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Calix[4]pyrroles with Long Alkyl Chains: Synthesis, Characterization, and Anion Binding Studies

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Calix[4]pyrrole derivatives bearing long n-alkyl ester chains have been synthesized from calix[4]pyrroles containing carboxylic acid functional groups. These systems, which contain ester groups on either the *meso*- carbon atoms of the calixpyrrole ring or the *β*-positions of individual pyrrole rings, were prepared from the corresponding carboxylic acids. Esterification was effected using dicyclohexylcarbodiimide/4-dimethylaminopyridine (DCC/DMAP) to obtain long alkyl chain substituted calix[4]pyrroles. In the context of this work, several brominated calixpyrrole derivatives were prepared using N-bromosuccinimide (NBS) as the brominating agent. Anion binding studies carried out by isothermal titration calorimetry (ITC) in 1,2-dichloroethane with Cl^- and $CH_3CO_2^-$ in the form of their respective tetrabutylammonium salts, revealed that the functionalized ester derivatives have anion binding affinities similar to those of the unsubstituted "parent" systems, octamethylcalix[4]pyrrole (1) and *β*-octabromocalix[4]pyrrole (2). The new alkylated systems proved soluble in nonpolar solvents, such as hexanes. Structure identification studies, carried out by single crystal X-ray diffraction analyses, revealed that the control ester system 4 contains two unique crystal structures per asymmetric unit. These asymmetric units interact via intermolecular hydrogen bonds in the solid state to produce a continuous intermolecular structure. Such interactions are not present in the case of the corresponding brominated ester 5.

Keywords: Calix[4]pyrrole; Anions; Hydrogen bonding; Receptors

INTRODUCTION

The area of anion recognition represents an emerging area of supramolecular chemistry whose impact in such disparate areas as biomedicine [1–3] and environmental chemistry [4–6] is becoming increasingly appreciated. Anions are ubiquitous in biological systems [7] and play important roles in regulating human health [8]. Their particular importance in the nuclear fuel cycle, is also well recognized [9]. In addition, anion receptors can be used as ion-selective receptors [10], phase-transfer catalysis, anion-selective optical sensors [11,12]. Moreover, chromatographic separation systems have been generated by attaching receptors to an appropriate stationary phase [13]. These and other practical considerations have led to spectacular growth within the anion recognition field. However, the weak nature of most anion–receptor interactions, particularly in the case of neutral anion receptor systems, reflecting the relatively low charge density of most anions [14], makes the design of selective and effective receptors one of ongoing challenge. Thus, while a number of research groups have designed elegant anion receptors, many of which have proven to be quite effective, there remains a need for simple, easy-to-make anion binding systems. In this context, the so-called calix[4]pyrroles have emerged as molecules of particular interest [13]. This is because the core structure may be accessed in one synthetic step and a large number of modifications are readily conceivable. In fact, to date, simple *meso*-alkyl substituted (**1**), halogenated (**2**) [15], C-Rim modified (**3**) [16], photoactive and chromophore-modified [10], strapped [17], ditopic [18], expanded [19], N-confused [20–22], and polyfunctional [23] calixpyrrole derivatives have been reported. Several of these functionalized systems are shown in Schemes 1 and 2. In this paper we detail the synthesis and structural characterization of a new set of highly

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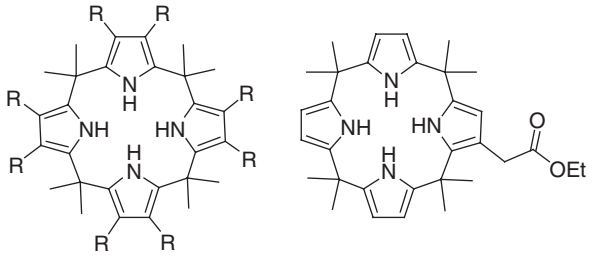


1. R=H
2. R=Br

3

SCHEME 1 Calix[4]pyrrole derivatives.

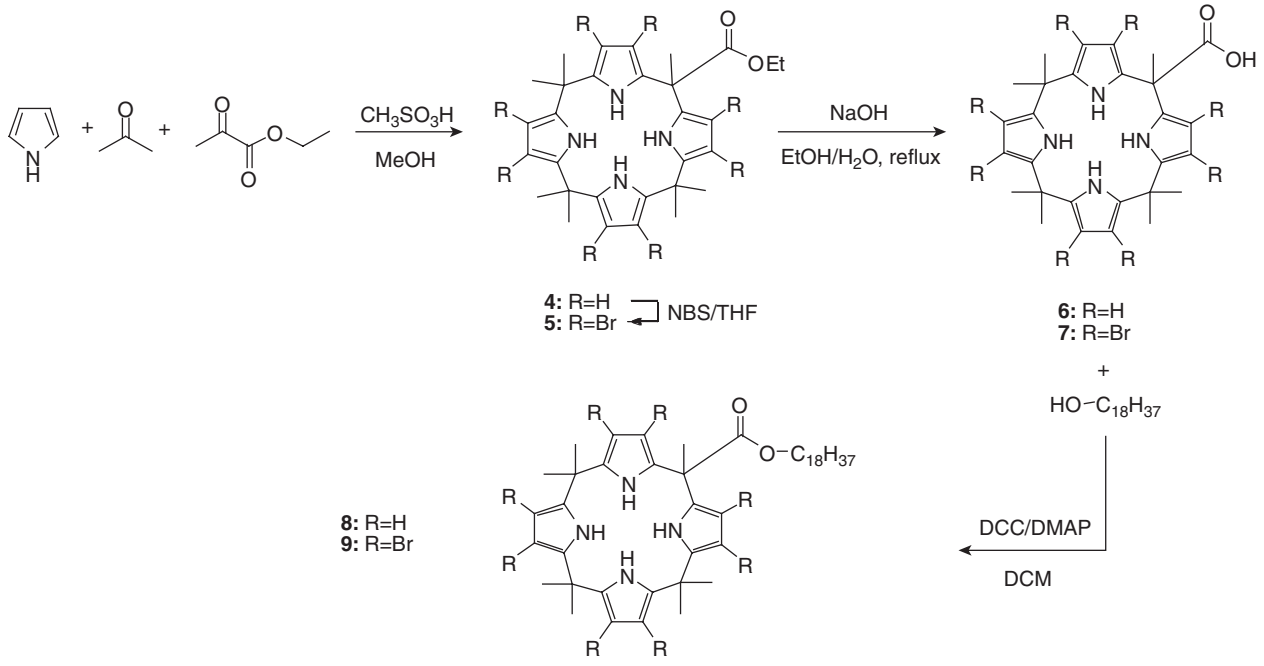
organic solubilized calixpyrroles, along with a summary of their chloride and acetate anion binding properties as determined by ITC measurements carried out in 1,2-dichloroethane.

