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Sodium cation complexation behavior of the heteroaromatic sidechains of histidine and tryptophan

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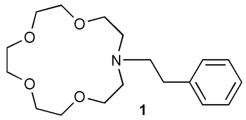
Three of the four essential amino acids that have aromatic sidechains exhibit cation–π interactions with Na^+ or K^+; histidine does not and is shown here to be a sigma donor.

Four of the 20 ‘essential’ amino acids possess aromatic sidechains.[1] They are phenylalanine (Phe, F, benzene), tyrosine (Tyr, Y, phenol), tryptophan (Trp, W, indole), and histidine (His, H, imidazole). The aromatic residues benzene, phenol, and indole are generally regarded as being π-donors that could complex alkali metal cations.[2–11] Recent X-ray crystal structure studies show that benzene,[12] phenol,[13] and indole[14] serve as neutral π-donors for alkali metals such as Na^+ and K^+.[15] In contrast, imidazole is electron deficient, which would make it a poor π-donor. The tertiary nitrogen atom of imidazole, however, is expected to function as a σ-donor for Lewis acids. That noted, to our knowledge there is no structural evidence of such a contact with Na^+, although *N*-methylimidazole is present in the K^+ coordination sphere in only one structure (CSD: PEBROD)[16] reported in the Cambridge Structural Database (CSD).

The present study had two goals. First, the two-armed lariat ether receptors that we have used to demonstrate cation–π interactions are sterically limited owing to the insertion of a cation into the macroring, the thickness of the macroring, and the size of the arene. We anticipated that 15-membered ring compounds having single arene-terminated sidearms would permit a closer and more focused study of the cation–aromatic interaction. Second, a single-armed lariat ether system terminated by imidazole might provide the first direct evidence for the possible nitrogen-to-sodium cation contact. We report the results of those studies here.

Compound **3** was obtained as previously described.[17] Compound **1** (73%, colorless oil) was prepared by alkylation of aza-15-crown-5 with 2-bromoethylbenzene. Compounds **2** (46%, light yellow oil) and **4** (25%, colorless oil) were prepared by treating tyramine with penta(ethylene glycol) ditosylate (reflux, Na_2CO_3, CH_3CN) or histamine dihydrochloride with penta(ethylene glycol) dimesylate (reflux, Na_2CO_3, CH_3CN). Crystals of each lariat ether complex with $NaBPh_4$ were grown under vapor diffusion conditions (ethanol–hexane) as previously described.[15] The complexes were obtained as follows: **1**·$NaBPh_4$, mp 202–203 °C, colorless parallelepipeds; **2**·$NaBPh_4$, mp 195–196 °C, colorless parallelepipeds; and **4**·$NaBPh_4$, mp 155–156 °C, colorless parallelepipeds. The observed solid state structures are shown in Fig. 1;† the BPh_4^- anion is not illustrated. The anion interlaces among molecules of complexes both blocking the ‘bottom’ of the complex and filling the apparent void.

The crown complex **1**·Na^+ is disordered but the BPh_4^- counter ion is not. The disordered structures are actually two superimposed but distinguishable complexes that are rotated ~22° relative to each other about a common Na–benzene centroid axis. The first of the two structures (shown in Fig. 1a) has a Na–N distance of 2.48 Å and average Na–O contacts of 2.40 Å. The second complex exhibits similar distance relationships: $d_{\text{Na–N}}$ = 2.56 Å and average Na–O contacts of 2.39 Å. The Na–centroid distances are 2.82 and 2.7 Å, respectively.



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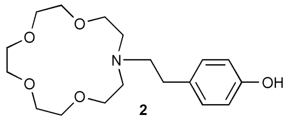

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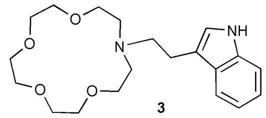

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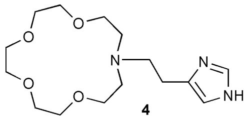

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Likewise, the sodium ion was perched ~0.68 Å above the mean plane of the macrocycle.

It is interesting to note that six donors to sodium (4 O, 1 N, π-system) in this complex all show strong contacts. The van der Waals radius of oxygen is 1.4 Å and the ionic radius of Na^+ is 0.98–1.02 Å. Thus, 2.4 Å is about the closest contact distance expected for this interaction. This is within experimental error of the average observed value for either complex (2.39, 2.40 Å). The π-interaction with the benzene ring is also strong, at least as judged by distances. An aromatic carbon atom is reported to have a van der Waals radius of 1.72–1.80 Å. These values suggest an arene thickness of 3.44–3.6 Å. If we estimate the arene thickness to be 3.5 Å, the half thickness is 1.75 Å. Adding this value to approximately 1 Å for the radius of sodium,[18] the minimum contact should be 2.75 Å. The observed value is 2.8 Å. We note also that the benzene ring is tilted about 8° from a line drawn from Na^+ perpendicular to the mean macroring plane.

