Cation-π Complexation of Potassium Cation with the Phenolic Sidechain of Tyrosine

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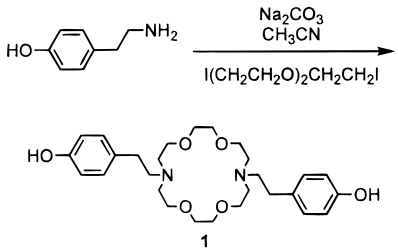
Introduction

Evidence has accumulated during the past two decades that cation-π interactions play an important role in macromolecular organization and in molecular recognition. In 1981, Kebarle and co-workers[1] demonstrated that the interaction between a molecule of benzene and K^+ was comparable in strength to the interaction between K^+ and a single H_2O molecule. The interaction between the ammonium ion and an aromatic residue is expected also to be favorable. Burley and Petsko noted a high tendency for amines to be located near aromatic amino acid side chains in a survey of high-resolution (2 Å or higher) protein structures.[2] They proposed that these "amino-aromatic interactions" contributed to protein stability. Since their report, a number of protein structures have been described that demonstrate ammonium cation-π interactions.[3] Theoretical studies by Dougherty[4] and others[5] suggested that the aromatic side chains of Phe, Trp, and Tyr should be strong donors for the biologically important alkali metal cations Na^+ and K^+. Experimental observation of Na^+ and K^+ cation-π interactions has been hampered by the lack of (1) sufficient resolution in protein structures[6] and (2) model systems (e.g., synthetic receptors) that could be used to observe such interactions. Current work in our laboratory is focused on the second issue.

We recently reported a synthetic receptor molecule that incorporates the side chain of Trp as 2-(3-indolyl)ethyl.[7] This receptor showed a close π-contact between indole and a bound Na^+ or K^+ at the pyrrolo (five-membered) subunit. We have prepared a related receptor, **1**, which incorporates the phenolic side chain of tyrosine as the π-donor group. This receptor complexes K^+ by using the phenolic sidearms as π-donor groups but not when the macrocycle-bound cation is Na^+.

Lariat ether[8] **1** was prepared in a single step from tyramine (18 mmol), 1,8-diiodo-3,6-dioxaoctane (18 mmol), and Na_2CO_3 (91 mmol) in refluxing CH_3CN (50 mL, 24 h).[9] The base provided the cation, and 1,8-diiodo-3,6-dioxaoctane was the source of the anion (Scheme 1). Crystallization of the crude product from acetone gave crystals of **1**·NaI[10] (14%, mp 213−214 °C) suitable for X-ray analysis. Free **1** was isolated by dissolving the NaI complex (0.475 g) in CH_3CN (100 mL), washing with H_2O (3 × 25 mL), and then adding $CHCl_3$ (20 mL) to separate the phases. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Free **1** was obtained as a light yellow solid (mp 176−178 °C) by recrystallization from EtOH. The **1**·KI complex was prepared by dissolving **1** in hot EtOH (1 mL) and then adding an equimolar solution of KI dissolved in acetone (3 mL). The complex **1**·KI was obtained as colorless crystals [mp ∼305 °C (dec)].

Scheme 1



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Crystals of **1**, **1**·NaI, and **1**·KI were analyzed by X-ray crystallography. Receptor molecule **1** showed a conformation typical of noncomplexed macrocycles (Figure 1A). The macroring assumed the typical "rectangular" arrangement in which one methylene adjacent to each nitrogen atom was turned inward.[7,11] The ethylphenol sidearms were turned away from the macrocycle and oriented in approximately opposite directions. Bond distances and angles for the free receptor were all essentially as expected.

The complex formed between **1** and NaI was unusual (Figure 1B) but similar to the structure of the NaI complex of *N*,*N*′-dibenzyl-4,13-diaza-18-crown-6[12,13] and *N*,*N*′-di(2-methylnaphthyl)-diaza-18-crown-6.[13] The overall shape of the macrocycle was saddle-like. The cation was "immersed" in the macroring, and the two sidearms were extended upward, appearing to provide a cradle for the iodide counteranion. The 6 macroring heteroatoms (Z) are organized around the bound Na^+ in "distorted" octahedral geometry. The Z−Na−Z angles are expected to be 60° for a planar structure and 90° for an octahedral structure. In this case, the angles were 70.14° ± 4.43°, reflecting the lack of planarity. Five of the O−C−Z angles were ∼69°, but the sixth was 74.57°, causing the large deviation. The N−Na−N angle was 122.15°. The two Na−N distances were 2.52 and 2.60 Å. The Na−O distances were 2.35, 2.35, 2.38, and 2.47 Å. A striking feature of the complex was the fact that the two phenolic residues were twisted with respect to the macroring and both hydroxyl groups participated in hydrogen bonds to iodide (Figure 1B). The two phenolic oxygen atoms were about equidistant from iodide ($D_{O\cdots I}$ = 3.46 and 3.47 Å).

