



(E)-3-(*meso*-Octamethylcalix[4]pyrrol-2-yl)propenal: a versatile precursor for calix[4]pyrrole-based chromogenic anion sensors

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ABSTRACT

The synthesis of (*E*)-3-(*meso*-octamethylcalix[4]pyrrol-2-yl)propenal and its use in Knoevenagel reactions are described. The resulting compounds display sharp changes in color in the presence of fluoride, acetate, and dihydrogen phosphate anions.

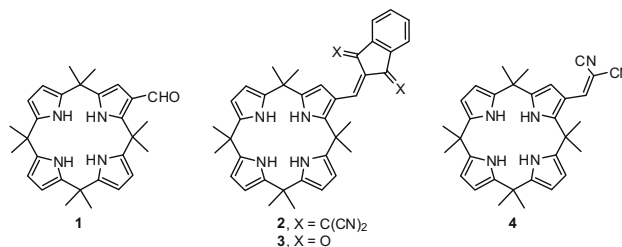
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In recent years, a considerable effort has been dedicated to the search for new sensors selective to cations, anions, or neutral molecules.¹ Chromogenic sensors, that is, those displaying a sharp change in color in the presence of a given substrate, are particularly interesting since visual detection can give immediate qualitative information of a particular chemical species. Currently, the colorimetric sensing techniques are also becoming increasingly appreciated for quantitative analysis.² In this context, selective anion sensors³ are particularly important due to the relevance of such species in many biological processes (over 70% of all cofactors and substrates involved in biology are of anionic nature).³¹ Moreover, some anions are associated with serious environmental problems, namely those involving the release of CN⁻ (an extremely toxic anion, which is lethal even in very small amounts)⁴ and radioactive nuclear waste products to waterways, or the eutrophication of lakes by phosphates.⁵ Therefore, finding selective, simple, and fast procedures for anion sensing is a goal pursued by many researchers.

Since 1996, when it was discovered that calix[4]pyrroles interact strongly with small anions,⁶ such as fluoride, chloride, and phosphate, many calix[4]pyrrole-based anion sensors were reported,^{7,8} some of them being naked-eye anion sensors.^{9–12}

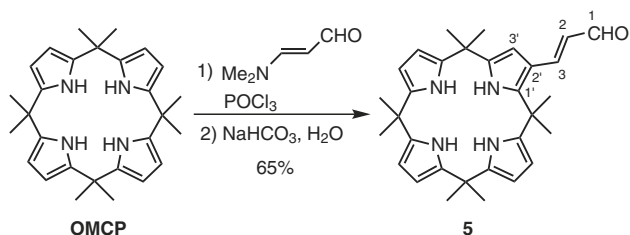
Calix[4]pyrrole-based chromogenic anion sensors can be prepared by chemical modification of *meso*-octamethylcalix[4]pyrrole (OMCP) which is obtained in one step, and in high yield, from pyrrole and acetone. In 2006,¹¹ Anzenbacher described the synthesis of *meso*-octamethylcalix[4]pyrrole-2-carbaldehyde (**1**) in 44% yield

by direct formylation of OMCP with the Vilsmeier reagent.¹³ Condensation of aldehyde **1** with methylene active compounds under Knoevenagel reaction conditions afforded colored push–pull chromophores (**2** and **3**, for instance) which showed good results in anion-binding studies.^{10,11} Aldehyde **1** was also condensed with malononitrile to yield calixpyrrole **4**, a cyanide-selective indicator.¹⁴ This methodology (Vilsmeier formylation followed by Knoevenagel condensation) was recently used to prepare two isomeric strapped calix[4]pyrroles bearing a 1,3-indanedione group at a β-pyrrolic position.¹⁵ The resulting strapped calix[4]pyrroles showed to be cyanide-selective chemosensors. Similarly, a *N*-confused calix[4]pyrrole-α-carbaldehyde was also used as a precursor of colored *N*-confused calixpyrrole derivatives.¹⁶

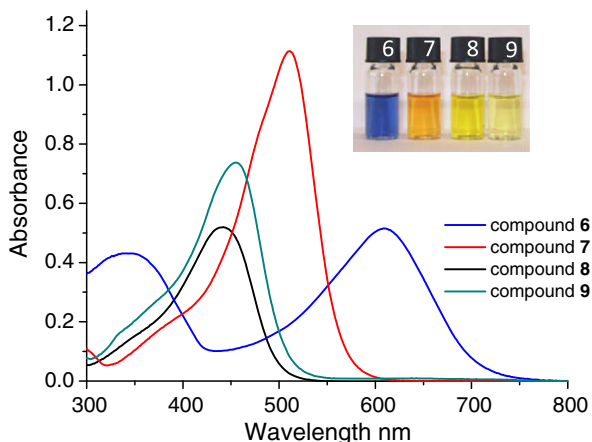


The interesting chromogenic anion sensors obtained from aldehyde **1** prompted us to synthesize calixpyrrole derivative **5** and to use it as a key intermediate to prepare new anion sensors. It was expected that calixpyrrole derivatives resulting from the Knoevenagel reaction between aldehyde **5** and methylene active compounds would display interesting UV–vis spectra since the new compounds should have an extra conjugated C–C double bond

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Scheme 1.

