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Synthesis, X-ray Structure, and Anion-Binding Properties of a Cryptand-Like Hybrid Calixpyrrole

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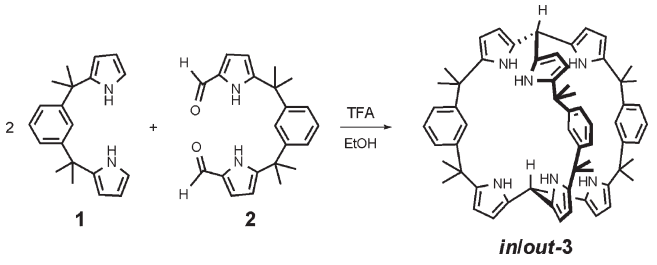
Received May 26, 2010



The novel cryptand *in*/*out*-**3**, containing two tripyrrolemethane units bridged by three 1,3- diisopropylidenbenzene arms, was readily synthesized by a convergent three-step synthesis. It binds fluoride by inclusion with excellent selectivity with respect to a number of other tested anions. The structure of the free receptor and that of its fluoride complex were investigated in solution by NMR spectroscopy. The solid-state X-ray structure of the free cryptand **3** was also determined.

Calixpyrroles are macrocycles containing pyrrole units linked to each other through quaternary carbon atoms (*meso* position). Since the discovery that calix[4]pyrrole is able to bind anions and small neutral molecules through the formation of hydrogen bonds,[1] these receptors have been the subject of intense study.[2] A large number of derivatives have been reported in which the anion-binding properties were modulated by varying the size of the macrocycle (i.e., by changing the number of pyrrole units or by the inclusion of other aromatic rings),[3,4] by changing the nature of substituents at the β-positions of the pyrrole rings,[5] by the use of substituents other than methyl at the *meso*-positions,[6] or by connecting two *meso* positions with an appropriate bridge (strapped calixpyrroles).[7] Cryptand-like calixpyrrole can be considered a special case of strapped calixpyrroles in which the strap is the same as half of the macroring. To date, only a few examples of such structures have been reported.[8,9] The host−guest chemistry of the tripyrrolemethane moiety, which can be found at the poles of these cryptands, has also recently been investigated.[10]

Recently, we reported the synthesis of calix[2]benzo[4]pyrrole containing *m*-phenylene units[4a] from the acid-catalyzed condensation of **1** and acetone. As a development of this work, here we report the synthesis of a bicyclic[3.3.3]tribenzohexapyrrole (Scheme 1) inspired by the bicyclic [3.3.3]nonapyrrole described previously by Sessler.[9]

Treatment of bis-pyrrole derivative **1**[11] with triethyl-*o*-formate/TFA gave the bis-formyl building block **2** in excellent yield. The acid-catalyzed condensation of **1** and **2** (stoichiometric ratio 2:1, respectively, in EtOH−TFA) can in principle yield two compounds: *in*/*out*-**3** and the two conformers *out*/*out*-**4**

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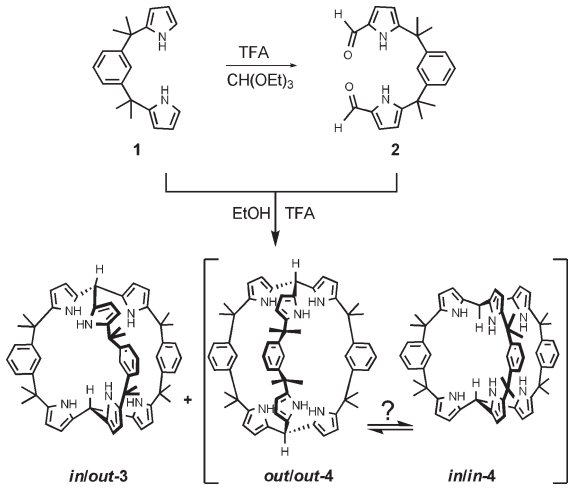
DOI: 10.1021/jo1010262 Published on Web 08/13/2010

SCHEME 1. Synthesis of *in*/*out*-Bicyclic [3.3.3]Tribenzoesapyrrole Cryptand 3[a]



[a]Stereoisomers *out*/*out*-**4** and *in*/*in*-**4** could not be found in the crude mixture.

