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The Indole Side Chain of Tryptophan as a Versatile π-Donor

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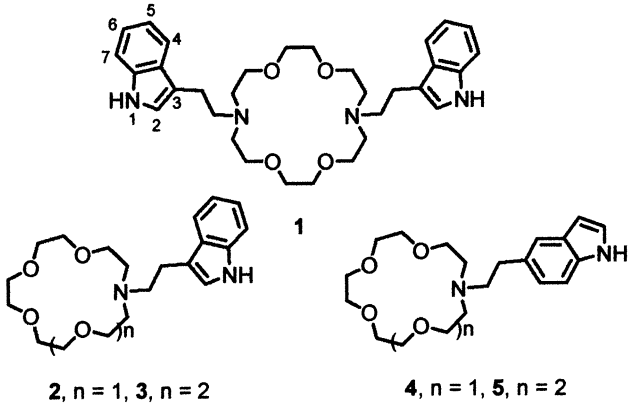
Hydrogen bonding[1] helps to define protein conformation and stabilize critical active-site arrangements.[2] Other weak forces such as hydrophobic and dipole−dipole interactions also contribute to stabilization, but documenting them has proved to be more challenging than the study of H-bonding.[3] Certain forces, such as C−H hydrogen bonding, were dismissed when first proposed[4] but are now recognized as being important contributors to conformational stabilization.[5] Alkali metal cation−π interactions[6] have received little attention, particularly in the biological context. A combination of mass spectral,[7−11] computational,[12−16] and solid-state studies[17,18] have helped to establish alkali metal cation−π interactions as relevant, if not yet clearly important, in biological systems.[15,16,19]

We have recently reported a two-armed lariat ether system as an experimental vehicle for the study of alkali metal cation−π interactions.[20] In complexes, Na^+ or K^+ is bound equatorially by the crown macroring, and the sidearm arenes occupy the axial positions. These receptors are potentially limited by the inherent thickness of the macroring, which may control the approach of a sidearm arene to the ring-bound cation. Steric factors may influence contact between the ring-bound cation and either the benzo or pyrrolo subcyclic units of indole. Calculations suggest that the benzene ring is the more electron-rich donor site but bis(indole) lariat (**1**) complexes showed binding exclusively to the pyrrolo subunit, possibly for steric reasons. We prepared single-armed, 15-membered-ring receptors to obviate the steric issues. Single-armed, 18-membered-ring analogues were prepared as well. We now report that cation−π interactions are observed with both Na^+ and K^+ when indole is part of a single sidearm linked either at the 3- or 5-position in 15- or 18-membered azacrown derivatives. The point of sidearm attachment in these complexes controls whether the benzo or pyrrolo subunit serves as π-donor for the ring-bound Na^+ or K^+ ion.

The compounds that are the subject of this report are shown as **1**−**5**. Compounds **2** and **3** were prepared as previously described.[21] Compounds **4** and **5** were synthesized as follows. 5-Formylindole was treated with CH_3PPh_3Br (NaH, DMSO) to give 5-vinylindole (95%). 2-(5-Indolyl)ethanol was obtained by hydroboration (BH_3·THF, 62%) and then converted into the corresponding tosylate (TsCl, Et_3N, CH_2Cl_2, 90%). Heating the tosylate (CH_3CN, reflux) with either aza-15-crown-5 or aza-18-crown-6 gave **4** (61%, oil) or **5** (67%, oil). Crystals suitable for X-ray analysis were grown under vapor diffusion conditions (ethanol/hexane).[20] The complexes obtained were **4**·$NaBPh_4$ (mp 202−203 °C, colorless rhombohedroids) and **5**·KPF_6 (mp 136−137 °C, colorless needles).



Structures of five alkali metal cation−π complexes are shown in Figure 1. The previously reported[20] structure of **1**·KI (Figure 1, panel a) shows the pyrrolo−K^+ contact typical of all **1**·MX complexes that we have studied. Potassium cation is embedded in the macroring, and the cation's apical positions are occupied by the pyrrolo subunit of indole. Indole's C2 atoms are closest to ring-bound K^+ at K−C2 distances of 3.29 and 3.34 Å. Iodide ion is excluded from the K^+ solvation sphere. The corresponding **1**·NaI complex has a Na^+−C2 distance of 3.23 Å.