The present study was motivated by a desire to obtain calixpyrroles that would not partition significantly into water when studied under potential interfacial conditions. Specifically, it grew out of an appreciation that certain calix[4]pyrroles could be used to reverse the so-called Hofmeister bias [24–26] and were thus potentially useful as anion extractants. Anion extraction is an application that could be of use both in the nuclear processing industry [24–26] and in terms of obtaining systems that could be used in such recognized environmental applications as minimizing surface water eutrophication resulting from agricultural runoff [27]. Highly organic soluble calixpyrrole derivatives are also potentially useful as through-membrane chloride anion carriers, an application that might have implications in the treatment of cystic fibrosis [28,29]. As a first step towards these long term goals, we sought to develop long chain n-alkyl ester modified, *meso*- and β-pyrrole functionalized calix[4]pyrroles bearing either hydrogen or bromine atoms in the β-pyrrolic positions that would prove soluble in nonpolar organic solvents. We also felt it necessary to test whether the modifications in question, including β-pyrrole bromination, affected the inherent anion recognition properties of the parent calix[4]pyrrole core. Towards this end, we have prepared the new ester-substituted systems **8**, **9**, **12**, and **13** (cf. Schemes 2 and 3) and analyzed their chloride and acetate anion binding properties, as well as for the first time those of the control system **2**, by ITC in 1,2-dichloroethane. We also report single crystal X-ray structures for the control ester systems **4** and **5**.

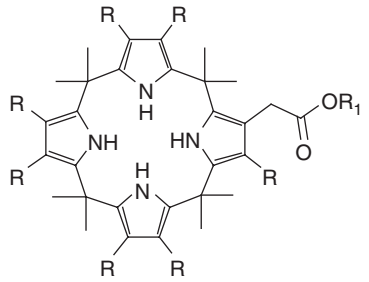
EXPERIMENTAL SECTION

General

Melting points were measured on a Mel-Temp II instrument and are uncorrected. Proton and ^{13}C-NMR spectra used in the characterization of products were recorded on Varian Unity 300 and 400 MHz spectrometers. Low-resolution FAB and CI mass spectra were obtained on a Finningan MAT TSQ 70 mass spectrometer. High resolution FAB and CI mass spectra were obtained on a VG ZAB2-E mass spectrometer.



SCHEME 2 Synthesis of *meso*-functionalized calix[4]pyrrole n-alkyl esters.



10: R=H, R_1=H
11: R=Br, R_1=Et
12: R=H, R_1=$C_{18}H_{37}$
13: R=Br, R_1=$C_{18}H_{37}$

SCHEME 3 C-Rim functionalized calix[4]pyrrole n-alkyl esters.

Materials

Tetrabutylammonium chloride (TBA-Cl) and tetrabutylammonium acetate (TBA-OAc) were dried under vacuum at 40°C for 24 h before use. All solvents were dried before use according to standard literature procedures. Unless specifically indicated, all other chemicals and reagents used in this study were purchased from commercial sources and used as received.

Synthesis of Mono Substituted Calix[4]pyrroles

Compound 4

Pyrrole (3 mL, 42 mmol) and ethyl pyruvate (1.15 mL, 10 mmol) were dissolved in methanol (50 mL) at 0°C and bubbled with Ar for 10 minutes. Acetone (2.34 mL, 30 mmol) was then added to the mixture. Following this addition, methanesulfonic acid (1.95 mL) was added drop-wise over the course of 10 minutes while shielding the reaction vessel from light. The mixture was then stirred first at 0°C for 3 hours and subsequently at room temperature overnight. The white precipitate that formed during this time was collected by filtration. Chromatographic purification (silica gel, dichloromethane/hexanes: 80/20) yielded calixpyrrole **4** as a yellow solid (0.7 g, 14%). M.p. decomposes over 200°C; ^{1}H NMR (300 MHz, [D_1]chloroform, 25°C): δ = 1.28 (t, J = 7.2 Hz, 3H; ester CH_3), 1.49–1.51 (m, 18H; *meso* CH_3), 1.72 (s, 3H; *meso* CH_3), 4.21 (q, J = 7.2 Hz, 2H; ester CH_2), 5.89–5.93 (m, 8H; pyrrole CH), 7.169 (br. s, 2H; pyrrole NH), 7.49 ppm (br. s, 2H; pyrrole NH); ^{13}C NMR (75 MHz, [D_1]chloroform, 25°C): δ = 14.11, 25.07, 28.26, 29.00, 29.36, 29.68, 35.20, 35.27, 47.31, 61.58, 102.80, 103.03, 103.12, 104.98, 131.76, 138.20, 138.63, 139.18, 167.12 ppm; LRMS (FAB MS): m/z [M^+]: 486; HRMS (FAB MS): m/z calcd for $C_{30}H_{38}N_4O_2$ [M^+]: 486.2995; found: 486.2997.

Compound 5

Calixpyrrole **4** (0.46 g, 0.95 mmol) and NBS (1.35 g, 7.6 mmol) were dissolved in dry THF (50 mL) under an Ar atmosphere with the reaction vessel shielded from light. The mixture was heated at reflux for 5 h and allowed to cool to room temperature. The solvent was removed under vacuum and the resulting solid purified by flash column chromatography (silica gel, dichloromethane/hexanes: 1/1) to afford **5** in the form of a white solid (0.96 g, 90%). M.p. decomposes over 160°C; ^{1}H NMR (400 MHz, [D_1]chloroform, 25°C): δ = 1.35 (t, J = 7.2 Hz, 3H; ester CH_3), 1.69–2.139 (21H; *meso* CH_3), 4.31 ppm (q, J = 7.2 Hz, 2H; ester CH_2), NH protons were not observed at room temperature; ^{13}C NMR (100 MHz, [D_1]chloroform, 25°C): δ = 25.25, 37.87, 46.41, 49.02, 51.09, 63.02, 64.72, 130.29, 161.07, 192.3 ppm; LRMS (FAB MS): m/z [M^+] 1117; HRMS (FAB MS): m/z calcd for $C_{30}H_{30}$ $Br_8N_4O_2$ [M^+]: 1117.5754; found: 1117.5762.

