Synthesis of a Bowl-Shaped, C₃ Symmetric Receptor with a Phosphate Functionality at the Cavity Bottom

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Received July 9, 1996

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 pentafluorophenyl furnished the cyclization precursor 5. The final step is an intermolecular macrolactamization between a hexafluorophenol ester 5 and (1R,2R)-1,2-diaminocyclohexane. 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 macrocycle 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-d₆ 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 ¹³C NMR spectrum presumably result from the partial asymmetric structure of overall C₃ 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 C₃ receptor 1. 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.

Molecular modeling via molecular dynamics followed by energy minimization finds the structure below as the lowest conformation, which is C₃ 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, C₃ 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 Cs₂CO₃ (8 g, 246 mmol). The reaction mixture was stirred at 60 °C for 5 h. H₂O 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 chromatographed 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 °C; IR (KBr) 2944, 1718, 1590, 1443, 1241, 1107, 752 cm⁻¹; ¹H NMR (80 MHz, CDCl₃) δ 8.21 (s, 3H, ArH), 7.69 (s, 6H, ArH), 4.61-4.11 (m, 12H, OCH₂), 3.88 (s, 18H, OCH₃).

**Hexakis(pentafluorphenyl)ester (5).** To a solution of hexaester (740 mg, 0.92 mmol) in 18 mL of THF-MeOH-H₂O (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-CH₂Cl₂ (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 volatiles 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 °C; IR (KBr) 1763, 1593, 1413, 1377, 1299, 1187, 995 cm⁻¹; ¹H NMR (80 MHz, CDCl₃) δ 8.60 (s, 3H, ArH), 7.98 (s, 6H, ArH), 4.74-4.29 (m, 12H, OCH₂).

C₃ symmetric macrocyclic receptor (2). To a solution of (1R,2R)-1,2-diaminocyclohexane (32 mg, 0.285 mmol) in 250 mL of dry THF was added a solution of hexakis(pentafluorophenyl)ester (164 mg, 0.995 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 CH₂Cl₂-MeOH (v/v, 10/1) and washed successively with 1 N HCl solution, saturated aqueous NaHCO₃ solution, and water. After drying over anhydrous MgSO₄, all volatiles were removed in vacuo. The crude residue was purified by column chromatography on silica gel eluting with CH₂Cl₂-MeOH (v/v, 10/1) and triturated with EtOAc to give 25 mg (29%) of 2 as a white solid.

mp > 300 °C dec.; IR (KBr) 3424, 2928, 1641, 1587, 1536, 1449, 1260, 1142, 1068, 1036 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 8.48 (d, J = 8.7 Hz, 3H, CONH), 7.91 (d, J = 8.3 Hz, 3H, CONH), 7.77 (s, 3H, ArH), 7.37 (s, 3H, ArH), 7.26 (s, 3H, ArH), 4.53-3.82 (m, 12H, OCH₂), 4.03-4.00 (m, 3H, NHCH), 3.84-3.82 (m, 3H, NHCH), 1.89-1.29 (m, 24H, CH₂'s).

¹³C NMR (50.29 MHz, DMSO-d₆) 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).

**Acknowledgment.** This work was supported by the Ministry of Education (BSRF-95-3416) and OCRC (ROSEP). We are grateful to Dr. Sung-Hwang for computational modeling.

**References**

First-Order Hyperpolarizabilities of α-Cyano-p-nitrostilbene Derivatives

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Received April 25, 1996

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.2h−11 The β value can be expressed as eq. 1, where ΔE is the energy of the molecular charge transfer, hv and 2hv are the energies of the fundamental and second harmonic waves, f is the oscillator strength, and Δμ is the difference between the ground- and excited state dipole moments.

\[ \beta = \frac{3e^2h^2}{2\pi m} \frac{\Delta E/\Delta \mu}{[\Delta E^2-(2hv)^2][\Delta E^2-(hv)^2]} \]  

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 19-73×10⁻²⁰ esu in CHCl₃. 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-cyano stilbenes than for the stilbenes. Comparison of the absorption maxima reveals that they are almost the same for Ia and IIa, whereas that for IIc is significantly shorter than IIc. Hence it is difficult to explain the smaller β values for the α-cyano stilbene derivatives only in terms of the λmax values. On the other hand, the result can readily be interpreted with the difference between the ground- and the excited state dipole moments. A semiempirical calculation has revealed that the ground state dipole moments for IIc and IIc are almost the same. 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 (Δμ) for IIc is smaller than that for IIc by approximately 14%. This would predict that the β value should be smaller for the former.