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Azatripyrrolic and Azatetrapyrrolic Macrocycles from the Mannich Reaction of Pyrrole: Receptors for Anions

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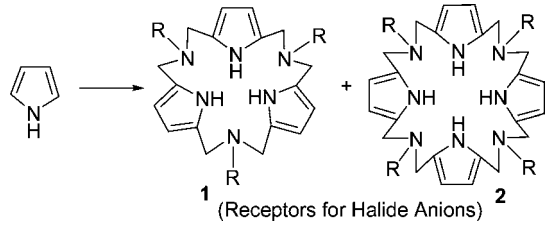
ABSTRACT



Azatripyrrolic 1 and azatetrapyrrolic 2 macrocycles were synthesized in a single step by the Mannich reaction of pyrrole in the presence of primary amine hydrochloride and were structurally characterized among several other higher analogue azapyrrolic macrocycles. Binding constants for the halide anion complexes are determined by ^{1}H NMR titrations and they show different binding stoichiometries.

Developing receptors that bind with anions through hydrogen bonds is an active area of research in supramolecular chemistry as anions play important roles in biological and environmental systems.[1,2] Recently, Gale has classified anion receptors, based on anion-binding groups such as pyrrole, indole, and amide, that are present as building blocks in the structures of the receptors.[3] In 1996, Sessler first reported the anion receptor study of a pyrrole-based receptor, *meso*-octamethylcalix[4]pyrrole.[4] To modulate the anion and ion-pair recognition capabilities of calixpyrrole type molecules, a variety of macrocycles such as calix[5]pyrrole,[5] calix[6]pyrrole,[6] hexadecafluorocalix[8]pyrrole,[7] calixbipyrrole,[8] strapped calixpyrrole,[9] calixpyrrole dimer,[10] *N*-confused calix[4]pyrrole[11,2e] and cryptand-like calixpyrrole[12] containing pyrrole rings have been synthesized mainly by the condensation reactions between the respective pyrrole systems and ketones; such a condensation reaction was first reported by Baeyer in 1886.[13]

In contrast to the reactions of pyrroles and ketones, the Mannich reaction of pyrrole was not utilized for making macrocycle molecules for anion receptor study. Instead, acyclic compounds have been synthesized by the Mannich reaction of pyrrole in the presence of primary and secondary amines.[14,15] Lindsey reported acyclic Mannich bases of dipyrromethane molecules obtained by using Eschenmoser's reagent.[16] In Mannich reactions, when secondary amines are used usually the desired compounds are obtained as single products. If primary amines are used, Mannich reactions can continue until all NH protons are replaced.[17] With the objective of preparing a new expanded calix[*n*]pyrrole that can act as an ion-pair receptor, we reinvestigated some of the Mannich reactions of pyrrole with an appropriate ratio of primary amine hydrochloride and formaldehyde and isolated a new class of azatripyrrolic (**1**) and azatetrapyrrolic (**2**) macrocycles containing three and four pyrrole rings linked by $CH_2N(R)CH_2$ units, respectively.[18] The synthesis, structural characterization, and halide anion-binding studies of these new macrocycles are reported in this paper.

The Mannich reaction between pyrrole and a mixture of methylamine hydrochloride and formaldehyde in a 1:1:2 molar ratio, respectively, in ethanol at room temperature

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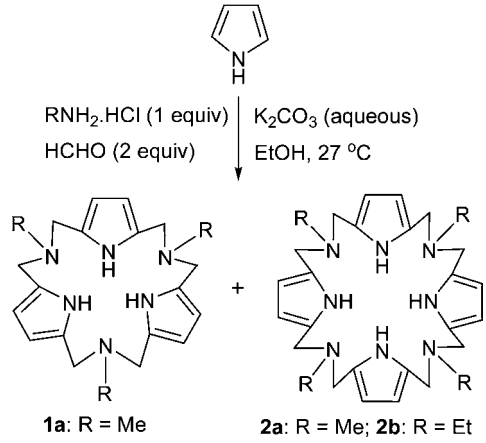
gives a mixture of products from which (**1a**·H_2O)$_2$ and **2a**·H_2O were isolated in 6% and 14% yields as crystalline materials, respectively, after basic alumina column chromatographic separation followed by fractional crystallization. When the reaction was carried out with ethylamine hydrochloride, only **2b**·H_2O was obtained in 19% crystalline yield (Scheme 1). As primary amines are used, the Mannich