and *in*/*in*-**4**, which might be conformationally stable, i.e., incapable of interconversion by, for example, passage of one "strap" into the cavity of the macroring defined by the other two bridges.[12] However, only one cryptand-like compound was isolated from this reaction. The ^{1}H and ^{13}C NMR spectra were consistent with the *in*/*out* configuration of the methyne *meso*-like hydrogen atoms and a C_{3v} time-averaged symmetry. In fact, the proton spectrum (Figure 2A) contained two different signals for the pyrrole-NH groups (δ 7.64 and 7.66, respectively) and two AB systems for the pyrroles β-CH (δ 4.98, 5.65, and 5.40, 5.86). The *meso*-like methyne protons appeared as two singlets (δ 4.82 and 5.22). These chemical shifts are analogous to those observed for the *in*-proton in the bicyclo[3.3.3]nonapyrrole derivative[9] and for the methyne proton of the "free" tripyrrolemethane unit,[10] respectively. Finally, the *m*-phenylene CH protons appear as four (and not three) different resonances because the molecule does not contain an "equatorial" plane of symmetry. These features rule out compounds **4** in which only one type of *meso*-like methyne protons are present and in which the pyrrole units at the two "polar caps" are equivalent.

Crystals of bicyclic macrocycle *in*/*out*-**3** were obtained from acetone. The X-ray crystal structure (Figure 1) confirmed the *in-out* configuration assigned on the basis of NMR data. The "in" methyne CH [C(24)] points toward the cavity of the diametrically positioned cup-like tripyrrolemethane unit based around C(1). The structure is partly self-filling, with a distance of 4.5124(16) Å between C(1) and C(24). The molecule has approximate C_3 symmetry about the C(1)···C(24) vector, and as each of the three *m*-phenylene arms is folded in the same sense the molecule has conformational chirality. It is important to note, however, that the molecule crystallized in a centrosymmetric space group and so there are equal numbers of both enantiomers present. Around each of the methyne carbon atoms the three pyrrole rings are canted in the same sense such that the N−H groups are on the same side as the methyne proton, and the

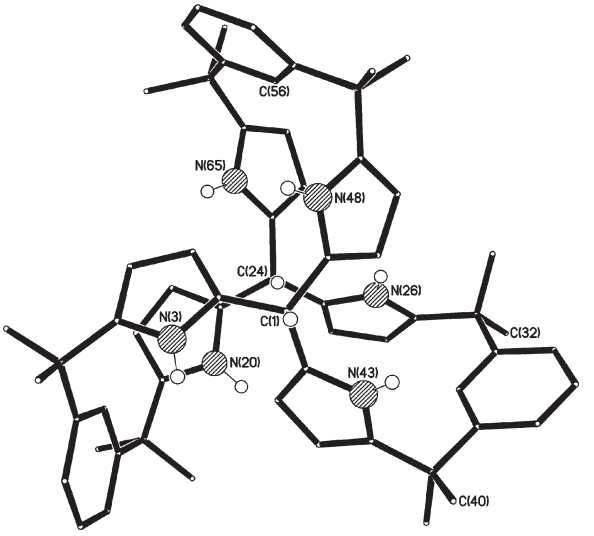


FIGURE 1. Molecular structure of *in*/*out*-**3**.

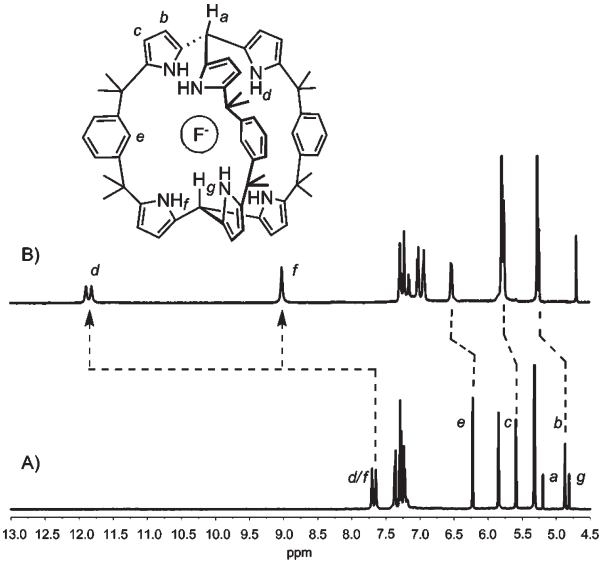


FIGURE 2. Partial ^{1}H NMR (CD_2Cl_2, 500 MHz) spectra of (A) the free receptor *in*/*out*-**3** and (B) of TBA[*in*/*out*-**3**·F^-] complex including the most significant assignments and CISs.

