Calix[2]bipyrrole[2]furan and Calix[2]bipyrrole[2]thiophene: New Pyrrolic Receptors Exhibiting a Preference for Carboxylate Anions

Jonathan L. Sessler,* Deqiang An, Won-Seob Cho, and Vincent Lynch

*Department of Chemistry and Biochemistry, Institute for Cellular and Molecular Biology,
The University of Texas at Austin, 1 University Station - A5300, Austin, TX 78712-0165, USA.*

Supporting Information

I. Experimental

II. ¹H NMR titration studies

III. ITC titration studies

IV. X-ray experimental section

I. Experimental

¹H NMR and ¹³C NMR spectra were recorded on a Varian Unity 400 MHz spectrometer. Chemical shifts are reported as δ in ppm using the residual solvent signal as an internal standard. High resolution mass spectra (HRMS) were obtained on a VG ZAB2-E mass spectrometer. 2,2'-Bipyrrole, 2,5-bis[(α -hydroxy- α , α -dimethyl)methyl]furan, and 2,5-bis[(α -hydroxy- α , α -dimethyl)methyl]thiophene were prepared according to literature procedures.^{1,2} All other reagents were obtained from commercial sources and used as received.

2,5-Bis[(α -(1H, 1'H-[2,2']bipyrro-5-yl)- α , α -dimethyl)methyl]furan (7).

2,2'-Bipyrrole **4** (1.32 g, 10 mmol) and 2,5-bis[(α -hydroxy- α,α -dimethyl)methyl]furan **5** (0.184 g, 1 mmol) were dissolved in dry acetonitrile (100 mL), and the mixture was degassed by bubbling Ar through the solution for 10 min. The mixture, kept under Ar, was then cooled to 0 °C using an ice-water bath. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.14 g, 1 mmol) was added, and the mixture was stirred at 0 °C for 40 min. The reaction was quenched with triethylamine, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, dichloromethane-hexanes 3:2 v/v). Yield: 73%. ^1H NMR (400 MHz, CDCl_3) δ 1.66 (s, 12H, *meso*-CH₃), 5.99-6.06 (m, 8H, β -pyrrole CH), 6.19 (q, 2H, α -pyrrole CH), 6.65 (s, 2H, β -furan CH), 7.96 (s, 4H, pyrrole-NH); ^{13}C NMR (100 MHz, CDCl_3) δ 27.57, 36.17, 103.60, 103.63, 104.01, 104.23, 109.11, 117.30, 124.85, 125.85, 137.91, 159.61; HR-MS (Cl^+) m/z (M^+) calcd for $\text{C}_{26}\text{H}_{28}\text{N}_4\text{O}$: 412.2263, found: 412.2260.

2,5-Bis[(α -(1H, 1'H-[2,2']bipyrro-5-yl)- α,α -dimethyl)methyl]thiophene (8**).**

2,2'-Bipyrrole **4** (1.32 g, 10 mmol) and 2,5-bis[(α -hydroxy- α,α -dimethyl)methyl]thiophene **6** (0.20 g, 1 mmol) were dissolved in dry acetonitrile (100 mL) and subject to reaction and purification using exactly the same procedure used to prepare **7**. Yield: 74%. ^1H NMR (400 MHz, CDCl_3) δ 1.70 (s, 12H, *meso*-CH₃), 6.04 (t, 2H, β -pyrrole CH), 6.07 (t, 2H, β -pyrrole CH), 6.09 (m, 2H, β -pyrrole CH), 6.19 (q, 2H, β -pyrrole CH), 6.58 (s, 2H, β -thiophene CH), 6.72 (m, 2H, α -pyrrole CH), 7.82 (s, 2H, pyrrole-NH), 8.15 (s, 2H, pyrrole-NH); ^{13}C NMR (100 MHz, CDCl_3) δ 31.08, 37.97, 103.18, 103.35, 104.87, 109.33, 117.44, 122.29, 124.99, 125.98, 139.54, 152.72; HR-MS (Cl^+) m/z ($\text{M} + \text{H}^+$) calcd for $\text{C}_{26}\text{H}_{29}\text{N}_4\text{S}$: 429.2113, found: 429.2102.

