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Synthesis, *p*-Nitrophenolate Complexation and Competitive Anion Signaling of Novel Calixpyrrole Dimer

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Abstract

A novel dimeric calixpyrrole has been synthesized. The dimer forms stable complexes with *p*-nitrophenolate ion with a concomitant reduction in extinction coefficient. The chromogenic anion is displaced by the addition of various anions like fluoride and acetate. Effective optical sensing of these anions is accomplished using the calixpyrrole dimer.

Introduction

Anion sensing has attracted considerable attention in recent years [1–6]. Among various strategies followed, dye displacement strategy has proved to be highly productive [7–9]. Both chromogenic and fluorogenic anion sensors were obtained by this approach. Chromogenic sensors which are in many cases ''naked-eye'' sensors, are likely to yield many applications including test strips, ion selective electrodes and other optical sensing devices [10].

Calixpyrroles have been recognized relatively recently as anion receptor moieties [11–14], and as a follow-up, novel chromogenic and fluorogenic anion sensing materials based on calixpyrroles were introduced [15–17]. In a recent work, [18] the parent calixpyrrole was shown to bind *p*-nitrophenolate ion and reduce its extinction coefficient. Addition of anions that displace the *p*-nitrophenolate anion is signaled by an increase in the absorbance at 430 nm.

As a part of our ongoing effort in developing novel chemosensing compounds for anions [19, 20] and in attempt to apply the indicator displacement strategy in a homoditopic receptor, we targeted the calixpyrrole dimer **1**. The synthesis followed reported procedures for compound **2** [17]. The deprotection of compound **2** was carried out with 40% aqueous KOH in MeOH under reflux conditions and this procedure, in our hands, resulted in a higher yield compared to the reported procedure. The 3-amino derivative obtained in this way was reacted with *iso*-phthaloyl chloride in dichloromethane to yield the desired dimer after silica-gel column chromatography purification. The ditopic calixpyrrole derivative was characterized fully in order to confirm the structure using NMR (^{1}H, ^{13}C, HMBC) and elemental analysis.

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Experimental

General

All chemicals and solvents purchased from Aldrich were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DPX-400 in $CDCl_3$ or DMSO-d_6 with TMS as internal reference. Absorption spectrometry was performed using Shimadzu-1600PC spectrophotometer. Column chromatography of all products was performed using Merck Silica Gel 60 (particle size: 0.040–0.063 mm, 230–400 mesh ASTM). Reactions were monitored by thin layer chromatography using fluorescent coated aluminum sheets. Tetrabutylammonium *p*-nitrophenolate was prepared by the titration of *p*-nitrophenol solution with tetrabutylammonium hydroxide in methanol.

Elemental analyses were performed by TUBITAK elemental analysis laboratory, Ankara.

*3-Aminophenyl-calixpyrrole (**2**)*

Compound **1**, the benzyloxycarbonyl protected calixpyrrole, (100 mg, 0.138 mmol) was dissolved in MeOH (10 ml). To this solution 40% aqueous KOH solution (10 ml) was added, refluxed overnight and then the organic materials were extracted with diethyl ether (50 ml) and washed with water (3 × 50 ml). The organic

phase was concentrated under reduced pressure and the residue was subjected to column chromatography (1:4 EtOAc:hexane). The major band corresponded to the desired product. Yield 65 mg (79.7%).

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 0.64–0.71 (t, 18 H, CH_3), 1.77–1.85 (m, 15 H, CH_2 and CH_3), 3.55 (bs, 2 H, NH_2), 5.89–5.93 (m, 8 H, CH), 6.23–6.29 (m, 1 H, CH), 6.35–6.41 (m, 1 H, CH), 6.49–6.52 (m, 1 H, CH), 6.95 (bs, 2 H, NH), 6.97 (t, 1 H, $J = 7.8$ Hz, CH), 7.18 (br s, 2 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 8.0, 8.1, 27.9, 28.0, 28.5, 28.7, 28.9, 43.1, 43.2, 44.8, 105.0, 105.5, 105.9, 106.1, 113.3, 114.8, 118.0, 128.6, 136.4, 136.5, 136.8, 136.9, 146.6, 149.2.