C(1)- and C(24)-based tripyrrolemethane moieties are staggered with respect to each other by ca. 41°.

Cryptand *in*/*out*-**3** was tested as a molecular receptor for several anions (F^-, Cl^-, NO_3^-, HSO_4^-, CH_3COO^-, $H_2PO_4^-$) as their TBA salts by ^{1}H NMR titration experiments in CD_2Cl_2.

Significant complexation-induced shift (CIS) of the NH protons, which is typical for the formation of host−guest complexes with anions in the case of calixpyrroles,[2c,4a,7a,d] was observed only for the binding of fluoride.

This complex was found to be kinetically slow on the NMR time scale, and its spectrum (see Figure 2) was consistent with a 1:1 stoichiometry. The association constant (K = 1562 ± 163 M^{-1}) could easily be determined by integration of the resonances of free and complexed cryptand.[13] In the complex, the NH protons appear as two signals of equal intensity, one as a

(12) The conformational *in*/*out* to *out*/*in* interconversion for cryptand **3** was tested by a high-temperature ^{1}H NMR experiment in 1,1,2,2-tetrachloroethane-d_2 up to 86 °C: No coalescence of the *in* and *out* methyne resonances was observed.

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doublet (δ 11.9, J_{HF} 40 Hz)[2c] and one as a singlet (δ 9.00), respectively. Only the pyrrole AB system that in free *in*/*out*-**3** resonates at higher chemical shifts (δ 4.82 and 5.22) is dramatically affected by the complexation, and it is shifted to low field. We believe that this is caused by a conformational rearrangement upon binding of fluoride, by which the tripyrrolemethane component having the "out" methyne configuration adopts a perching conformation with all of the three NH protons pointing toward the center of the cryptand containing the fluoride ion. Consequently, the β-pyrrole CH units that were partly filling the cryptand in the free receptor and hence shielded and resonating at unusually high fields (also see the X-ray structure, Figure 1) are ejected from the cavity and resonate at the usual δ values in the complex. Moreover, in the complex, the three "isolated" phenylene protons resonate as a singlet and are shifted to lower field ($\Delta\delta$ 0.35). These spectral features demonstrate that *in*/*out*-**3** is capable of forming an inclusion complex with fluoride. The formation of a 1:1 inclusion complex is also supported by the presence of the corresponding negative ion in the ESI-MS spectrum and consistent with the observed high selectivity toward fluoride compared to all other tested anions.

The 1:1 binding constant reported previously for the tripyrrolemethane group with TBAF in CD_3CN is 41000 M^{-1},[10] a value that is considerably larger that that observed by us for TBA[*in*/*out*-**3**·F^-] in CD_2Cl_2. In order to compare the binding constants, we tested the complexation of *in*/*out*-**3** with TBAF in CD_3CN and found that in this solvent the cryptand still forms a 1:1 inclusion complex exhibiting ^{1}H NMR spectral features similar to those observed in CD_2Cl_2 (see the Supporting Information), but with a binding constant beyond the limit of NMR method, and estimated[14] to be above the value of 10^5 M^{-1}. This result is likely to derive from differences in the ion-pairing of TBAF in the two solvents, i.e., reduced ion pairing of the salt in the more polar acetonitrile.

Unfortunately, our attempts to obtain crystals of the *n*-TBA[*in*/*out*-**3**·F^-] complex have not been successful to date. However, further evidence for the above-described mode of binding of fluoride by cryptand *in*/*out*-**3** was provided by a computational modeling experiment. The crystallographically determined structure of the *in*/*out* cryptand **3** was imported into Cerius2 (v. 3.5, Accelrys, Inc., San Diego), and the three pyrrole rings of the "out" unit were reoriented to bring their NH groups inside the cavity. A fluoride ion was inserted into the cryptand, and charge equilibration was used to redistribute atomic charges within the complex. The system was then minimized (molecular mechanics, Dreiding II[15] force field), resulting in a structure with an almost perfect 3-fold rotation axis through the fluoride ion. In the minimized structure (Figure 3), the cryptand forms three strong hydrogen bonds to fluoride via the reoriented pyrrole NH groups. The H-bond parameters are very close to those reported in a previous paper,[4a] averaging ca. 2.97 Å (N···F), 2.01 Å (H···F), and 169° (N−H···F), with the fluoride ion perching symmetrically on the three NH groups. The "in" methyne CH unit also points directly at the fluoride ion, though making a somewhat longer contact, with parameters 3.44 Å (C···F), 2.36 Å (H···F), and 178° (C−H···F). This completes a "tetrahedral" coordination of the fluoride ion, with three close NH and one more distant CH unit forming the anion-binding pocket. The three remaining NH hydrogens are also oriented inward with a geometry (average H···F = 3.06 Å, N−H−F = 137°) that allows only a modest interaction with the fluoride. The final model is thus in excellent agreement with the ^{1}H NMR data.