Compound 6

Calixpyrrole **4** (1.11 g, 2.28 mmol) was dissolved in 80 mL EtOH and heated to reflux under an Ar atmosphere. Once reflux was established, NaOH (0.3 g, 7.7 mmol in 50 mL H_2O) was added drop-wise. Heating at reflux was then continued for 5 h, after which the mixture was allowed to cool to room temperature. The bulk of the volatiles were then removed under vacuum. The remaining, largely aqueous solution was acidified with HCl (0.2 M) until a white precipitate was obtained. This precipitate, corresponding to product **6** (0.95 g, 91%), was collected by filtration and dried under reduced pressure. M.p. decomposes over 190°C; ^{1}H NMR (300 MHz, [D_1]chloroform, 25°C): δ = 1.52–1.54 (m, 18H; *meso* CH_3), 1.76 (s, 3H; *meso* CH_3), 5.92–6.01 (m, 8H; pyrrole CH), 7.11 (br. s, 2H, pyrrole NH), 7.42 ppm (br. s, 2H; pyrrole NH); ^{13}C NMR (75 MHz, [D_1]chloroform, 25°C): δ = 25.00, 28.31, 29.05, 29.37, 29.51, 35.15, 35.26, 47.23, 102.79, 103.19, 103.33, 105.52, 130.77, 137.96, 138.58, 139.47, 178.61 ppm; LRMS (FAB MS): m/z [M^+] 458; HRMS (FAB MS): m/z calcd for $C_{28}H_{34}N_4O_2$ [M^+]: 458.2682; found: 458.2690.

Compound 7

This compound was prepared from **5** (0.86 g, 0.77 mmol) using the same procedure used to produce **6**. The product was a white solid (0.71 g, 85%). M.p. decomposes over 170°C; ^{1}H NMR (300 MHz, [D_1]chloroform, 25°C): δ = 0.86–2.16 ppm (21H; *meso* CH_3), NH protons were not observed at room temperature; ^{13}C NMR (75 MHz, [D_1] chloroform, 25°C): δ = 14.36, 24.58, 29.47, 35.60,

47.55, 61.83, 63.397, 103.54, 103.62, 105.31, 132.18, 139.27, 172.94 ppm; LRMS (FAB MS): m/z [M^+] 1090; HRMS (FAB MS): m/z calcd for $C_{28}H_{26}N_4O_2$ [M^+]: 1089.5441; found: 1089.5450.

Compound 10

This compound was prepared from **3** (0.23 g, 0.45 mmol) using the same procedure used to produce **6**. The product was a white solid (0.2 g, 93%). M.p. decomposes over 180°C; ^{1}H NMR (300 MHz, [D_1]chloroform, 25°C): δ = 1.48–1.59 (24H; *meso* CH_3), 3.71 (s, 2H; CH_2), 5.75–5.92 (br. m, 7H; pyrrole CH), 6.96 (s, 2H; pyrrole NH), 7.16 (s, 1H; pyrrole NH), 7.78 ppm (s, 1H; pyrrole NH); ^{13}C NMR (75 MHz, [D_1]chloroform, 25°C): δ = 28.81, 29.03, 29.13, 33.35, 34.95, 35.10, 35.20, 36.78, 101.78, 102.24, 102.58, 102.77, 106.72, 108.67, 133.48, 136.96, 138.02, 138.12, 138.56, 138.88, 139.43, 178.96 ppm; LRMS (CI): m/z [M^+] 487; HRMS (FAB MS): m/z calcd for $C_{30}H_{38}N_4O_2$ [M^+]: 486.6483; found: 486.6492.

Compound 11

This compound was prepared from **3** (0.5 g, 0.97 mmol) using the same procedure used to produce **5**. The product was a white solid (0.92 g, 89%). M.p. decomposes over 180°C; ^{1}H NMR (400 MHz, [D_1]chloroform, 25°C): δ = 0.88 (t, J = 7.2 Hz, 3H; ester CH_3), 1.24–1.82 (m, 24H; *meso* CH_3), 3.35 (s, 2H; CH_2), 4.09 (q, J = 7.2 Hz, 3H; ester CH_2), 6.64 (s, 1H; pyrrole NH), 6.79 (s, 1H; pyrrole NH), 7.95 (s, 1H; pyrrole NH), 8.48 ppm (s, 1H; pyrrole NH); ^{13}C NMR (75 MHz, [D_1] chloroform, 25°C): δ = 14.12, 26.06, 37.48, 37.75, 37.93, 38.28, 49.68, 94.16, 96.08, 99.94, 100.52, 110.41, 130.41, 190.38 ppm; LRMS (CI): m/z [M^+] 1067; HRMS (FAB MS): m/z calcd for $C_{32}H_{35}Br_7N_4O_2$ [M^+]: 1065.6982; found: 1065.6990.

Synthesis of Long Alkyl Chain Substituted Calix[4]pyrroles

Compound 8

Acid **6** (100 mg, 0.22 mmol), 1-octadecanol (65 mg, 0.24 mmol), and 4-dimethylaminopyridine (DMAP) (2.7 mg, 0.022 mmol) were dissolved in 4 mL dichloromethane under an Ar atmosphere. At this point, dicyclohexylcarbodiimide (DCC) (45.4 mg, 0.22 mmol) mixed in 1 mL dichloromethane was added to the mixture. The reaction mixture stirred for 24 h and the insoluble matter was filtrated off. The resulting filtrate was collected and was washed with first 0.5 N HCl (10 mL), followed by saturated $NaHCO_3$ (10 mL), and then finally water (10 mL). The organic layer was then dried over Na_2SO_4 and the solvent was removed under vacuum. Column chromatography (silica gel, dichloromethane/hexanes: 80/20) afforded **8** in the form of a yellowish solid (79.8 mg, 51%). M.p. 65°C; ^{1}H NMR (400 MHz, [D_1]chloroform, 25°C): δ = 0.88 (t, J = 6.9 Hz, 3H; long alkyl tail CH_3), 1.6 (br. s, 28H; long alkyl tail CH_2), 1.51–1.53 (br. m, 18H; *meso* CH_3), 1.61–1.65 (br. m, 2H; long alkyl tail CH_2), 1.75 (s, 3H; *meso* CH_3), 2.17 (m, 2H; long alkyl tail CH_2), 4.14 (t, J = 6.9 Hz, 2H; long tail CH_2), 5.90–5.94 (m, 8H; pyrrole CH), 7.07 (br. s, 2H; pyrrole NH), 7.42 (br. s, 2H; pyrrole NH); ^{13}C NMR (75 MHz, [D_1]chloroform, 25°C): δ = 14.11, 22.68, 25.01, 25.87, 28.28, 28.50, 28.97, 29.19, 29.30, 29.48, 29.57, 29.69, 31.90, 35.15, 35.23, 47.30, 54.14, 65.77, 102.82, 103.04, 103.13, 104.98, 131.75, 138.11, 138.49, 139.06, 172.84 ppm; LRMS (CI): m/z [M^+] 711; HRMS (FAB MS): m/z calcd for $C_{46}H_{70}N_4O_2$ [M^+]: 711.5499; found: 711.4483.