Figure 1. Absorption spectra of sensors **6–9** (5×10^{-5} M in CH_2Cl_2).

when compared with those obtained from aldehyde **1**. The results described in this Letter confirm that our assumption was correct.

Calixpyrrole **5** was obtained from the reaction of OMCP, 3-(dimethylamino)propenal, and POCl_3 followed by hydrolysis of the resulting intermediate (Scheme 1).¹⁷ TLC of the resulting solid showed only one spot ($R_f = 0.32$; silica gel, CHCl_3) and a red baseline. Purification by column chromatography (silica gel) and crystallization from dichloromethane/hexane afforded aldehyde **5** in 65% yield as a yellow solid. The ^1H NMR spectrum of this compound shows the distinctive signals corresponding to the resonances of H-2 at 6.37 ppm (dd, $J = 8.0$ and 15 Hz), H-3 at

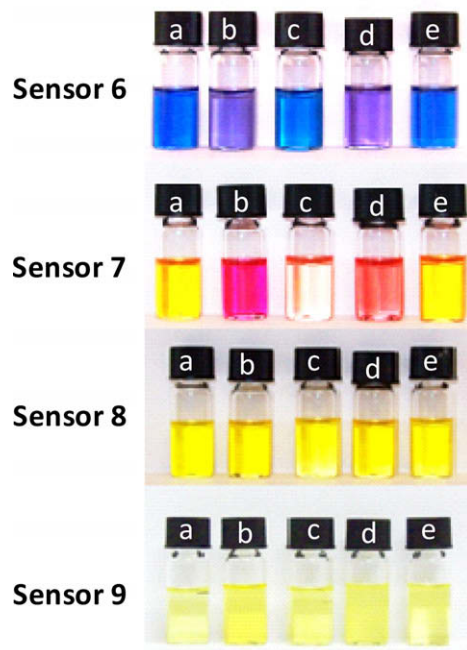
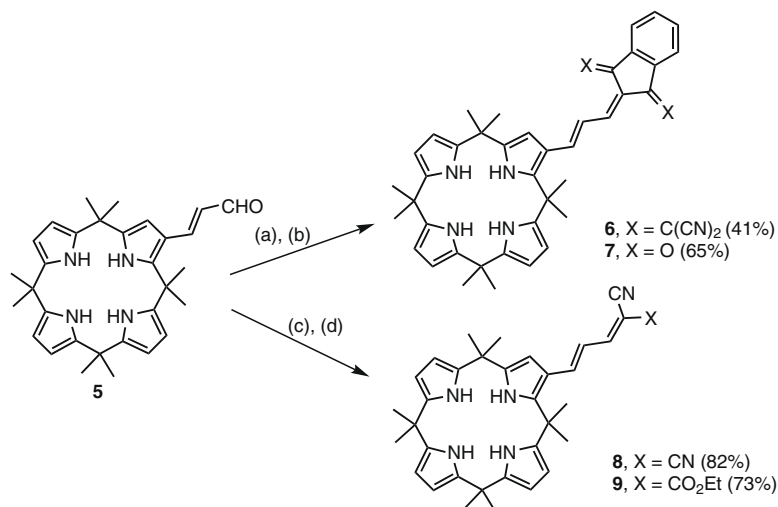


Figure 2. (a) Sensor without anion; (b) sensor with F^- ; (c) sensor with Cl^- ; (d) sensor with AcO^- ; (e) sensor with H_2PO_4^- . All solutions are in CH_2Cl_2 . Ten equivalents of anion were added in the form of tetrabutylammonium (TBA) salt.

7.78 ppm (d, $J = 15$ Hz), and the CHO proton at 9.55 ppm (d, $J = 8.0$ Hz). The resonance of H-3' appears at 6.21 ppm as a doublet ($J = 1.7$ Hz) due to coupling with the NH proton. The *trans* configuration of the C–C double bond is evident from the H-2–H-3 coupling constant (15 Hz). The ^{13}C NMR spectrum is also consistent with the structure **5**, showing the resonance of C-1 at 193.6 ppm.

