Pyxophanes: selective gas phase ion complexation by 1,6,13,18-tetraoxa[6.6]paracyclophane-3,15-diyne

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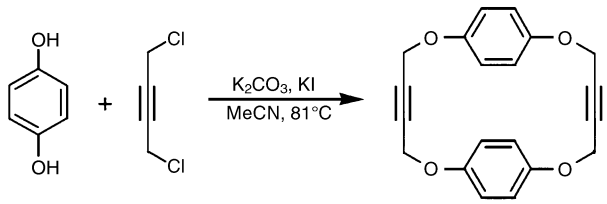
Compound 1, synthesized from hydroquinone and 1,4-dichlorobut-2-yne, was characterized by X-ray crystallography and shown by electrospray ionization mass spectrometry to form 1 : 1 complexes with sodium and 2 : 1 complexes with potassium cation.

The interaction of arenes with alkali metal and ammonium ion cations is of considerable theoretical interest but of even greater potential import in biology. Three of the essential amino acids contain aromatic sidechains capable of serving as π-donors. Together, phenylalanine (Phe, F), tryptophan (Trp, W), and tyrosine (Tyr, Y) comprise 8.4% of the amino acids in all known protein sequences. The ability of arenes to complex K^+ was demonstrated experimentally by Kebarle and coworkers in 1981.[1] Additional experiments by the groups of Castleman[2] and Lisy[3] confirmed their observations and extended them to Na^+. Burley and Petsko surveyed data available in the Protein Data Bank and demonstrated the plausibility of ammonium ion–arene interactions in proteins.[4]

Important as this work was, cation–π interactions received little additional attention until it was postulated that the selectivity of protein channels could be understood in terms of K^+–arene interactions.[5] By using site directed mutagenesis, Heginbotham, MacKinnon and coworkers[6] showed that the selectivity filter of the shaker K^+ channel of *Drosophila melanogaster* did not require a cation–π interaction. The crystal structure of the K^+-selective KcsA K1 channel of *Streptomyces lividans* recently reported by MacKinnon and coworkers shows no evidence for K^+–arene interactions.[7] Still, the potential importance of such interactions is great. In recent work of our own, we reported the first crystal structure data confirming K^+–arene, cation–π interactions for the sidechains of phenylalanine,[8] tryptophan,[9] and tyrosine.[10]

We now propose that the ideal 'π-receptor' molecule would possess two arenes held rigidly face-to-face at a distance appropriate to bind an alkali metal cation. For Na^+, this distance should be *ca.* 2 Å, depending on the exact coordination number. To maintain rigidity, electron richness, and symmetry, we chose acetylene units to serve as spacers. Aryl ether links were selected for covalent attachment. Because the oxygen atoms were adjacent to an arene, their π-donicity was expected to be minimal and synthetic access should be facilitated. The target compound **1** was dubbed a 'pyxophane' after the word 'pyx', meaning chest.[11]

Pyxophane **1** was synthesized by alkylation of hydroquinone with 1,4-dichlorobut-2-yne, followed by oligomerization (or dimerization) and cyclization (Scheme 1). Hydroquinone, butyne, potassium carbonate and potassium iodide were heated at reflux for 24 h in acetonitrile. The solvent was removed and the residue was extracted with dichloromethane. The extract was purified by chromatographing over silica using dichloromethane. The purified product was recrystallized from toluene to afford **1** as fine white needles (5% yield, mp 265–266 °C).



Scheme 1

The solid state structure of **1** (Fig. 1) was obtained by X-ray methods.[12] In the solid state, the molecule lies in a chair conformation with an arene–arene distance of 5.5 Å and an alkyne–alkyne distance of 7.0 Å. By subtracting the arene and alkyne thicknesses (3.4 Å), we deduce a cavity size of 2.1 × 3.6 Å. This distance suggests that a sodium cation, with a diameter of 1.98 Å, should be able to easily fit into the host molecule but a larger cation such as K^+ (2.7 Å diameter) should not.

Cyclophane **1** is related to the cyclophanes synthesized by Jarvi and Whitlock,[13] the primary difference being in the rigid spacer length. In their studies, they used longer diyne spacers which afforded a larger cavity, a necessity for the incorporation of organic guest molecules.

Electrospray ionization mass spectrometry (ESI-MS) is the ideal tool to assess alkali metal cation complexation in the low polarity environments of non-polar solvent and vacuum. Such an environment is clearly relevant to the *ca.* 30 Å non-polar span of a phospholipid bilayer commonly referred to as the insulator regime or the 'hydrocarbon slab'. The study involved three steps. First, an attempt was made to detect intramolecular complexation of Na^+ by **1**. This should lead to an ion of the type $[\mathbf{1}\cdot Na]^+$ having a weight of (320 + 23 =) 343 Da. The corresponding experiments with K^+, Rb^+, and Cs^+ are not expected to produce ions of the type $[\mathbf{1}\cdot M]^+$ because these metal ions are too large to bind intrapyxially. If 2 : 1 complexation is required, the dominant ion will be $[\mathbf{1}_2\cdot M]^+$. The absence of a

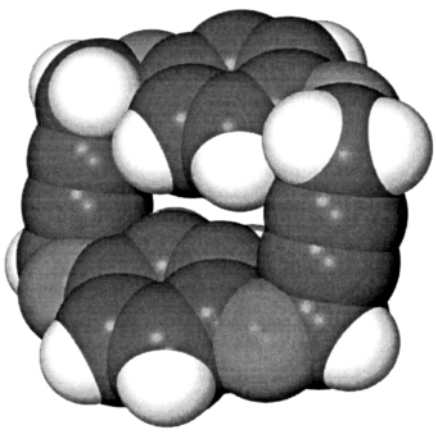


Fig. 1 Solid state structure of pyxophane **1** shown in the CPK metaphor.

