, 1107, 752 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 8.21 (s, 3H, Ar*H*), 7.69 (s, 6H, Ar*H*), 4.61-4.11 (m, 12H, OCH_2), 3.88 (s, 18H, OCH_3).

Hexakis(pentaflurophenyl)ester (5). To a solution of hexaester (740 mg, 0.92 mmol) in 18 mL of THF-MeOH-H_2O (v/v, 5 : 3 : 1) was added 11 mL of 1 N NaOH solution. The mixture was stirred at rt for 5 h and acidified with 1 N HCl solution. The resulting mixture was extracted with EtOAc and evaporated to dryness *in vacuo* to give crude hexaacid **4**. The crude hexaacid **4** was dissolved in 30 mL of THF-CH_2Cl_2 (v/v, 1/2) and pentafluorophenol (1.52 mg, 8.26 mmol) and EDC (1.58 mg, 8.26 mmol) were added. The reaction mixture was stirred at rt for 7 h and all volitiles were removed at reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/*n*-hexane (v/v, 2/1) to give 0.47 g (30%) of **5** as an amorphous white solid.

mp 58-60 ℃; IR (KBr) 1763, 1593, 1513, 1443, 1377, 1299, 1187, 995 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 8.60 (s, 3H, Ar*H*), 7.98 (s, 6H, Ar*H*), 4.74-4.29 (m, 12H, OCH_2).

C_3 symmetric macrocyclic receptor (2). To a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (32 mg, 0.285 mmol) in 250 mL of dry THF was added a solution of hexakis(pentaflurophenyl)ester (164 mg, 0.095 mmol) in 20 mL of THF for 15 h by syringe pump. After stirring at rt for 6 h , solvent was removed in vacuo. And the residue was dissolved in CH_2Cl_2-MeOH (v/v, 10/1) and washed successively with 1 N HCl solution, saturated aqueous $NaHCO_3$ solution, and water. After drying over anhydrous $MgSO_4$, all volatiles were removed *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with CH_2Cl_2-MeOH (v/v, 10/1) and triturated with EtOAC to give 25 mg (29%) of **2** as a white solid.

mp > 300 ℃ dec.; IR (KBr) 3424, 2928, 1641, 1587, 1536, 1449, 1260, 1142, 1068, 1036 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.48 (d, J=8.7 Hz, 3H, CON*H*), 7.91 (d, J=8.3 Hz, 3H, CON*H*), 7.77 (s, 3H, Ar*H*), 7.37 (s, 3H, Ar*H*), 7.26 (s, 3H, Ar*H*), 4.53-3.82 (m, 12H, OCH_2), 4.03-4.00 (m, 3H, NHC*H*), 3.84-3.82 (m, 3H, NHC*H*), 1.89-1.29 (m, 24H, CH_2's); ^{13}C NMR (50.29 MHz, DMSO-d_6) δ 165.3, 164.6, 157.1, 135.4, 118.8, 118.8, 117.9, 115.0, 66.9, 65.4, 53.5, 52.5, 32.0, 25.0, 24.6; MS (FAB, glycerol) m/z 958 (M+1).

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7. To obtain the minimum energy structure, molecular dynamics and molecular mechanics calculations were carried out with the CVFF force field[8] and the DISCOVER simulation package of MSI.[8] Molecular dynamics was run at 800 K for 1000 ps with 1 fs time step, and the resulting trajectory analyzed. Of 1,000 conformers obtained in the dynamics simulation, the lowest energy structure was selected, and then the energy minimization with conjugate gradient algorithm[9] was performed on this structure to a gradient norm of less than 0.001 kcal/mol per Å.
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First-Order Hyperpolarizabilities of α-Cyano-*p*-nitrostilbene Derivatives

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It has been clearly established that π donor-acceptor compounds with small CT energy and large differences between the ground- and excited-state dipole moments as well as large oscillator strength can exhibit large molecular second-order optical nonlinearities.[2b,8~11] The β value can be expressed as eq. 1, where ΔE is the energy of the molecular charge transfer, $h\nu$ and $2h\nu$ are the energies of the fundamental and second harmonic waves, f is the oscillator strength, and $\Delta\mu$ is the difference between the ground- and excited state dipole moments.[12]

$$\beta = \frac{3e^2\hbar^2}{2m} \frac{\Delta E f \Delta\mu}{[\Delta E^2 - (2h\nu)^2][\Delta E^2 - (h\nu)^2]} \quad (1)$$

Table 1. Linear and Nonlinear Optical Properties of Various Stilbene Derivatives

Compound	λ_{max}, nm[a]	10^{30} β, esu[b]	10^{30} β(0), esu[c]
Ia	370[d]	56[e]	46[e]
IIa	368	0[f]	0
IIb	382	0[f]	0
IIIb	386	77	32
Ic	437[d]	84[e]	63[e]
IIc	488[g]	399[g]	50

[a]Solvent was methanol except otherwise noted. [b]Measured by Hyper-Rayleigh scattering with 1064 nm fundamental radiation in methanol except otherwise noted. [c]Calculated by using the two-level model.[15] [d]Solvent was $CHCl_3$. [e]Literature values determined by EFFISH in $CHCl_3$.[13] [f]Small scattering was detected. [g]Solvent was DMSO.

One of the most well known NLO chromophores is the stilbene derivatives. Thus disubstituted stilbenes with various donor-acceptor pairs exhibit the β value of $19\text{-}73\times10^{-30}$ esu in $CHCl_3$.[13] We were interested in learning whether a cyano substituent at either of the olefinic carbons of this compound might enhance the molecular hyperpolarizability (β). It was expected that the cyano group would change not only the dipole moment but the ΔE and f values, which would in turn change the β values. Accordingly, we have synthesized compounds **IIa-c** and **IIIb** and compared their β values with those for the stilbene derivatives **I**.

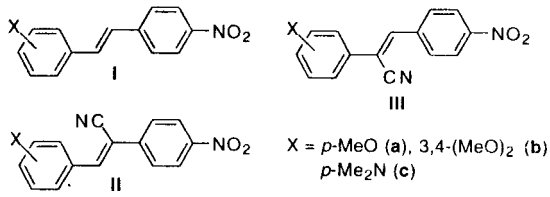

Table 1 compares the β values of the various stilbene derivatives. In general, the β values are always smaller for the α-cyanostilbenes than for the stilbenes. Comparison of the absorption maxima reveals that they are almost the same for **Ia** and **IIa**, whereas that for **Ic** is significantly shorter than **IIc**. Hence it is difficult to explain the smaller β values for the α-cyanostilbene derivatives only in terms of the λ_{max} values. On the other hand, the result can readily be interpreted with the difference between the ground and the excited state dipole moments. A semiemperical calculation has revealed that the ground state dipole moments for **Ic** and **IIc** are almost the same.[14] However, the excited state dipole moment is significantly smaller for the former due to the increased charge transfer from the dimethylamino to the cyano group (Figure 1). Accordingly, the difference between the ground and the excited state dipole moments ($\Delta\mu$) for **IIc** is smaller than that for **Ic** by approximately 14%. This would predict that the β value should be smaller for the former