Calix[2]bipyrrole[2]furan (9).

2,5-Bis[(α -(1H, 1'H-[2,2']bipyrro-5-yl)- α,α -dimethyl)methyl]furan **7** (83 mg, 0.2 mmol) and 2,5-bis[(α -hydroxy- α,α -dimethyl)methyl]furan **5** (37 mg, 0.2 mmol) were dissolved in dry acetonitrile (200 mL), and the mixture was degassed by bubbling Ar through the solution for 10 min. The mixture, kept under Ar, was then cooled to 0 °C using an ice-water bath. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (29 mg, 0.2 mmol) was added, and the mixture was stirred at 0 °C for 2 h. The reaction was quenched with triethylamine, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, dichloromethane-hexanes 4:1 v/v). Yield: 38%. ^1H NMR (400 MHz, CDCl_3) δ 1.61 (s, 24H, *meso*-CH₃), 5.76 (t, 2H, β -pyrrole CH), 5.95 (m, 8H, 4 β -pyrrole CH + 4 β -furan CH), 7.68 (s, 4H, pyrrole-NH); ^{13}C NMR (100 MHz, CDCl_3) δ 27.16, 35.88, 102.84, 103.06, 103.57, 125.26, 137.22, 159.75; HR-MS (Cl^+) m/z (M^+) calcd for $\text{C}_{36}\text{H}_{40}\text{N}_4\text{O}_2$: 560.3151, found: 560.3149.

Calix[2]bipyrrole[2]thiophene (10).

2,5-Bis[(α -(1H, 1'H-[2,2']bipyrro-5-yl)- α,α -dimethyl)methyl]thiophene **8** (86 mg, 0.2 mmol) and 2,5-bis[(α -hydroxy- α,α -dimethyl)methyl]thiophene **6** (40 mg, 0.2 mmol) were dissolved in dry acetonitrile (200 mL) and subject to reaction and purification using exactly the same procedure used to prepare **9**. Yield: 22%. ^1H NMR (400 MHz, CDCl_3) δ 1.67 (s, 24H, *meso*-CH₃), 5.96-6.00 (overlapping triplets, 8H, β -pyrrole CH), 6.66 (s, 4H, β -thiophene CH), 7.66 (s, 4H, pyrrole NH); ^{13}C NMR (100 MHz, CDCl_3) δ 30.45, 37.59, 104.25, 104.57, 121.35, 125.32, 139.67, 153.52; HR-MS (Cl^+) m/z ($\text{M} + \text{H}^+$) calcd for $\text{C}_{36}\text{H}_{41}\text{N}_4\text{S}_2$: 593.2773, found: 593.2757.

References:

1. Groenendaal, L.; Peerlings, H. W. I.; van Dongen, J. L. J.; Havinga, E. E.; Vekemans, J. A. J. M.; Meijer, E. W. *Macromolecules* **1995**, 28, 116-123. Burger, U.; Dreier, F. *Helv. Chim. Acta* **1980**, 63, 1190-1197.
2. Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. I* **1977**, 887.

II. ^1H NMR titration studies

Proton NMR-based titration studies were carried out using a Varian Unity Plus 400 MHz NMR spectrometer. The receptors, as 2.0×10^{-3} M solutions, were titrated by adding known quantities of concentrated solution of the anions in question (in the form of their tetrabutylammonium salts). All tetrabutylammonium anions were purchased from Fluka and used without further purification. The anion solutions used to effect the titration contained the receptors at a concentration of 2.0×10^{-3} M so as to obviate a need to account for dilution effects during the titrations. The data were fit to a 1:1 binding profile according to the method of Wilcox¹ using the changes in the pyrrolic NH resonances in the ^1H NMR spectra. Acetonitrile- d_3 were purchased from Cambridge Isotope Laboratories, Inc. and dried over molecular sieves (4 Å) before use.