Scheme 1. Synthesis of Macrocycles **1a**, **2a**, and **2b**



reactions continue until all NH protons are replaced to give cyclic molecules. This is in contrast to the reaction that gives acyclic molecule when the pyrrole/formaldehyde/primary amine hydrochloride molar ratio is 1:1:0.5, respectively.[15] In analogy to azacalixarenes,[19] **1** and **2** are proposed to be named hexahomotriazacalix[3]pyrrole or triazacalix[3]pyrrole and octahomotetraazacalix[4]pyrrole or tetraazacalix[4]pyrrole, respectively. The structures of the compounds **1** and **2**[20] were determined by single-crystal X-ray diffraction studies and confirmed by spectroscopic and high-resolution (+)ESI-MS methods.

The ^{1}H NMR spectrum of **1a** is similar to that of **2a** in terms of signal pattern and chemical shift positions except for the NH resonance, which appears as a broad singlet at δ 9.03 and 9.82, respectively. The (+)ESI-MS spectra of **1a** and **2a** showed molecular ion peaks *m*/*z* at 367.2612 and 489.3354, respectively, corresponding to [M + H$^+$]. As **1a** and **2a** have the same mole ratio of pyrrole/formaldehyde/amine and are isolated from the same reaction, the reaction mixture for the methyl derivative obtained after the workup procedure was analysized by ^{1}H NMR, LC-MS, and high-resolution (+)ESI-MS. The ^{1}H NMR spectrum of the reaction mixture showed the presence of new NH resonances in addition to those of **1a** and **2a**, indicating the presence of possibly larger ring aza[*n*]pyrrolic derivatives. In support of this, the LC-MS of the reaction mixture showed the molecular ion peaks *m*/*z* of [M + H$^+$] for the larger size aza[*n*]pyrrolic macrocycles containing five to nine pyrrole rings, besides *m*/*z* of **1a** and **2a**. The presence of these large

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(20) The structure of **2b** has also been determined by a single-crystal X-ray diffraction study; details are provided in the Supporting Information.

aza[*n*]pyrrolic macrocycles ($n = 3-9$) is confirmed by the high-resolution (+)ESI-MS spectra (see the Supporting Information).

The X-ray structure of (**1a**·H_2O)$_2$ reveals a dimer composed of two molecules of **1a** bridged by two water molecules in the asymmetric unit (Figure 1). Each bowl-shaped macrocycle consists of three pyrrole rings connected by three $CH_2N(Me)CH_2$ segments at the αα′-positions of the pyrrole ring. All three pyrrole NH protons are hydrogen bonded to the oxygen atom of the bridging water molecule. The water molecule bridges via H-bonding to the NMe groups, one from each **1a** molecule. Because of the H-bonding, the average bond angles (C−N−C) around the nitrogen atoms of the NMe groups, for example, N6 (109.7°) and N2 (110.1°), are lower than that of N4 (112.1°), which is not involved in hydrogen bonding.

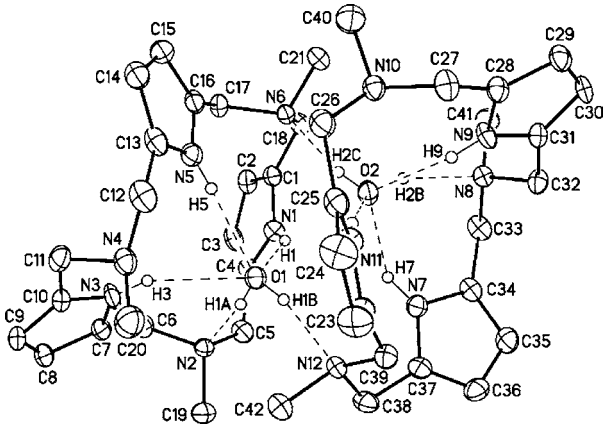

Figure 1. X-ray structure of (**1a**·H_2O)$_2$ with 30% probability ellipsoids. H-atoms are partially omitted for clarity. Selected bond lengths (Å) and angles (deg): N3···O1, 3.073(5); H3···O1, 2.30(5); N3−H3···O1, 153(4); N5···O1, 3.118(6); H5···O1, 2.31(5); N5−H5···O1, 168(4); N1···O1, 2.875(5); H1···O1, 2.11(5); N1−H1···O1, 146(4); O1···N2, 2.865(5); H1A···N2, 2.05(6); O1−H1A···N2, 165(5); O1···N12, 2.861(5); H1B···N12, 1.96(5); O1−H1B···N12, 166(4).