Aldehyde **5** was then condensed with some methylene active compounds to get new 2-substituted calixpyrrole derivatives (Scheme 2). In order to compare the reactivities of aldehydes **1** and **5**, and also the anion sensing properties of the corresponding derivatives, we decided to react **5** with 1,3-bis(dicyanomethylidene)indane and 1,3-indanedione. The Knoevenagel reactions were carried out as described¹¹ and the desired compounds **6** and **7** were obtained in 41% and 65% yield, respectively.^{18,19} These yields are



Scheme 2. Knoevenagel reactions with methylene active compounds. Reagents and conditions: (a) 1,3-bis(dicyanomethylidene)indane, AC_2O , reflux, 30 min; (b) indane-1,3-dione, Et_3N , THF, rt, 24 h; (c) malononitrile, Et_3N , CH_2Cl_2 , rt, 24 h; (d) ethyl cyanoacetate, Et_3N , CH_2Cl_2 , rt, 24 h.

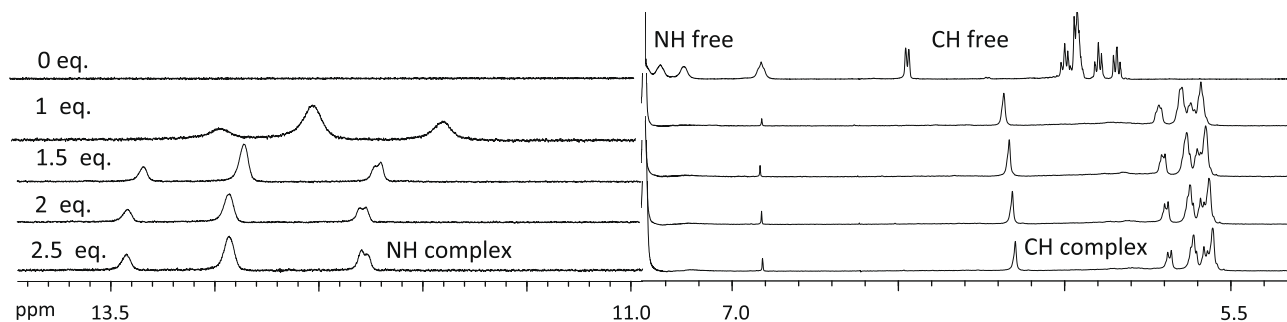


Figure 3. Selected regions of the ^1H NMR spectra of sensor **7** in CDCl_3 titrated with fluoride.

higher than those reported for similar reactions with **1** (35% and 53%, respectively).¹¹ Aldehyde **5** was also reacted with malononitrile and ethyl cyanoacetate, at room temperature and in the presence of triethylamine, to afford sensors **8** and **9** in 82% and 73% yield, respectively.^{20,21}

Compounds **6–9** showed quite different absorption spectra, displaying blue, orange, and yellow colors (Fig. 1). Some of the new compounds showed a significant color modification when in contact with different anions (Fig. 2). The addition of fluoride, chloride, and acetate anions to sensor **7** resulted in an impressive change in color while minor changes were observed for compounds **8** and **9**. The addition of nitrate, nitrite, and bromide anions caused almost no change in the color of the four sensor solutions, indicating a low affinity for these anions. The calculated affinity constants for sensor **7**, in DMSO and using a 1:1 binding model, are $>10^6 \text{ M}^{-1}$ for fluoride, $4.16 \times 10^4 \text{ M}^{-1}$ for acetate, and $6.58 \times 10^3 \text{ M}^{-1}$ for dihydrogen phosphate anion. These values compare favorably with those reported for compound **3** ($>10^6$, 1.57×10^4 , and $4.56 \times 10^3 \text{ M}^{-1}$, respectively).¹¹

Some ^1H NMR anion-binding studies were also carried out with sensor **7** and fluoride anion. As shown in Figure 3, the resonances corresponding to the calixpyrrole NH protons at 6.95–7.24 ppm exhibited a downfield shift to 12.20–13.50 ppm upon the addition of two equivalents of F^- , indicating that these NH protons are involved in hydrogen-bonding interactions with F^- . This demonstrates that the color changes observed upon addition of the studied anions correspond to the formation of supramolecular systems and not to the deprotonation of the sensors.

In conclusion, we describe here the synthesis of the new calixpyrrole derivative **5**. This aldehyde is obtained in good yield and, in the solid state, it is stable for months at room temperature, while compound **1** is very unstable both in solution and in the solid state.²² Aldehyde **5** also gives higher yields in Knoevenagel condensations when compared to **1**. In that way, it can be anticipated that this new aldehyde can be a useful precursor for other calixpyrrole-based anion sensors.