By far, the most remarkable result of this survey is that seen in Figure 1, panel C. The structure of **1**·K^+ shows the first evidence for cation-π interaction between the phenolic side chain

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(10) Data for **1**·NaI: ^{1}H NMR (CD_3OD, ref to 3.31 ppm): 2.59−2.65 (m, phenolCH_2, 4H), 2.74−2.80 (m, $CH_2N(CH_2)_2$, 12H), 3.63 (t, NCH_2CH_2O, 8H), 3.67 (s, OCH_2CH_2O, 8H), 6.69 (d, H2- & H6-phenol, 4H), 6.96 (d, H3- & H5-phenol, 4H). Anal. calcd for $C_{28}H_{42}O_6N_2NaI$: C, 51.54%; H, 6.49%; N, 4.29%. Found: C, 51.55%; H, 6.51%; N, 4.34%.
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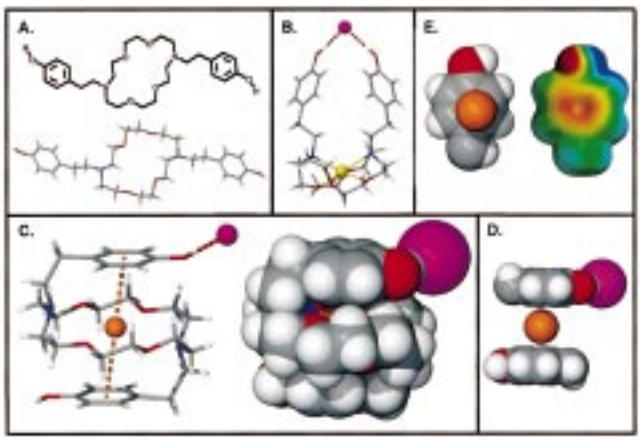

Figure 1. (A) Structural drawing of **1** and its solid-state structure shown in stick representation. (B) Structure of **1**·Na^+. (C) Structure of **1**·K^+. Dotted line indicates closest contact between ion and centroids. (D) Cutaway view of **1**·K^+ showing arenes, bound cation, and H-bonded I^-. (E) Orientation of K^+ with respect to K^+ (left) and calculated (6-31G**) electrostatic potential surface for 4-methylphenol.

of tyrosine and a K^+ cation. The macroring is nearly planar and in the D_{3d} conformation. Distances between the heteroatom donors and the bound K^+ are as expected.[7] In contrast to the other two structures, the sidearms are organized over and under the macroring making π-contacts with K^+. The arenes occupy the apical sites of the cation excluding solvent, water, and the iodide counterion (Figure 1D). As apparent from panels C−E of Figure 1, K^+ is offset slightly from the center of benzene. The K^+− centroid distance is 3.44 Å. The van der Waals' radius for 8-coordinate K^+ is 1.51 Å,[14] and the half-thickness for an aromatic ring is 1.75 Å. These values predict a K^+-centroid distance between the arene and K^+ of 3.26 Å. The experimentally determined value is 3.44 Å. The position of the cation relative to the arene agrees with the predicted acentric electrostatic surface (calculation conducted as described in ref 4) of 4-methylphenol (Figure 1E, red = negative charge).

The apparent "selectivity" observed between Na^+ and K^+ complexation deserves comment. In principle, Na^+, which has a higher charge density, should be more strongly complexed by a π-donor than should be K^+. This has been confirmed experimentally for benzene with Na^+ and K^+ (gas phase, difference in binding energy is 8.8 kcal/mol),[1,15] and phenol is anticipated to behave similarly. Although essentially featureless spheres, Na^+ and K^+ differ significantly in size (1.95 vs 2.66 Å).[14] Since no cation-π interaction is observed between Na^+ and **1**, we surmise that the difference in steric interactions, in particular the thickness of the macrocycle relative to the sizes of Na^+ and K^+, prevents the observation of a Na^+-arene interaction in this model system. The important principle is nonetheless clearly demonstrated for the K^+ ion case.

The results presented here, added to our previous studies of indolyl side chain complexation, remove any doubt about whether π complexation is a legitimate mode of cation binding for alkali metal cations. Solution studies are currently underway for this receptor, and related systems and will be reported in due course.

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Supporting Information Available: Crystal data and structure refinement for **1**, **1**·**NaI**, and **1**·**KI**. This material is available free of charge via the Internet at http://pubs.acs.org.

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