The X-ray structure of **2a**·H_2O reveals that the macrocycle consists of four pyrrole rings linked by four $CH_2N(Me)CH_2$ segments (Figure 2) and adopts a bowl-shaped conformation when viewed from the sides of the $CH_2N(Me)CH_2$ segments (see the Supporting Information). The *cis* and *trans* conformations of the $CH_2N(Me)CH_2$ segments are supported by the dihedral angles, for example, C(19)−N(6)−C(21)−C(22) = 68.7° and C(21)−N(6)−C(19)−C(18) = −162.3°, which are analogous to tetramethyltetraazaparacyclophane.[21] All NH protons are pointed toward the cavity in which one water molecule is trapped. The NH protons as hydrogen-bond donors and the amine nitrogen atoms as hydrogen-bond acceptors are involved in hydrogen bonding with the disordered water molecule. The 92:8 preference for one of two disordered water molecule locations remains unclear.

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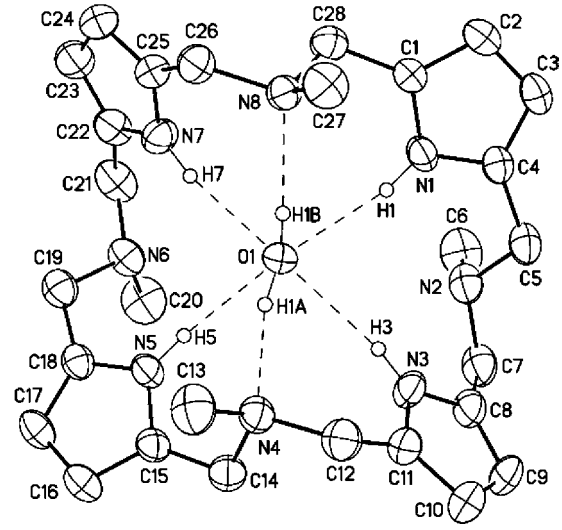

Figure 2. X-ray structure of **2a**·H_2O (front view) with 30% probability ellipsoids. The disordered oxygen atom and some of the H-atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): N3···O1, 3.0736(19); H3···O1, 2.27; N3−H3···O1, 156.1; N7···O1, 3.0951(19); H7···O1, 2.29; N7−H7···O1, 156.1; N5···O1, 3.082(2); H5···O1, 2.30; N5−H5···O1, 151.9; N1···O1, 3.044(2); H1···O1, 2.25; N1−H1···O1, 154.3; O1···N4, 2.8486(19); H1A···N4, 2.015(11); O1−H1A···N4, 164.0(15); O1···N8, 2.8356(19); H1B···N8, 2.005(11); O1−H1B···N8, 167.4(16).

However, only one water molecule per macrocycle is accommodated.

We investigated the halide anion receptor capabilities of the macrocycles **1a** and **2a** by ^{1}H NMR titrations, which involved addition of an incremental amount of the anions to a solution of **1a** or **2a** in acetone-d_6 followed by monitoring of the NH resonance (Figure 3). For example, when aliquots of fluoride anion were added to solution of **1a**, the NH resonance shifted downfield (from δ 9.88 to 14.31) gradually

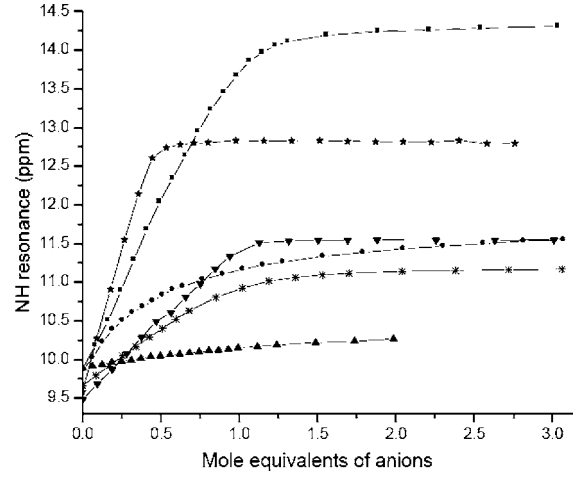

Figure 3. ^{1}H NMR titration curves for **1a** and **2a** with F^-, Cl^-, and Br^- anions: -■- **1a** and F^-; -●- **1a** and Cl^-; -▲- **1a** and Br^-; -★-**2a** and F^-; -▼- **2a** and Cl^-; -*- **2a** and Br^-.