*Calixpyrrole dimer (**3**)*

A mixture of amino-modified calixpyrrole (**2**) (0.2 mmol, 114 mg), *iso*-phthaloyl dichloride (7.74 mmol, 16 mg), CH_2Cl_2 (3 ml) and Et_3N (0.5 ml) was stirred overnight at room temperature. Dichloromethane was added to the reaction mixture and the solution was washed with saturated $NaHCO_3$(3 × 15 ml). The organic phase was collected, dried with Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified by column chromatography (MeOH/$CHCl_3$, 5/95). Yield 155 mg (59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 0.51–0.62 (m, 36 H, CH_3), 1.18–1.22 (br s, 6 H, CH_3), 1.65–1.82 (m, 24 H, CH_2), 5.61–5.68 (br m, 4 H, pyr-CH), 5.78–5.88 (br m, 12 H, pyr-CH), 6.75 (d, 2 H, $J = 7.8$ Hz), 6.89–7.01 (m, 5 H), 7.13–7.21 (m, 7 H), 7.53 (t, 1 H, $J = 7.7$ Hz), 7.68 (d, 2 H, $J = 8.4$ Hz), 7.74 (br s, 2 H, CONH), 7.95 (d, 2 H, $J = 7.6$ Hz), 8.83 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 8.5, 29.0, 29.2, 30.1, 30.3, 31.2, 43.3, 44.9, 45.0, 104.1, 105.1, 105.3, 105.5, 117.1, 119.4, 124.3, 124.4, 125.3, 125.7, 131.8, 132.5, 133.0, 135.1, 135.3, 135.7, 135.8, 136.1, 137.3, 137.5, 137.6, 137.9, 138.1, 148.7, 148.8, 163.1.

For $C_{86}H_{104}N_{10}O_2$, calcd.: C 78.86, H 8.00, N 10.69%, found: C 78.94, H 8.22, N 10.61. 2D NMR of the dimer shows correlations that support the proposed structure:

The ^{13}C peak at 163.1 ppm is clearly due to the amide carbonyl carbon. This peak shows the different correlations with the singlet proton (1H) at 8.83 (the aromatic H between the two carbonyls on the iso-phthaloyl ring) and with the somewhat broadened singlet (2H) at 7.74 which is most likely the amide hydrogens. Other correlations are also in accordance with the expected structure.

Results and discussion

In order to investigate the binding interaction of *p*-nitrophenolate anion with calixpyrrole dimer, 36.5 μM solution of the anion (the counterion was tetrabutylammonium cation) in dichloromethane was prepared. To this solution, increasing amounts of the dimer from a concentrated stock solution was added. As the anion concentration was varied from 0 to 0.75 mM, the *p*-nitrophenolate peak at 430 nm disappeared. Figure 2 shows the change in the absorption spectrum during this titration. Benesi-Hildebrand plot (1/Δ (Absorbance)

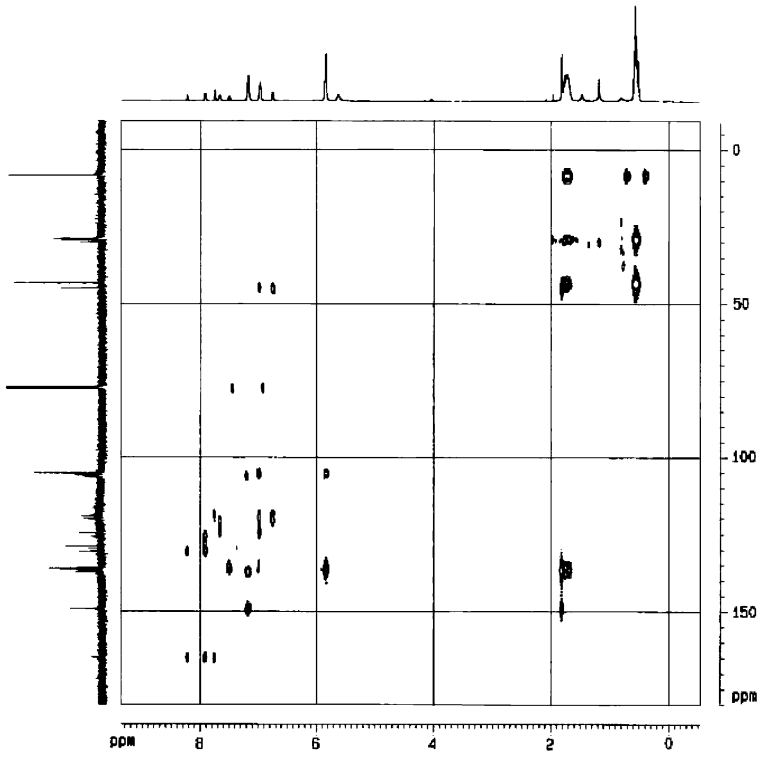

Figure 1. HMBC spectrum of the dimer in $CDCl_3$.