Compound 9

This compound was prepared from **7** (180 mg, 0.16 mmol) using a procedure analogous to that used to prepare **8**. The product was a white solid (0.16 g, 72%). M.p. 75°C; ^{1}H NMR (300 MHz, [D_1] chloroform, 25°C): δ = 0.88–5.46 (m, 58H; long alkyl tail CH_3, CH_2 and *meso* CH_3), 6.74 (br. s, 2H; pyrrole NH), 8.04 (br. s, 1H; pyrrole NH), 11.81 (br. s, 1H; pyrrole NH); ^{13}C NMR (75 MHz, [D_1]chloroform, 25°C): δ = 14.34, 23.16, 25.43, 27.18, 28.35, 28.82, 29.32, 29.41, 29.54, 29.65, 29.78, 32.49, 36.14, 37.46, 49.40, 57.73, 67.12, 103.63, 104.11, 104.19, 105.67, 135.46, 141.13, 143.82, 144.19, 174.54 ppm; LRMS (FAB): m/z [M^+] 1342; HRMS (FAB MS): m/z calcd for $C_{46}H_{62}Br_8N_4O_2$ [M^+]: 1342.24208; found: 1342.24251.

Compound 12

This compound was prepared from **10** (100 mg, 0.2 mmol) using a procedure analogous to that used to prepare **8**. The product was a white solid (110.8 mg, 75%). M.p. 70°C; ^{1}H NMR (400 MHz, [D_1]chloroform, 25°C): δ = 0.91 (t, J = 6.8 Hz, 3H; long alkyl tail CH_3), 1.29 (br. s, 28H; long alkyl tail CH_2), 1.49–1.58 (br. m, 24H; *meso* CH_3), 1.66–1.69 (br. m, 4H; long alkyl tail CH_2), 3.64 (s, 2H; CH_2), 4.15 (t, J = 6.8 Hz, 2H; long alkyl tail CH_2), 5.71–5.94 (m, 7H; pyrrole CH), 7.96 (d, 2H; pyrrole NH), 7.09 (br. s, 1H; pyrrole NH), 8.49 ppm (br. s, 1H; pyrrole NH); ^{13}C NMR (100 MHz, [D_1]chloroform, 25°C): δ = 14.10, 22.67, 25.93, 28.55, 28.61, 28.87, 29.24, 29.34, 29.53, 29.57, 29.63, 29.68, 31.90, 34.86, 35.11, 35.18, 36.72, 38.34, 65.15, 101.02, 101.94, 102.29, 102.42, 102.72, 103.09, 106.61, 109.42, 133.52, 136.73, 137.35, 137.88, 138.36, 138.96, 139.47, 139.88 ppm; LRMS (CI): m/z [M^-] 739; HRMS (FAB MS): m/z calcd for $C_{46}H_{70}N_4O_2$ [M^+] 739.5890; found: 739.5858.

Compound 13

This compound was prepared from **12** (68 mg, 0.09 mmol) using a procedure analogous to that used to produce **5**. The product was a white solid (106.9 mg, 90%). M.p. 92°C; ^{1}H NMR (300 MHz, [D_1]chloroform, 25°C): δ = 0.88 (t, J = 6.9 Hz, 3H; long alkyl tail CH_3), 1.26 (br. s, 28H; long alkyl tail CH_2), 1.59 (br. m, 4H; long alkyl tail CH_2), 1.71–1.83 (br. m, 24H; *meso*-CH_3), 3.35 (s, 2H; CH_2), 4.00 (br. t, J = 6.9 Hz, 2H; long alkyl tail CH_2), 6.64 (s, 1H; pyrrole NH), 6.79 (s, 1H; pyrrole NH), 7.95 (s, 1H; pyrrole NH), 8.48 ppm (s, 1H; pyrrole NH); ^{13}C NMR (75 MHz, [D_1]chloroform, 25°C): δ = 14.12, 22.68, 25.88, 27.28, 28.52, 29.64, 29.69, 31.41, 31.91, 37.48, 37.73, 37.93, 38.28, 65.18, 95.39, 95.87, 96.07, 96.43, 99.82, 99.93, 100.51, 129.91, 129.97, 130.37, 131.10, 131.34, 131.85, 171.84; LRMS (FAB MS): m/z [M^+] 1290; HRMS (FAB MS): m/z calcd for $C_{48}H_{67}Br_7N_4O_2$ [M^+] 1290.9564; found: 1290.9576.

RESULTS AND DISCUSSION

Synthesis and Crystal Structures

Although a large number of approaches leading to highly organic solvent soluble calix[4]pyrroles can be conceived, one of the more attractive strategies involves the use of long n-alkyl esters as the key solubilizing substituent. Such systems can be obtained from calix[4]pyrroles bearing carboxylic acids and/or smaller ester substituents in either the *meso*- and β-positions. Over the last decade, we have developed several syntheses of monofunctional calix[4]pyrrole carboxylic acids and esters and have recently extended these efforts to prepare polyfunctional calix[4]pyrroles containing carboxylic acid and ester functional groups [23]. We have also reported the synthesis of β-pyrrole brominated calixpyrroles, including **2**, generated from the corresponding hydrido systems, but as yet have not extended this chemistry into the corresponding ester or carboxylic acid functionalized series. Given this, our synthetic goal was not only to produce long n-alkyl chain esters of carboxy-functionalized calix pyrroles, but also to develop methods for obtaining the corresponding β-pyrrole brominated systems, either by effecting bromination at an early stage and carrying the product through the remaining synthetic steps or by brominating after the final esterification. In point of fact, both of these latter strategies were pursued.

In this study, we wish to present long alkyl chain substituted calix[4]pyrroles starting from basic and readily available calix[4]pyrrole compounds (e.g., **1**, **3** and **4**). Synthesis and binding results of **1**, **2** and **3** have been reported in previous publications. We have selected the esterification of the carboxylic acid containing calix[4]pyrroles (**6**, **7** and **10**) for the synthesis of long alkyl chain substituted compounds which are soluble in nonpolar solvents (e.g., hexane and pentane). We also wish to report the results of anion binding studies carried out by ITC.