Fig. 1 ^1H NMR titration curve for compound **9** and chloride anion in CD_3CN . $[\mathbf{9}] = 2.0 \times 10^{-3}$ M. $[\text{Cl}^-] = 0 - 41.2 \times 10^{-3}$ M. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 2 Job Plot for the binding of compound **9** and chloride anion in CD_3CN .

Fig. 3 ^1H NMR titration curve for compound **9** and bromide anion in CD_3CN . $[\mathbf{9}] = 2.0 \times 10^{-3}$ M. $[\text{Br}^-] = 0 - 39.4 \times 10^{-3}$ M. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 4 ^1H NMR titration curve for compound **9** and hydrogen sulfate ion in CD_3CN . $[\mathbf{9}] = 2.0 \times 10^{-3}$ M. $[\text{HSO}_4^-] = 0 - 39.4 \times 10^{-3}$ M. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 5 ^1H NMR titration curve for compound **10** and chloride anion in CD_3CN . $[\mathbf{10}] = 2.0 \times 10^{-3}$ M. $[\text{Cl}^-] = 0 - 44.0 \times 10^{-3}$ M. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 6 ^1H NMR titration curve for compound **10** and bromide anion in CD_3CN . $[\mathbf{10}] = 2.0 \times 10^{-3}$ M. $[\text{Br}^-] = 0 - 39.4 \times 10^{-3}$ M. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 7 ^1H NMR titration curve for compound **10** and hydrogen sulfate ion in CD_3CN . $[\mathbf{10}] = 2.0 \times 10^{-3}$ M. $[\text{HSO}_4^-] = 0 - 36.9 \times 10^{-3}$ M. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 8 ^1H NMR titration curve for compound **10** and benzoate ion in CD_3CN . $[\mathbf{10}] = 2.0 \times 10^{-3}$ M. $[\text{PhCO}_2^-] = 0 - 39.4 \times 10^{-3}$ M. No reliable binding constant could be obtained from this titration curve.

Fig. 9 ^1H NMR titration curve for compound **4** and bromide anion in CD_3CN . $[\mathbf{4}] = 2.0 \times 10^{-3}$ M. $[\text{Br}^-] = 0 - 37.0 \times 10^{-3}$ M. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 10 ^1H NMR titration curve for compound **4** and hydrogen sulfate ion in CD_3CN . $[\mathbf{4}] = 2.0 \times 10^{-3}$ M. $[\text{HSO}_4^-] = 0 - 39.2 \times 10^{-3}$ M. The curve shows the fit of the experimental data to a 1:1 binding profile.

References:

1. Wilcox, C. S. in *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H. J., Dürr, H., Eds.; VCH: Weinheim, **1991**.

III. ITC titration studies

Microcalorimetric titration (experimental temperature: 30 °C) was performed using an isothermal titration calorimeter (ITC) purchased from Microcal Inc., MA. The ORIGIN software provided by Microcal Inc. was used to calculate the biniding constant (K_a) and the enthalpy change (ΔH). CH_3CN was HPLC grade (Fisher) and not otherwise dried before use.

Fig. 11 ITC titration curves produced from the titration of compound **9** (1 mM) with chloride anion (34.2 mM) in CH_3CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 12 ITC titration curves produced from the titration of compound **9** (0.1 mM) with benzoate ion (3.1 mM) in CH_3CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 13 ITC titration curves produced from the titration of compound **9** (0.1 mM) with acetate ion (3.7 mM) in CH₃CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 14 ITC titration curves produced from the titration of compound **10** (1 mM) with chloride anion (34.2 mM) in CH₃CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 15 ITC titration curves produced from the titration of compound **10** (0.1 mM) with benzoate ion (3.4 mM) in CH₃CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 16 ITC titration curves produced from the titration of compound **10** (0.1 mM) with acetate ion (2.9 mM) in CH₃CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 17 ITC titration curves produced from the titration of compound **1** (0.1 mM) with benzoate ion (2.9 mM) in CH₃CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 18 ITC titration curves produced from the titration of compound **1** (0.17 mM) with acetate ion (2.78 mM) in CH₃CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 19 ITC titration curves produced from the titration of compound **2** (0.11 mM) with benzoate ion (2.92 mM) in CH_3CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 20 ITC titration curves produced from the titration of compound **4** (0.99 mM) with chloride anion (26.4 mM) in CH_3CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 21 ITC titration curves produced from the titration of compound **4** (0.5 mM) with benzoate ion (15.9 mM) in CH₃CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