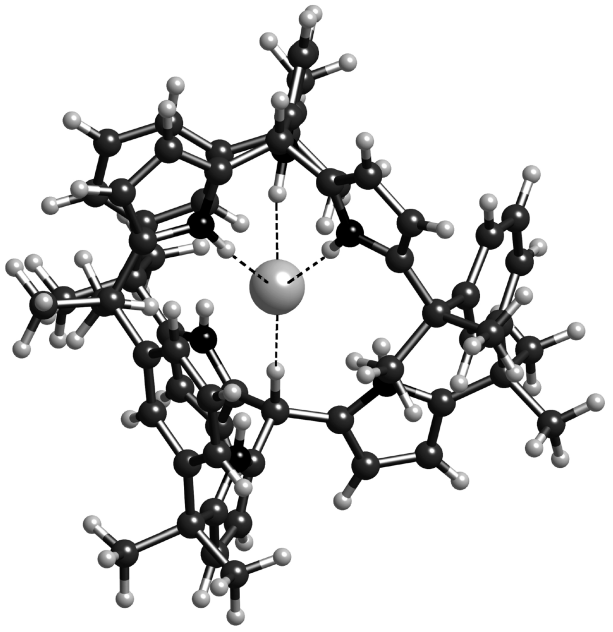

FIGURE 3. Dreiding II force field minimized molecular model of the complex [*in*/*out*-**3**·F^-] showing a geometry consistent with that assigned on the basis of its ^{1}H NMR spectrum.

Encouraged by these results, we attempted alternative syntheses of the cryptands **4** which could be prepared together with *in*/*out*-**3** by the acid-promoted condensation of 1,3-bis(1′,1′-dimethylhydroxymethyl)benzene with tripyrrolylmethane. However, these reactions were fruitless, and in spite of our efforts, cryptand(s) **4** remain elusive.

Experimental Section

1,3-Bis[1′-(pyrrol-2-yl)-1′,1′-(dimethyl)methyl]benzene (**1**) was prepared as described in ref 11.

1,3-Bis[1′-(pyrrol-2-carboxaldehyde-5-yl)-1′,1′-(dimethyl)methyl]-benzene (2). Triethyl orthoformate (2 mL) was added to a mixture of **1** (1 g, 3.4 mmol) and TFA (5 mL) at −10 °C under Ar. The red mixture was stirred at this temperature for 5 min and then poured onto ice (600 mL) and EtOAc (300 mL). The organic phase was separated, washed with aq $NaHCO_3$ (3 × 200 mL), dried ($MgSO_4$), and concentrated. The resulting red oil was subjected to column chromatography (SiO_2, hexane/EtOAc 3:1) to give a yellow solid as the main fraction, which was characterized without further purification as **2**: 72% yield (0.85 g); mp 155−6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 12H, CH_3), 6.18 (m, 2H, CH-Py), 6.88 (m, 2H, CH-Py), 6.99 (m, 1H, CH-Ar), 7.08 (m, 2H, CH-Ar), 7.23 (m, 1H, CH-Ar), 8.85 (sbr, 2H, NH), 9.37 (s, 2H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.6 (CH_3), 39.9 [C(CH3)2], 108.5, 121.7 (CH-Py), 123.8, 124.4, 128.6 (CH-Ar), 132.0, 147.5, 149.6 (Cq), 178.5 (CHO); ESI-MS (+) *m*/*z* calcd for $C_{22}H_{24}N_2O_2$ M = 348.2, found $[M + H]^+$ 349.2. A good match between measured (accurate MS-ESI) and calculated isotopic pattern was obtained (see the Supporting Information).

(14) This estimate was made by assuming that up to 5% of the initially present host and guest species might be uncomplexed and undetectable in the ^{1}H NMR spectrum of a solution containing host and guest with initial concentrations 10^{-3} M. By this calculation, the minimum value of 10^5 M^{-1} is a very conservative estimate.