Schemes 3 and 4 provide a summary of the new preparative chemistry presented in this report. It reveals that the key organic solubilization step involves the esterification of compounds **6**, **7**, and **10**. These systems, in turn, were prepared from the simpler ester systems **3**, **4**, and **5**. The synthesis of the key starting material **3** has been reported earlier [16,30,31], whereas the mono ester substituted calix[4]pyrrole **4** was prepared from the mixed condensation reaction of acetone and requisite ketoester using the same strategy used previously to generate polyfunctional calix[4]pyrroles [23]. Bromination of **4** with NBS proved just as effective as in the case of **1** (yielding **2** as the product) and allowed for the isolation of the hepta bromine-functionalized calix[4]-pyrrole **5** in 90% yield. Using this same brominating agent, compounds **11** and **13** were obtained in an analogous manner starting from **3** and **12**, respectively. Hydrolysis of the ester compounds **3**, **4**, and **5** under basic conditions in an ethanol/water mixture provided **10**, **6** and **7**, respectively.

The actual attachment of the long n-alkyl ester chains to the carboxylic acid substituted calix[4]pyrroles (**6**, **7** and **10)** was carried out using dicyclohexylcarbodiimide/4-dimethylaminopyridine (DCC/DMAP) in dichloromethane. This provided **8**, **9**, and **12** in good yield. Unfortunately, compound **11** was found to decompose under the conditions of ester hydrolysis conditions applied to **4** and **5**. However, as noted above, we were able to prepare compound **13** via direct bromination of **12**. Thus, both the initial, and "post-synthetic modification" bromination strategies had to be employed to obtain the final ester functionalized perbrominated products **9** and **13**.

Characterization of all the new compounds was carried out using ^{1}H and ^{13}C NMR spectroscopy, as well as low resolution (LRMS) and high resolution mass spectrometry (HRMS). Compounds **4** and **5** were also characterized by X-ray diffraction analysis. Single crystals of **4** were grown by slow evaporation of a solution of **4** in dichloromethane and diethyl ether. X-ray structural analysis of this compound revealed that the molecule has two crystallographically unique molecules, designated **4a** and **4b**, per asymmetric unit (Figs. 1 and 2). Both unique molecules adopt 1,3-alternate conformations as is true in general for the anion-free forms of simple calix[4]pyrroles [32]. The ester group of structure **4a** is found to be tilted out of the plane defined by C15—C5—C21 with a torsion angle of 125.55° while in molecule **4b** the corresponding angle is 136.38° (as defined by C15′—C5′—C21′).

In the case of both structures, the individual calix[4]pyrrole units interact with one another via

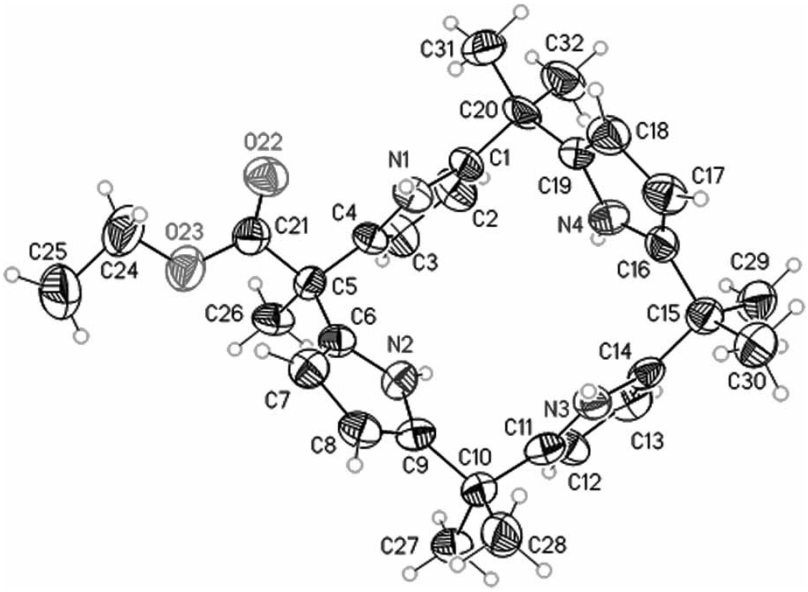


FIGURE 1 View of the molecule in **4a** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

H-bonding (Fig. 3). The geometry of these interactions are: N3···H3N···O22′; N···O 3.344(6) Å, H···O 2.46 Å, N—H···O 168°; N1′-H1′N···O22, N···O 3.068(6)Å, H···O 2.17 Å, and N—H···O 176°. These interactions create a one by one continuous crystal series of two unique crystals.

Solution ^{1}H-NMR studies spectroscopic studies were carried out to see if these interactions are maintained in $CDCl_3$ solution. Both dilution and low temperature measurements were made. However, no appreciable shifts in the NH proton (or other) signals were observed in any of these experiments. It is thus concluded that the intermolecular interactions observed under the conditions of the X-ray diffraction analysis are a particular feature of the solid state.

Diffraction grade crystals of **5** were obtained by slow evaporation of a dichloromethane/diethyl ether solution. X-ray analysis of **5** revealed that compound **5**, in spite of the bulky bromine units on the β-positions of pyrrole rings, adopts