and remained constant after additon of nearly 1 equiv of fluoride anion. Conversely, the pyrrole β-CH resonance shifted to the upfield region. The binding constant values K_a were determined by the EQNMR program[22] and verified by the Hirose two-parameter method[23] using the NH resonances and are given in Table 1.

Table 1. Binding Constants (K_a, M^{-1}) Determined by ^1H NMR Titration for the Formation of Complexes of **1a** and **2a** with Halide Anions as Their Tetrabutylammonium Salts in Acetone-d_6 at 298 K

	F^-	G:H[a]	Cl^-	G:H	Br^-	G:H
1a	1138[b]	1:1	3182[c]	1:2	243[b]	1:2
2a	[d]	1:2	13586[c]	1:1	1181[b]	1:1

[a] G = anion, H = receptor. [b] <10% error. [c] <20% error. [d] K_a could not be accurately determined by ^1H NMR titration, which showed log K_a in the range of 6−7 M^{-1} using the β-CH or NH resonance.

Job's plots[24] confirmed the 1:1 binding stoichiometry for **1a**:F^-, **2a**:Cl^-, and **2a**:Br^- complexes. Job's plots for **1a** with chloride and bromide anions showed a maximum at a 0.6 mol fraction of **1a**, indicating the formation of mainly a 1:2 complex with a small contribution probably from a 1:1 complex. The integrated intensities of the NH resonance, which is broadening, keep decreasing gradually during the titration and Job's plot experiments. Furthermore, the ^1H NMR spectrum of a solution of **1a** or **2a** in acetone-d_6 containing 4 or 5 equiv of fluoride anion, respectively, showed a disappearance of the NH resonance in less than 40 min, indicating deprotonation of all NH protons by fluoride anion. In view of this data, the β-CH resonance was followed for determining both K_a and the binding stoichiometry for F^- complex of **2a**, for which the Job's plot showed a maximum at the 0.6 mol fraction of **2a**, indicating the formation of complexes as observed for **1a** with Cl^- or Br^-. These binding stoichiometries are probably dictated by the number and acidity of the NH protons, the lone pairs of the amine groups, and the flexibility of the macrocycle.[25] Unfortunately, our attempts to crystallize these halide complexes are failed.

In contrast to the binding order ($F^- > Cl^- > Br^-$) observed for octamethylcalix[4]pyrrole[4,5b] and acyclic pyrrole systems such as tris(pyrrolyl-α-methyl)amine[26] and tripyrrolemethane,[27] **1a** has a higher K_a value for the chloride anion as compared to the fluoride anion, probably owing to the formation of a 1:2 complex.

In conclusion, we have synthesized two novel macrocyclic molecules **1** and **2** that act as receptors for halide anions with different binding stoichiometries. Compound **1a** is a unique macrocycle molecule given that, to the best of our knowledge, the corresponding calix[3]pyrrole is not known. Although both **1** and **2** are formed in low yields mainly owing to the formation of several larger size azacalix[*n*]pyrrole macrocycles ($n = 5-9$) as shown by LCMS, **2** represents an important new class of expanded calix[4]pyrrole macrocycle. Unlike calix[*n*]pyrrole systems, **1** and **2** have inbuilt H-bond acceptors (tertiary amine N) for binding with Lewis acids and H-bond donors (pyrrole NH) for binding with anions, which are necessary requirements to be a ditopic ion-pair receptor. These findings open up a new area of research. As pyrrole β-CH positions are available for chemical modifications, different derivatives of **1** and **2** could conveniently be prepared for modulating both the anion and ion-pair recognition capabilities. Currently, we are attempting to crystallize both small and large anion complexes of **1** and **2** and to isolate other higher analogue azapyrrolic macrocycles.

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Supporting Information Available: Synthetic procedures; NMR, IR, HRMS, and LC-MS data; crystallographic data (CIF); structure refinement data;[28] details of binding constants calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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