Fig. 22 ITC titration curves produced from the titration of compound **4** (0.21 mM) with acetate ion (6 mM) in CH₃CN at 30 °C. The curve shows the fit of the experimental data to a 1:1 binding profile.

IV. X-ray experimental section

X-ray experimental for C₃₆H₄₀N₄O₂ (**9**): Crystals grew as grey lathes by vapor diffusion of hexanes into a chloroform solution of **9**. The data crystal was cut from a long lathe and had approximate dimensions; 0.20 x 0.17 x 0.17 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoK α radiation ($\lambda = 0.71073\text{\AA}$). A total of 360 frames of data were collected using ω -scans with a scan range of 1° and a counting time of 151 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Data reduction were performed using DENZO-SMN.¹ The structure was solved by direct methods using SIR97² and refined by full-matrix least-squares on F² with anisotropic displacement parameters for the non-H atoms using SHELXL-97.³ The hydrogen atom positions were observed in a ΔF map and refined with isotropic displacement parameters.

The function, $\sum w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.019*P)^2 + (1.5031*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.136, with $R(F)$ equal to 0.0946 and a goodness of fit, S , = 1.20. Definitions used for calculating $R(F)$, $R_w(F^2)$ and the goodness of fit, S , are given below.⁴ The data were corrected for secondary extinction effects. The correction takes the form: $F_{\text{corr}} = kF_c/[1 + (8(2)\times 10^{-6}) * F_c^2 \lambda^3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).⁵ Figures 23 (atom labeling scheme) and 24 (unit cell packing diagram) were generated using SHELXTL/PC.⁶

Crystal data and structure refinement for 9:

Empirical formula	C ₃₆ H ₄₀ N ₄ O ₂	
Formula weight	560.72	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2 ₁ /c	
Unit cell dimensions	a = 10.60460(10) Å	α = 90°.
	b = 18.4424(4) Å	β = 107.2090(10)°.
	c = 7.9205(2) Å	γ = 90°.
Volume	1479.70(5) Å ³	
Z	2	
Density (calculated)	1.258 Mg/m ³	
Absorption coefficient	0.079 mm ⁻¹	
F(000)	600	
Crystal size	0.20 x 0.17 x 0.17 mm	
Theta range for data collection	2.91 to 27.50°.	
Index ranges	-13 ≤ h ≤ 13, -22 ≤ k ≤ 23, -10 ≤ l ≤ 10	
Reflections collected	6179	
Independent reflections	3392 [R(int) = 0.0540]	
Completeness to theta = 27.50°	99.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F ²	

Data / restraints / parameters	3392 / 0 / 271
Goodness-of-fit on F^2	1.198
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0946$, $wR2 = 0.1249$
R indices (all data)	$R1 = 0.1372$, $wR2 = 0.1356$
Extinction coefficient	$8(2) \times 10^{-6}$
Largest diff. peak and hole	0.249 and $-0.229 \text{ e. \AA}^{-3}$

Figure 23. View of **9** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. The molecule lies around a crystallographic inversion center at $\frac{1}{2}, \frac{1}{2}, \frac{1}{2}$. Atoms with labels appended by a ' are related by $1-x, 1-y, 1-z$.

Figure 24. Unit cell packing diagram for **9**. The view is approximately down the **a** axis.