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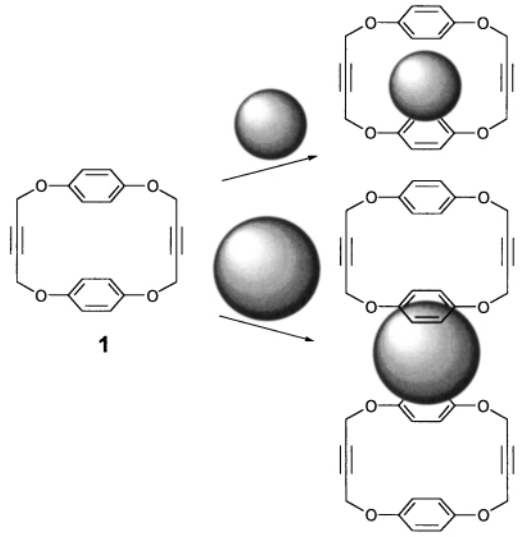

Scheme 2

1·M^+ ion and the presence of one corresponding to $\mathbf{1}_2$·M^+ would be good evidence for 'external' dimer complex formation. Finally, an experiment identical in other respects to those described above but involving Na^+ and 1,4-dimethoxybenzene **2** should not exhibit any significant complexation (neither **2**·M^+ nor $\mathbf{2}_2$·M^+).

The mass spectrometric analyses were conducted using an electrospray ion source (ESI/MS).[14] Pyxophane **1** (typically 1.5 mg) and dry NaCl were dissolved in 1 mL of $CHCl_3$ and the spray solution was prepared by adding 1 mL of MeOH–$CHCl_3$ (1 : 1, v/v) and 40 μL of 100 μM NaOH to 60 μL of the sample solution. After mixing, 20 μL of the sample solution was loop injected by continuous infusion (10 μL min^{-1} MeOH–$CHCl_3$ (1 : 1, v/v)). The instrument continuously scanned (magnetic) at 20 s $decade^{-1}$ of mass over the range from 2000 to 400 Da. The inlet temperature was *ca.* 55 °C. The base peak (100% relative abundance) in the ESI-MS spectrum was observed at *m/z* 343.1 which corresponds to an ion having the composition [**1**·Na]$^+$. A small peak at *m/z* 663.2 (*ca.* 7%) corresponds to [$\mathbf{1}_2$·Na]$^+$.

The binding selectivity was evaluated by comparing the intensity of the electrospray ion signal for the [M·Na]$^+$ complex, with the intensity of the signals for [M·K]$^+$, [M·Cs]$^+$, and [M·Rb]$^+$. These complexes were produced and analyzed separately. By far, the strongest binding was observed for Na^+ as evidenced by an intense *m/z* 343 ion [**1**·Na]$^+$. Although Cs^+ (ionic diameter = 3.32 Å) showed a moderately intense *m/z* 453 ion indicating some affinity for **1**, neither K^+ (2.66 Å) nor Rb^+ (2.94 Å) showed any significant binding. Further, the [M·Na]$^+$ ion was associated with higher mass ions consistent with solvent complexation, offering additional evidence that the Na^+ ion is occupying the central cavity of **1**. As controls, methoxybenzene (anisole) and 1,4-dimethoxybenzene **2** were run under conditions identical to those under which [**1**·Na]$^+$ was found to be the base peak in the spectrum. Sodium complexation was not observed for either compound. The complexation results are suggested by Scheme 2 in which the spheres represent Na^+ (smaller) and K^+ or Rb^+.

The preliminary data presented here support size-selective π-complexation of alkali metal cations. Additional complexation studies in both the gas and solution phases are underway with these and closely related host molecules.

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Notes and references

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11 The second definition given in the shorter *Oxford English Dictionary* is: 'At the Royal Mint, the chest in which specimen gold and silver coins are deposited to be tested annually. Esp. in *trial of the pyx*, the annual test of such specimen coins'.
12 *Crystal data* for **1**: $C_{20}H_{16}O_4$, M = 320.34, space group $P2_1/c$, a = 9.819(2), b = 10.582(3), c = 7.85(2) Å, β = 109.81(2); V = 764.45 Å^3, Z = 2, μ = 5.4 cm^{-1}, λ = 1.5418 Å, 1300 reflections measured, R_w = 0.0533 for 811 reflections with $I > 4\sigma(I)$. CCDC 182/1832. See http://www.rsc.org/suppdata/cc/b0/b005443g/ for crystallographic files in .cif format.
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14 Only sectors one and two, a reversed geometry BE, extended mass range configuration (Vacuum Generators ZAB-T), were used for the mass analysis. The electrospray ion source operated as follows: spray needle voltage, 8940 V; counter electrode, 5255 V; sampling cone, 4200 V; accelerating voltage, 4120 V; source temperature, 75% power (*ca.* 55 °C). Sample preparation was as follows: 1.5 mg of sample was dissolved in 1 mL $CHCl_3$.