Acknowledgments

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- POCl_3 (0.67 mL, 7.2 mmol) and 3-(dimethylamino)propenal (0.43 mL, 4.3 mmol) were added to a solution of octamethylcalix[4]pyrrole (2.50 g, 5.8 mmol) in 1,2-dichloroethane (100 mL) at 0 °C under N_2 atmosphere. After 4 h, a saturated aqueous solution of NaHCO_3 (500 mL) was added and the resulting mixture was stirred for 16 h at rt. The organic phase was separated, washed with brine (200 mL) and then with water. The solution was dried (Na_2SO_4), concentrated under vacuum, and the reaction product was purified by column chromatography (silica gel) using chloroform as the eluent. Compound **5** was crystallized from dichloromethane/hexane affording 1.35 g (65% yield) of a yellow solid with mp 230–231 °C (dec). ^1H NMR (300 MHz, CDCl_3): δ = 1.49–1.55 (m, 24H, CH_3), 5.85–6.04 (m, 6H, H- β), 6.21 (d, J = 1.7 Hz, 1H, H- β), 6.37 (dd, J = 8.0 and 15 Hz, 1H, H-2), 6.95 (br, 1H, NH), 7.06 (br, 1H, NH), 7.15 (br, 1H, NH), 7.24 (br, 1H, NH), 7.78 (d, J = 15 Hz, 1H, H-3), 9.55 (d, J = 8.0 Hz, 1H, CHO). ^{13}C NMR (300 MHz, CDCl_3): δ = 28.6, 28.7, 29.2, 29.7, 35.1, 35.2, 37.4, 101.4, 102.8, 103.0, 103.1, 103.8, 104.0, 104.1, 115.2, 124.6, 136.7, 137.0, 137.4, 138.1, 138.8, 139.3, 139.5, 141.7, 147.5, 193.6. HRMS-ESI: calcd for $\text{C}_{31}\text{H}_{39}\text{N}_4\text{O}$ ($\text{M}+\text{H}$) $^+$: 483.3118, found 483.3110.
- A mixture of compound **5** (50 mg, 0.10 mmol) and 1,3-bis(dicyanomethylidene)indane (32 mg, 0.13 mmol) in acetic anhydride (3 mL) was heated at reflux for 30 min. Removal of the solvent under vacuum afforded a black solid which was submitted to column chromatography (silica gel) using dichloromethane as the eluent. Compound **6** was obtained as a purple solid (29 mg, 41% yield) with mp >300 °C. ^1H NMR (300 MHz, CDCl_3): δ = 1.53–1.56 (m, 24H, CH_3), 5.84–6.02 (m, 6H, H- β), 6.45 (d, J = 2.7 Hz, 1H, H- β), 6.88–6.97 (m, 2H, H-2 and NH), 7.34 (br, 1H, NH), 7.41 (br, 1H, NH), 7.72 (dd, J = 3.2 and 5.7 Hz, 2H, H-Ar), 7.81 (d, J = 13.7 Hz, 1H, H-3), 8.28 (d, J = 12.5 Hz, 1H, H-1), 8.56 (dd, J = 3.2 and 5.7 Hz, 2H, H-Ar). ^{13}C NMR (300 MHz, CDCl_3): δ = 20.5, 22.2, 28.5, 28.5, 28.9, 29.01, 29.02, 29.7, 29.8, 35.1, 35.1, 35.2, 37.8, 38.1, 101.2, 101.3, 102.8, 103.02, 103.03, 103.3, 103.9, 104.0, 104.1, 104.3, 104.4, 104.5, 104.8, 114.2, 119.4, 122.4, 124.4, 134.1, 135.9, 136.4, 137.4, 138.6, 139.3, 139.4, 140.2, 146.0, 147.9, 149.4, 151.9, 166.4. HRMS-ESI: calcd for $\text{C}_{46}\text{H}_{43}\text{N}_8$ ($\text{M}+\text{H}$) $^+$: 707.3605, found 707.3615.