X-ray Experimental for $C_{36}H_{40}N_4S_2 \cdot 2C_4H_8O$ (**10**•2THF): Crystals grew as faint yellow prisms by slow diffusion of H_2O and MeOH into a THF solution of **10**. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with $MoK\alpha$ radiation ($\lambda = 0.71073\text{\AA}$). A total of 207 frames of data were collected using ω -scans with a scan range of 2° and a counting time of 326 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Data reduction were performed using DENZO-SMN.¹ The structure was solved by direct methods using SIR97² and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.³ The hydrogen atoms were calculated in ideal positions with isotropic displacement parameters set to $1.2 \times U_{eq}$ of the attached atom ($1.5 \times U_{eq}$ for methyl hydrogen atoms).

The function, $\sum w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.02 \cdot P)^2]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.188, with $R(F)$ equal to 0.123 and a goodness of fit, S , = 3.37. Definitions used for calculating $R(F)$, $R_w(F^2)$ and the goodness of fit, S , are given below.⁴ The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).⁵ Figures 25 (atom labeling scheme) and 26 (unit cell packing diagram) were generated using SHELXTL/PC.⁶

Crystal data and structure refinement for 10•2THF:

Empirical formula	C ₄₄ H ₅₆ N ₄ O ₂ S ₂	
Formula weight	737.05	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2 ₁ /n	
Unit cell dimensions	a = 10.0674(3) Å	α = 90°.
	b = 20.8027(5) Å	β = 97.053(1)°.
	c = 19.2138(6) Å	γ = 90°.
Volume	3993.5(2) Å ³	
Z	4	
Density (calculated)	1.226 Mg/m ³	
Absorption coefficient	0.175 mm ⁻¹	
F(000)	1584	
Crystal size	0.26 x 0.21 x 0.21 mm	
Theta range for data collection	2.93 to 25.00°.	
Index ranges	-11 ≤ h ≤ 11, -23 ≤ k ≤ 24, -22 ≤ l ≤ 22	
Reflections collected	12651	
Independent reflections	6996 [R(int) = 0.0373]	
Completeness to theta = 25.00°	99.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F ²	

Data / restraints / parameters	6996 / 138 / 522
Goodness-of-fit on F^2	3.072
Final R indices [$I > 2\sigma(I)$]	R1 = 0.1223, wR2 = 0.1846
R indices (all data)	R1 = 0.1571, wR2 = 0.1885
Largest diff. peak and hole	0.724 and -0.418 e.Å ⁻³

Fig. 25 View of complex of **10** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 30% probability level. Most hydrogen atoms have been removed for clarity. Dashed lines are indicative of H-bonding interactions. The complex lies around a crystallographic inversion center at $\frac{1}{2}, \frac{1}{2}, \frac{1}{2}$.

Fig. 26 Unit cell packing diagram for **10•2THF**. The view is approximately down the **a** axis. Dashed lines are indicative of the H-bonding interactions between the THF molecules and the pyrrole NH moieties.

References:

- 1) Otwinowski, Z.; Minor, W. In *DENZO-SMN., Methods in Enzymology*, **276**: Macromolecular Crystallography, part A, 307 – 326, Carter, Jr., C. W., Sweets, R. M., Eds.; Academic Press **1997**.
- 2) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. SIR97. A program for crystal structure solution. *J. Appl. Cryst.* **1999**, 32, 115-119.
- 3) Sheldrick, G. M. SHELXL97. *Program for the Refinement of Crystal Structures*. **1994**; University of Gottingen, Germany.
- 4) $R_w(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2 / \Sigma w(|F_o|^4)\}^{1/2}$ where w is the weight given each reflection.
 $R(F) = \Sigma(|F_o| - |F_c|) / \Sigma |F_o|$ for reflections with $F_o > 4(\sigma(F_o))$.
 $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2 / (n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.
- 5) International Tables for X-ray Crystallography. Vol. C, Tables 4.2.6.8 and 6.1.1.4, Wilson, A. J. C., Eds.; Boston: Kluwer Academic Press, **1992**.
- 6) Sheldrick, G. M. SHELXTL/PC (Version 5.03), **1994**. Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.