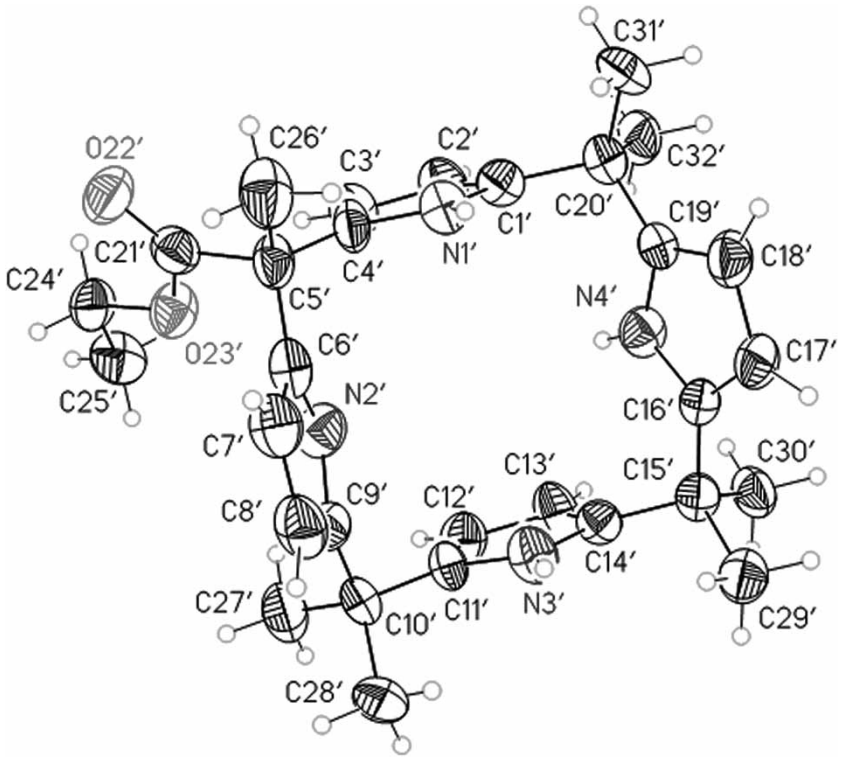


FIGURE 2 View of the molecule in **4b** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

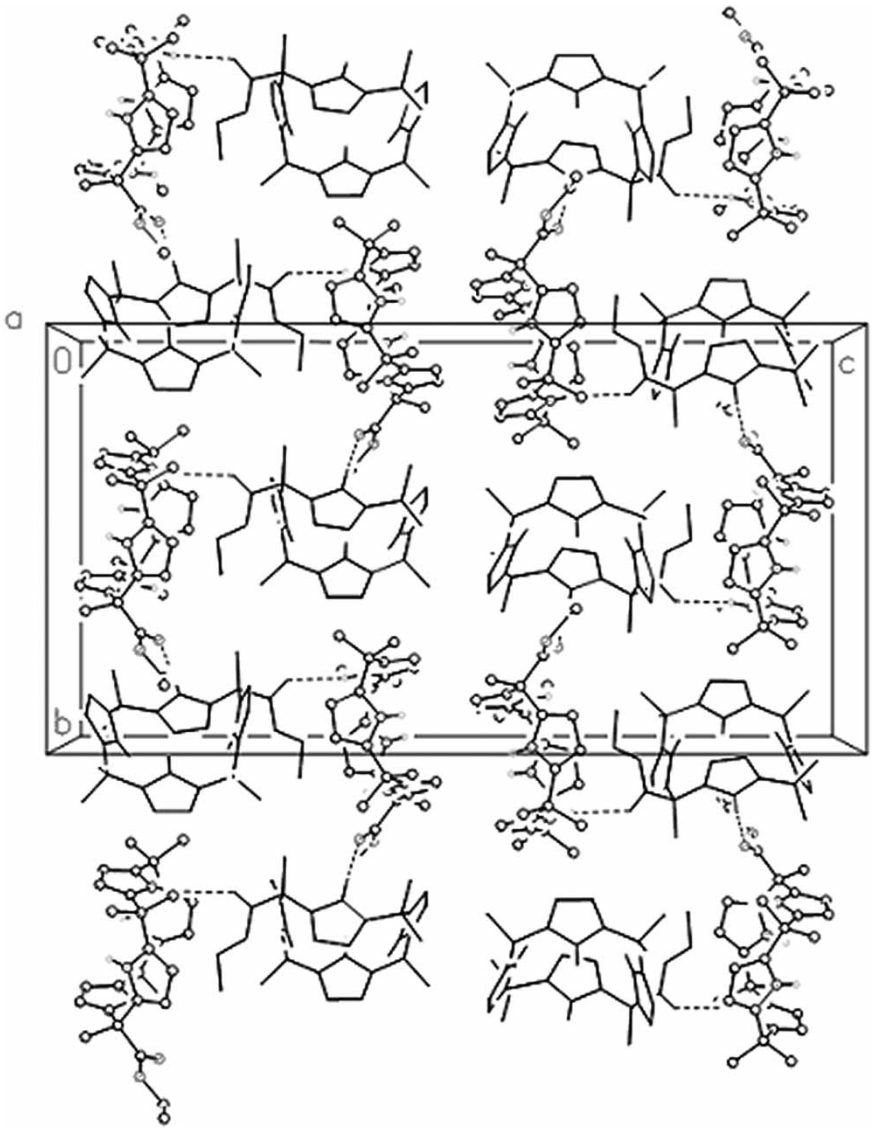


FIGURE 3 Unit cell packing diagram for **4**. The view is approximately down the **a** axis. Molecules **4a** are shown in ball-and-stick format while molecules **4b** are in wireframe display format. Dashed lines are indicative of H-bonding interactions. The geometry of these interactions are: N3···H3N···O22′ (related by $1-x, \frac{1}{2}+y, \frac{3}{2}-z$); N···O 3.344(6) Å, H···O 2.46 Å, N—H···O 168°; N1′—H1′N···O22, N···O 3.068(6) Å, H···O 2.17 Å, N—H···O 176°.

a 1,3-alternate conformation. However, two of the opposing pyrrole units (containing N2 and N4, respectively) are found to be tilted more in toward the central ring cavity when compared to the corresponding pyrrole units of **4** (Fig. 4). Presumably, this reflects substituent-induced steric effects. In the event, in contrast to what proved true for **4**, there is no evidence for appreciable hydrogen bonding-based intermolecular interactions in the case of **5**, as can be inferred from an inspection of the unit cell packing diagram of **9** shown in Fig. 5.

NMR Studies

In general, it is possible to observe the N—H proton signals of calix[4]pyrroles using ^{1}H-NMR spectroscopy, at least when common deuterated aprotic solvents, such as $CDCl_3$, CD_2Cl_2 and d_6-DMSO, are used. However, in the case of compound **5**, the N—H proton signals are not seen at room temperature when the spectrum is recorded in any of these solvents. Accordingly, efforts were made to record the ^{1}H-NMR spectrum under a range of temperatures. The appearance of N—H proton signals at -40°C in CD_2Cl_2 that are not observable over the temperature range 27°C to -20°C (Fig. 6), leads us to suggest that the electron withdrawing Br subunits make the N—H protons more acidic, and hence more labile, than is true in the case of the corresponding non-brominated calix[4]pyrrole **4**. This increased acidity was expected to be reflected in the anion binding properties of this system, as well as those of other brominated derivatives. Included among the latter is **2**, a prototypical compound that has been the