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Cryptand *in*/*out*-3. A mixture of **1** (0.60 g, 2.05 mmol) and **2** (0.36 g, 1.02 mmol) in EtOH dry (250 mL) was degassed by bubbling with Ar for 5 min, and TFA (1.57 mL, 20.5 mmol) was added under Ar at 0 °C. The mixture was stirred for 4 h at rt, quenched by addition of aqueous $NaHCO_3$ (50 mL), concentrated, and diluted with CH_2Cl_2 (50 mL). The organic layer was separated, washed with aq $NaHCO_3$ (3 × 50 mL), dried ($MgSO_4$), and concentrated. The resulting brown oil was subjected to column chromatography (SiO_2, hexane/EtOAc 95:5) to give an orange solid as the main fraction which was crystallized from acetone to give *in*/*out*-**3**: 0.14 g, 15%; mp 168 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 18H, CH_3), 1.66 (s, 18H, CH_3), 4.83 (m, 1H, CH-*in*), 4.98 and 5.65 (2 × m, 6H, CH-Py), 5.22 (m, 1H, CH-*out*), 5.40 and 5.86 (2 × m, 6H, CH-Py), 6.22 (m, 3H, CH-Ar), 7.20 (m, 3H, CH-Ar), 7.27 (m, 3H, CH-Ar), 7.35 (m, 3H, CH-Ar), 7.64 (sb, 3H NH), 7.66 (sb, 3H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.9, 30.1 (CH3), 36.6 (CH-*in*), 36.8 (CH-*out*), 39.0, 39.6 ($C(CH_3)_2$), 101.8, 104.2, 104.7, 105.0 (CH-Py), 120.9, 123.2, 126.6, 127.9 (CH-Ar), 130.0, 131.8, 137.2, 142.1, 148.3, 151.5 (Cq); ESI-MS (+) m/z calcd for $C_{62}H_{68}N_6$ M = 896.5, found $[M + H]^+$ 896.8. Elemental analysis gave inconsistent results because variable amounts of residual acetone solvent were retained after prolonged drying (see the X-ray structure in the Supporting Information).

Crystal data for *in*/*out*-3: $C_{62}H_{68}N_6 \cdot 3C_3H_6O$, M = 1071.46, monoclinic, $P2_1/n$ (no. 14), a = 13.3422(2) Å, b = 22.6427(4) Å, c = 21.7077(3) Å, β = 102.5717(16)°, V = 6400.74(18) Å^3, Z = 4, D_c = 1.112 g cm^{-3}, μ(Mo Kα) = 0.068 mm^{-1}, T = 173 K, yellow prisms, Oxford Diffraction Xcalibur 3 diffractometer; 20074 independent measured reflections (R_{int} = 0.0218), F^2 refinement, R_1(obs) = 0.0511, wR_2(all) = 0.1328, 11778 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 66°], 789 parameters. CCDC 768744.

^{1}H NMR Complexation Studies and Titrations. The *n*-TBA salts were dried in a vacuum oven for at least 24 h. Solvents were used as supplied in sealed ampules, and care was taken to minimize exposure to moisture. The anions were added as measured volumes of solution (ca. 0.035 M) in CD_2Cl_2 to a solution of *in*/*out*-**3** (0.0025 M) in the same solvent (0.7 mL), and the total volume was kept constant by evaporation with anhydrous nitrogen. After each addition, the stoichiometric ratios between salts and *in*/*out*-**3** were also redetermined from the resonance intensities of the host proton toward those of the TBA cation. Quantitative ^{1}H NMR integrations were obtained by the use of appropriate pulse delays in all cases. Slow exchange was observed in the titration of *in*/*out*-**3** with F^- anion, and the K values were determined from the ratios of the intensities of bound and free species for solutions having different ratios of cryptand and salt.[13] Measurements were averaged and found to be reproducible to within 15%.

Acknowledgment. We thank the University of Messina for financial support.

Supporting Information Available: Details of experimental procedures, ^{1}H and ^{13}C NMR spectra for compounds **2** and **3**, and ^{1}H NMR spectra used for determination of the association constant for the TBA[*in*/*out*-**3**·F^-] complex, MS spectra for the new compounds, X-ray crystallographic file (CIF) for *in*/*out*-**3**, and atomic coordinates for the Dreiding II force field minimized molecular model of the complex [*in*/*out*-**3**·F^-]. This material is available free of charge via the Internet at http://pubs.acs.org. The CIF files are also available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: +44(0) 1223 336033 or e-mail deposit@ccdc.cam.ac.uk], under CCDC ref no. 768744.