Sodium does not fit as well in a 15-crown-5 macroring as does K^+ in 18-crown-6. The cation is said to "perch" on the 15-membered ring rather than "nest" in it.[22] We expected 15-membered-ring complexes to exhibit little macroring−sidearm steric hindrance. Further, when a single sidearm is present, we expected the arene to exert its full donor group effect upon the bound cation. The π-donor interaction between Na^+ and indole in **2**·$NaBPh_4$ is apparent in panel b of Figure 1. Two nearly identical complexes are found in the unit cell. The average O−Na^+ distances are typical, i.e., 2.36 and 2.37 Å. Likewise, the Na^+−N bonds, although longer (2.52, 2.60 Å), are also typical. In this case, the pyrrolo centroid is 2.62 and 2.71 Å from Na^+. The Na^+−C2 distances are 2.85 and 2.88 Å. In both complexes, the pyrrolo group as a whole is the donor; this is supported by the tilt of the indole ring, which is $\leq 5°$ from perpendicular in both cases. The diffuse tetraphenylborate anion is not in contact with Na^+ (Na^+−B distance >7 Å) in either complex.

The situation is different for the KPF_6 complex of **3**. In **3**·KPF_6, C2 is 3.22 Å from K^+, and the centroid-to-K^+ distance is 3.57 Å. The K^+−C2 distance in **3** is similar to that observed in **1**·KI. The K−centroid−C2 angle is 64°. The ~26° tilt from the perpendicular may be seen in Figure 1, panel c. Potassium−oxygen contacts in the macroring average a typical 2.76 Å, with a nitrogen−potassium distance of 3.0 Å.

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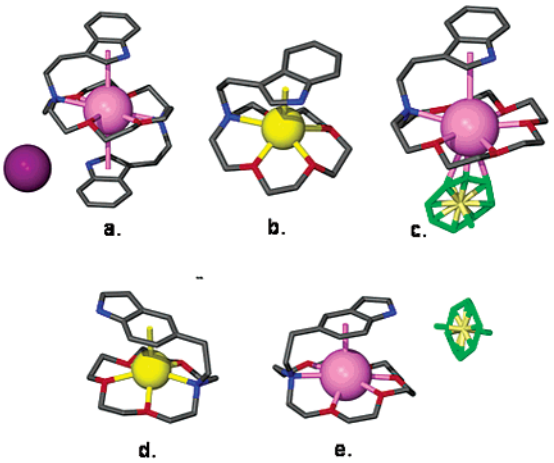

Figure 1.

Compounds **4** and **5** are isomers of **2** and **3**, respectively. The structures of **4**·$NaBPh_4$ and **5**·KPF_6 are shown in Figure 1 (panels d and e). When the sidearm is attached to indole's 5- rather than its 3-position, the cation-to-arene interaction occurs with the benzo, rather than the pyrrolo, subcyclic unit. Even so, the isomeric complexes show similar σ-bond distances (**4**, Na^+−O average 2.38 Å; **5**, K^+−O average 2.78 Å). The Na^+−arene distance in **4**·$NaBPh_4$ is 2.75 Å, but the contact angle is ∼19° from perpendicular. The K^+−arene contact angle in **5**·KPF_6 is nearly perpendicular, and the distance from the metal ion to the centroid is only 2.97 Å. Note that in both complexes, the M^+−C2 distance is >4.5 Å.

The ionic radii[23] of Na^+ and K^+ are ∼1.0−1.2 and ∼1.4−1.5 Å, respectively, depending on coordination number. The half-thickness of an arene is reported to be 1.72−1.80 Å.[24] Adding these values, the shortest possible Na^+−π and K^+−π contacts should be ∼2.7 and ∼3.1 Å. In **4**·$NaBPh_4$ and **5**·KPF_6, the observed distances are 2.75 and 2.97 Å, respectively. In the previously reported two-armed complexes, the M^+−π contacts were all in the 3.4−3.5 Å range. Moreover, indole was observed to π-complex exclusively with its pyrrolo, rather than its benzo, subunit.

The new receptor systems presented here show that indole, the arene terminus of tryptophan, is a versatile π-donor. Whether the five- or six-membered ring interacts most directly with Na^+ or K^+ is determined by structural as well as electronic factors. In nature, indole is not attached to a constraining macroring, and it seems likely that either aromatic subunit of indole may be available for cation complexation. The abundance of Na^+ and K^+ ions in all living systems makes interactions such as those modeled here probable if not imperative.

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