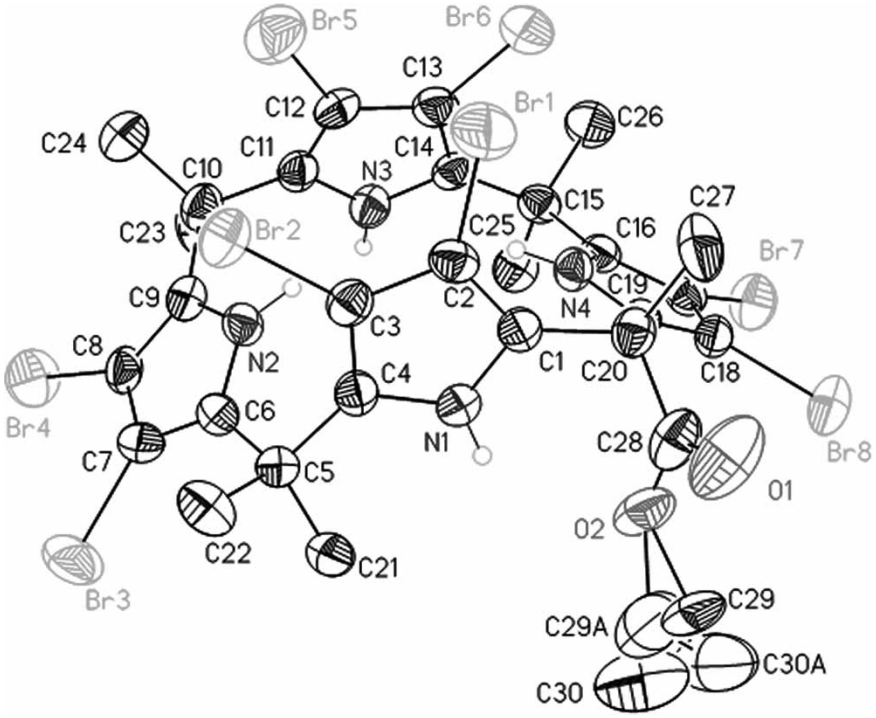


FIGURE 4 View of **5** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. The methyl hydrogen atoms have been removed for clarity. The ethyl group was disordered as shown.

subject of previous ^{1}H-NMR, but not ITC, based binding studies [31].

In contrast to what proved true for the pyrrolic N—H protons, the ester CH_2 protons were easily observable in the case of **5**. These are seen to be split into two multiplet peaks with a $J = 7$ Hz at low temperature. This splitting starts with a single peak at room temperature that undergoes broadening at 0°C and is fully apparent at -40°C. Such temperature dependence is consistent with a steric effect at low temperature that is sufficient to limit rotation of the pyrrole rings adjacent to the ester unit. As can be seen from the X-ray crystal structure of **5** (Fig. 4), one of the pyrrole rings adjacent to the ester unit lies almost perpendicular to the core of the compound while the other one sits almost parallel. Hence, each ester CH_2 proton can exist in a different chemical environment, a phenomenon

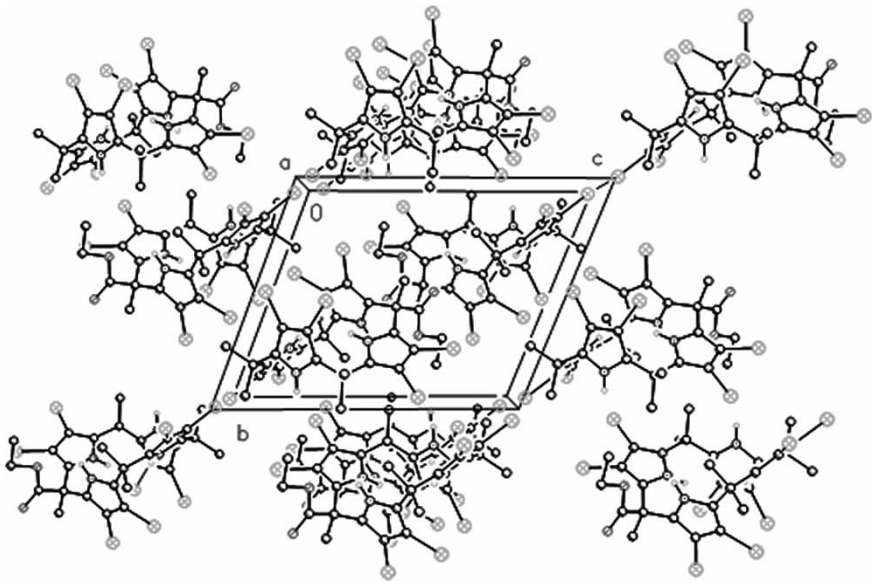


FIGURE 5 Unit cell packing diagram for **5**. The view is approximately down the **a** axis.