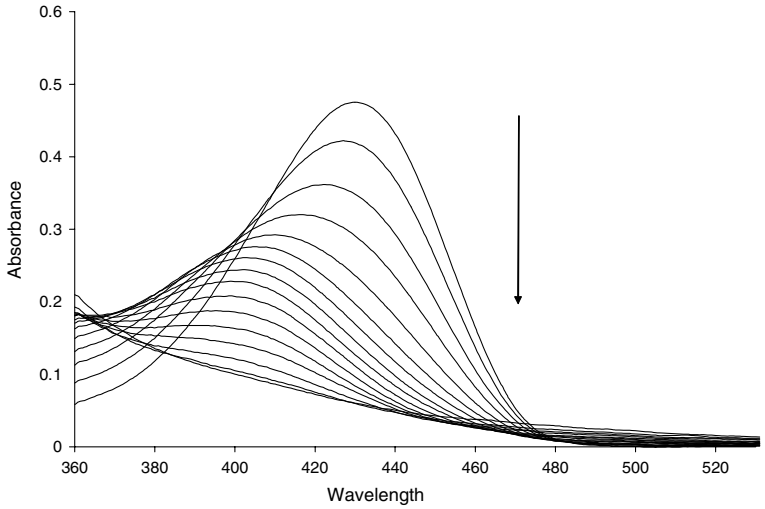

Figure 2. Changes of absorption spectra of *p*-nitrophenolate anion (3.65×10^{-5} mol dm^{-3}) upon addition of calix[4]pyrrole dimer in CH_2Cl_2 (0, 3.8×10^{-5}, 7.6×10^{-5}, 1.1×10^{-4}, 1.5×10^{-4}, 1.9×10^{-4}, 2.3×10^{-4}, 2.6×10^{-4}, 3.0×10^{-4}, 3.4×10^{-4}, 3.8×10^{-4}, 4.2×10^{-4}, 4.5×10^{-4}, 4.9×10^{-4}, 5.3×10^{-4}, 5.7×10^{-4} mol dm^{-3}).

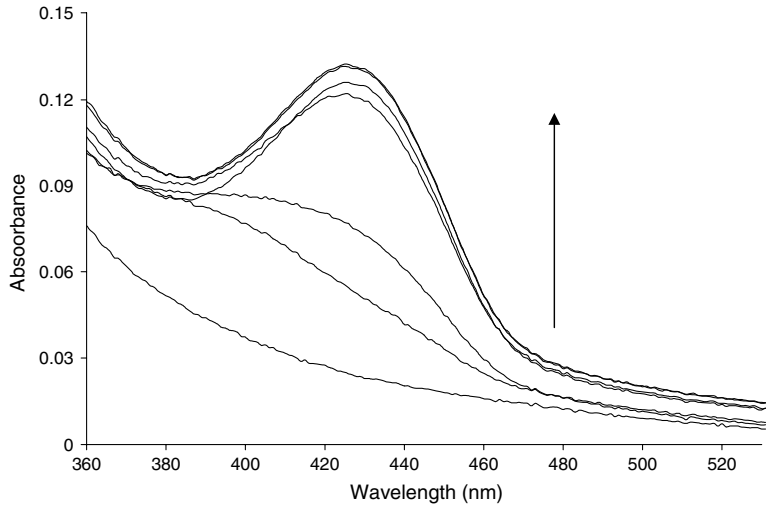

Figure 3. The change in the absorption spectrum of the calix[4]pyrrole dimer **3** (5×10^{-4} mol dm^{-3})-*p*-nitrophenolate complex (6×10^{-6} mol dm^{-3}) on the addition of fluoride in the form of tetrabutylammonium salt in acetonitrile. The fluoride concentration was varied as follows: 0, 2×10^{-4}, 4×10^{-4}, 8×10^{-4}, 1.4×10^{-3}, 2.4×10^{-3}, 3.2×10^{-3} mol dm^{-3}.

versus 1/[dimer]) yields a macroscopic dissociation constant (an average for both binding sites) of 4.0×10^{-4} M for 1:2 binding.