19. A solution of aldehyde **5** (100 mg, 0.21 mmol), indane-1,3-dione (38 mg, 0.26 mmol), and triethylamine (0.036 mL, 0.26 mmol) in dry THF (2 mL) was heated at reflux for 24 h. The solvent was evaporated under vacuum and the residue was dissolved in dichloromethane and washed with water. The organic layer was dried (Na_2SO_4) and purified by column chromatography (silica gel) using dichloromethane/ethyl acetate (20:1) as the eluent. Compound **7** was obtained as a red solid (84 mg, 65% yield) with mp 257–258 °C (dec). ^1H NMR (300 MHz, CDCl_3): δ = 1.52–1.57 (m, 24H, CH_3), 5.85–6.00 (m, 6H, H- β), 6.47 (d, J = 2.79 Hz, 1H, H- β), 6.93 (br, 1H, NH), 7.14 (br, 1H, NH), 7.21 (br, 1H, NH), 7.64 (d, J = 12.2 Hz, 1H, H-1), 7.72–7.76 (m, 3H, H-3 and 2H-Ar), 7.89–7.92 (m, 2H, 2H-Ar) 8.05 (dd, J = 12.2 and 14.6 Hz, H-2). ^{13}C NMR (300 MHz, CDCl_3): δ = 28.6, 28.7, 29.2, 29.7, 35.1, 35.2, 37.7, 101.5, 102.8, 103.0, 103.7, 103.9, 104.1, 104.2, 118.0, 120.1, 122.4, 122.7, 123.9, 134.4, 134.5, 136.6, 137.0, 137.4, 138.2, 139.3, 139.4, 139.7, 140.7, 142.0, 143.3, 147.1, 147.6, 191.26, 191.31. HRMS-ESI: Calcd for $\text{C}_{40}\text{H}_{43}\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 611.3381, found 611.3372.
20. A solution of compound **5** (100 mg, 0.21 mmol), malononitrile (15 mg, 0.23 mmol), and triethylamine (0.030 mL, 0.22 mmol) in CH_2Cl_2 was stirred at room temperature for 24 h. Compound **8** was obtained by filtration of the reaction mixture (91 mg, 82% yield). Mp 289–290 °C (dec). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 1.49–1.70 (m, 24H, CH_3), 5.67–5.91 (m, 6H, H- β), 6.33 (s, 1H, H- β), 6.68 (dd, J = 11.9 and 13.9 Hz, 1H, H-2), 8.05 (d, J = 13.9 Hz, 1H, H-3), 8.24 (d, J = 11.9 Hz, 1H, H-1), 9.07 (br, 1H, NH), 9.16 (br, 1H, NH), 9.74 (br, 2H, NH). ^{13}C NMR (300 MHz, $\text{DMSO}-d_6$): δ = 28.0, 28.7, 29.4, 29.7, 34.2, 34.4, 34.8, 37.5, 45.8, 71.2, 101.7, 102.0, 102.4, 102.8, 103.1, 113.7, 115.7, 116.2, 116.3, 136.6, 136.8, 138.3, 138.6, 138.7, 139.3, 141.1, 146.7, 163.2. HRMS-ESI: calcd for $\text{C}_{34}\text{H}_{39}\text{N}_6$ ($\text{M}+\text{H}$) $^+$: 531.3231, found 531.3238.
21. A solution of aldehyde **5** (100 mg, 0.21 mmol), ethyl cyanoacetate (0.024 mL, 0.22 mmol), and triethylamine (0.030 mL, 0.22 mmol) in CH_2Cl_2 was stirred at room temperature for 24 h. Compound **9** was obtained by filtration of the reaction mixture (88 mg, 73% yield). Mp 272–273 °C (dec). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 1.26 (t, J = 3.5 Hz, 2H, $-\text{OCH}_2\text{CH}_3$), 1.50–1.71 (m, 24H, CH_3), 4.21 (q, J = 7.1 Hz, 2H, $-\text{OCH}_2\text{CH}_3$), 5.66–5.92 (m, 7H, H- β), 6.22 (s, 1H, H- β), 6.63 (dd, J = 12.0 and 14.2 Hz, 1H, H-2), 8.07 (d, J = 14.2 Hz, 1H, H-3), 8.24 (d, J = 12.0 Hz, 1H, H-1), 9.07 (br, 2H, NH), 9.76 (br, 2H, NH). ^{13}C NMR (300 MHz, $\text{DMSO}-d_6$): δ = 14.3, 22.2, 27.9, 29.7, 29.7, 34.1, 34.3, 34.6, 37.1, 61.2, 95.4, 101.3, 101.6, 101.9, 102.1, 102.7, 116.0, 117.2, 137.0, 138.5, 138.7, 138.9, 139.4, 140.8, 144.8, 147.5, 158.1, 163.0. HRMS-ESI: calcd for $\text{C}_{36}\text{H}_{44}\text{N}_5\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 578.3490, found 578.3485.
22. Compound **1** rapidly decomposes in solution (50% after 1 day) and in the solid state at room temperature (80% after 2 days), as indicated in Ref. 12.