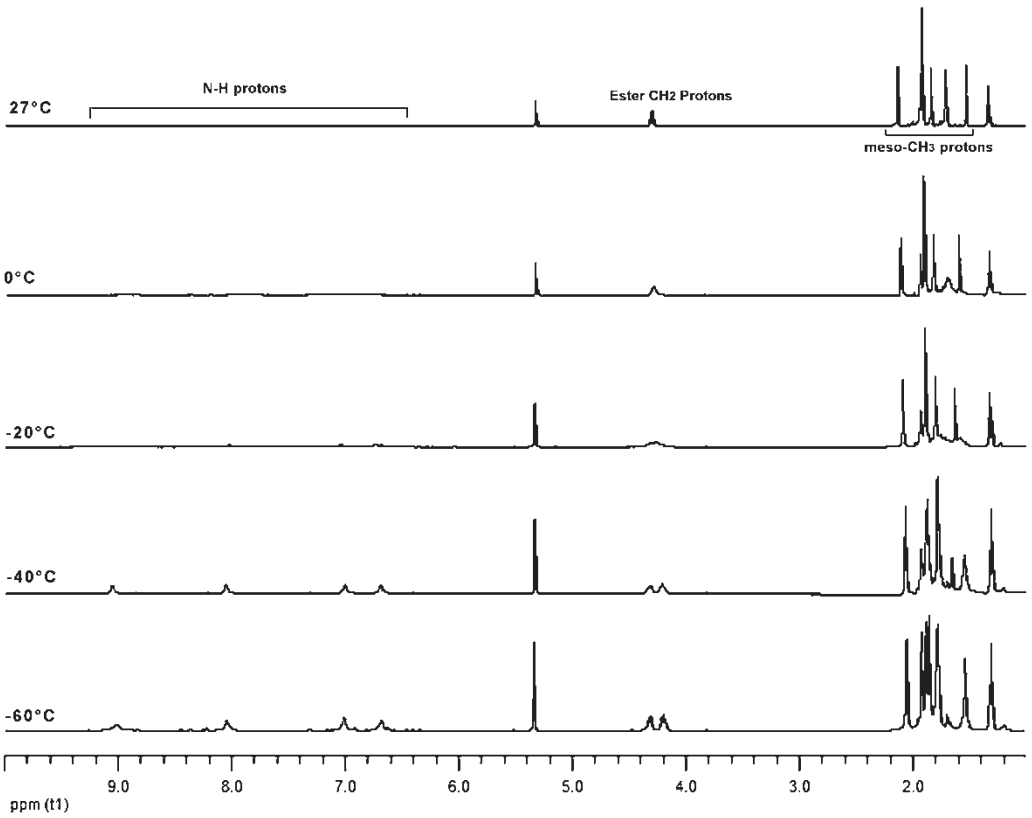


FIGURE 6 ^{1}H-NMR spectrum of **5** in CD_2Cl_2 recorded at various temperatures.

reflected in the splitting seen at low temperature. This proposed steric hindrance also affects the *meso*-CH_3 protons and results in different chemical shifts being seen for these signals at lower temperatures (Fig. 6).

Anion Binding Studies

Although the long chain esters of this study proved fully soluble in such apolar solvents as pentanes and hexanes, anion binding measurements were carried out in 1,2-dichloroethane. This relatively apolar solvent was chosen, since 1) the substituted calix[4]pyrroles of interest (i.e., **8**, **9**, **12**, and **13**) are not soluble in more polar solvents commonly used for such analyses, e.g., CH_3CN and DMSO, and 2) 1,2-dichloroethane was used in a recently published solvent dependence analysis of the chloride anion binding properties of **1** [33]. Thus, ready reference to these benchmark data could be made and, with this goal in mind, the chloride and acetate anion binding properties of **8**, **9**, **12**, and **13** were analyzed in 1,2-dichlorethane at room temperature using ITC.

Table I shows the binding constants for the novel calix[4] pyrroles of this study interacting with Cl^- and $CH_3CO_2^-$ (studied as the corresponding tetrabutylammonium (TBA) salts). Also included in Table I are previously reported chloride anion affinities of **1** [33,34], as well those for compound **2** determined using ITC for the first time. The results in Table I reveal that the unfunctionalized and β-pyrrole perbrominated calix[4]pyrroles **1** and **2** bind chloride anion with similar affinity, with the brominated species proving to be somewhat *less* effective as a chloride anion receptor. This result is somewhat surprising. Based on previous studies involving fluorinated calix[4]pyrroles [35], it was expected that the presence of the electron withdrawing substituents on the β-positions of the pyrrole rings would lead to an enhanced chloride anion affinity. However, the fact that this

TABLE I Chloride and acetate anion-binding affinities (M^{-1}) measured in 1,2-dichloroethane (as the tetrabutylammonium salts) using ITC. Estimated errors are less than 10%

	Cl^-	$CH_3CO_2^-$
1	$2.8 \times 10^{4\dagger}$	4.4×10^4
2	1.8×10^4	3.5×10^3
3	2.4×10^3	1.5×10^3
4	9.4×10^3	5.1×10^3
5	2.9×10^3	1.9×10^3
8	5.8×10^3	6.8×10^3
9	1.8×10^3	n.d.‡
11	2.8×10^3	1.5×10^3
12	2.0×10^3	n.d.‡
13	1.8×10^3	n.d.‡

† From reference [31].
‡ n.d.: not determined.

is not observed leads us to suggest that conformational effects play a critical role. Compound **2** possesses considerably bulkier substituents (i.e., bromine atoms) in the β-pyrrolic positions than does **1**; as a result, it is unable to adjust its conformation in favor of the cone conformation (dominant in the anion bound form) as readily as **1**. To the extent such an analysis is correct, it would lead to a reduction in the chloride anion affinity based on an analysis of electronic factors alone. Consistent with this conclusion is the finding that the acetate anion affinity of **2** is also lower than that of **1**. This same trend is seen in the case of the brominated ester derivatives, with the chloride and acetate anion affinities of the ethyl ester system **4** being substantially higher than those of the corresponding brominated derivative **5**. Likewise, the chloride anion affinity of the long n-alkyl ester **8** proved ca. 3 times larger than that of the analogous brominated product **9**. Interestingly, however, the chloride anion affinities of **12** and **13**, both of which were among the lowest observed for the present study set, proved nearly identical.

The other major conclusion supported by the data in Table I is that functionalization of the calix[4]pyrrole core with an acetyl ester group serves to reduce the anion binding affinity by a factor of 2–10 depending on the system involved (e.g., *meso* vs. β-pyrrole substituted) but that the effect of the long chain n-alkyl ester *per se* is small. For instance, the chloride anion affinity of the ethyl ester **4** is roughly 2 times lower than that of **1**, whereas that of the long chain analogue **8** is lower by only a factor of ca. 3 (again compared to **1**). The relative effect of long chain ester functionalization is even less dramatic in the case of the β-pyrrole substituted esters. For instance, the chloride anion affinity of **3** and **12**, albeit substantially reduced compared to that of **1**, are basically the same within error. Similar across the board trends are revealed in the case of acetate anion binding, although affinity constants for compounds **9**, **12**, and **13** could not be determined because of competing, but as yet unidentified, interactions observed in the ITC traces.

CONCLUSION

In conclusion, we have synthesized new mono carboxylic acid and ester functionalized calix[4]-pyrroles bearing both short and long n-alky chains on the ester positions. ^{1}H-NMR studies revealed that the brominated derivative **5** [36] gives rise to non-observable N—H peaks at room temperature (CD_2Cl_2), but that these signals can be readily detected at lower temperatures (i.e., below −20°C). These results are consistent with the brominated calix[4]pyrroles of this study being endowed with more acidic N—H protons. However, this presumed greater acidity is not reflected in higher chloride or acetate binding affinities relative to the hydrogen atom substituted forms, at least as judged from ITC measurements carried out at room temperature in 1,2-dichloroethane. These same anion binding studies revealed that all the new compounds, including the long n-alkyl esters, display relatively good anion binding affinities, albeit ones that are somewhat reduced compared to those of the parent calix[4]pyrrole (**1**). This combination of decent anion affinity and high solubility in nonpolar solvents, such as hexanes, makes the ester systems **8**, **9**, **12**, and **13** potentially attractive for use in further applications including anion extraction and transport. Studies along these lines are currently in progress.

Acknowledgements

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