We then demonstrated that a chromogenic response was obtained by displacing the bound *p*-nitrophenolate anion by various anions. We studied six different anions; the halide series, acetate and bisulfate. Fluoride ion was the most effective in displacing the *p*-nitrophenolate anion (Figure 3), free *p*-nitrophenolate peak was clearly identifiable at 0.8 mM of fluoride ion addition. Among the other anions, acetate was also somewhat effective in displacing *p*-nitrophenolate. The recovered *p*-nitrophenolate absorbance on the addition of anions is shown in Figure 4. Chloride, bromide, iodide and bisulfate ions caused insignificant change over the background absorbance at 430 nm.

Thus, we have shown that the dimeric calixpyrrole receptor is a receptor of *p*-nitrophenolate ion. The displacement of *p*-nitrophenolate with various inorganic anions demonstrates that the complex can be exploited in accordance with dye displacement strategy effectively signaling inorganic anions with a color change from nearly colorless to yellow-orange. Further work in refining anion signaling based on this strategy is in progress.

Acknowledgements

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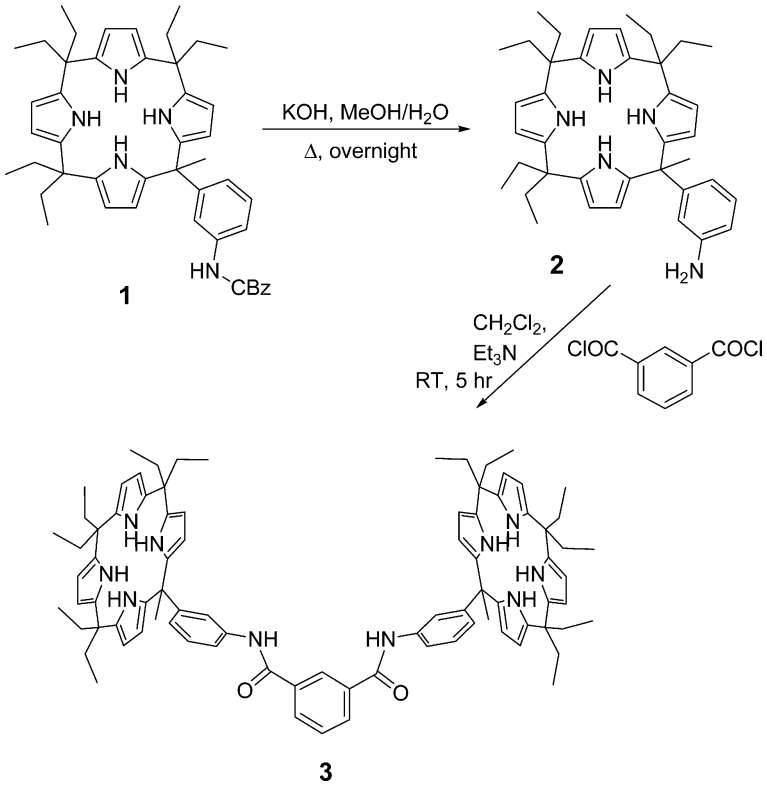

Scheme 1.

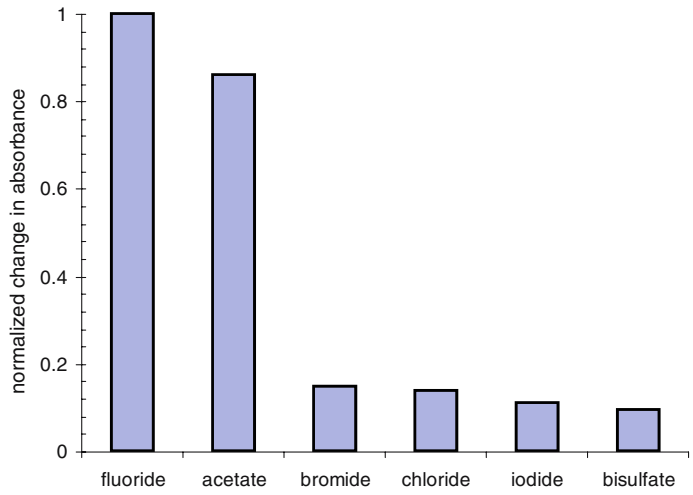

Figure 4. Normalized absorbance change for the displacement of *p*-nitrophenolate (at 430 nm) by the indicated anions at 3.2 mM concentration. Dimer concentration was 0.5 mM and *p*-nitrophenolate concentration was 6.0 μM. The background absorbance value of the *p*-nitrophenolate-dimer complex at 430 nm was subtracted from all absorbance values and then the change was normalized.

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