Phenol-sidearmed receptor **2** forms a $NaBPh_4$ complex that is similar in most respects to **1**·$NaBPh_4$. The Na–N and average Na–O distances are 2.56 and 2.42 Å, respectively. The Na–arene distance is almost identical to that observed in **1**·$NaBPh_4$ at 2.82 Å. Although this is a remarkably close contact, the phenol residue is tilted about 12° from a perpendicular line dropped to Na^+. The tilt is slightly greater for **2**·$NaBPh_4$ than for

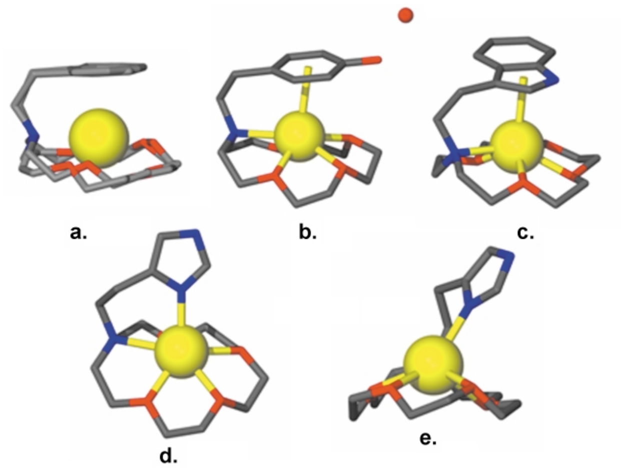

Fig. 1 Top, left to right: **1**·$NaBPh_4$, **2**·$NaBPh_4$·H_2O, **3**·$NaBPh_4$.[17] Bottom, two views of **4**·$NaBPh_4$ (anions not shown).

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1·$NaBPh_4$, a difference that may be attributable to an H-bond interaction between phenol and a water molecule (see Fig. 1b).

The unit cell for indole-sidearmed receptor **3** contains two distinct complexes of **3**·$NaBPh_4$ that are very similar but not identical. The Na–N bond distances are 2.52 and 2.60 Å, respectively. The average Na–O distances for the respective complexes are 2.39 and 2.42 Å. The contact distances between Na^+ and pyrrolo centroid of the indole are 2.71 and 2.62 Å in these two complexes. Indole is more electron rich than either phenol or benzene so the π-contact should be more favorable and the contact distance shorter. In these complexes, the Na–centroid distance is less than the estimated sum of the radii (2.75 Å, see above). As in previous structures,[15] the ring-bound metal cation is in contact with the pyrrolo subunit rather than the indole benzene ring.

The structure of **4**·$NaBPh_4$ (R_w = 0.068) constitutes a dramatic departure from the Na^+–arene π-complexes of **1**–**3**. The perching conformation of Na^+ and the σ-interaction between Na^+ and imidazole is apparent in panel d of Fig. 1. The four macroring oxygen donors contact Na^+ at distances of 2.36, 2.37, 2.46 and 2.48 Å. The Na^+ to macroring N distance is 2.6 Å, slightly longer than for the harder oxygen donors. Surprisingly, the Na^+ to imidazole nitrogen contact is 2.36 Å, as short as the shortest O–Na^+ distance. The sodium cation is 0.75 Å above the hypothetical plane formed by the five-ring donor atoms. The apical contact to imidazole appears vertical in Fig. 1 but is actually canted to the rear of the figure by nearly 30°.

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Notes and references

† *Crystal data*: for **1**·$NaBPh_4$: $C_{42}H_{49}BNNaO_4$, a = 10.7846(10), b = 26.228(3), c = 13.0227(13) Å, β = 95.557(2)°, monoclinic, space group $P2_1/c$, CCDC 191120. For **2**·$NaBPh_4$·$0.5H_2O$: $C_{42}H_{50}BNNaO_{5.50}$, a = 17.7598(11), b = 17.7598(11), c = 47.817(4) Å, orthorhombic, space group $I4_1/a$, CCDC 189430. For **4**·$NaBPh_4$: $C_{39}H_{47}BN_3NaO_4$, a = 13.6901(13), b = 18.9528(18), c = 27.676(3) Å, orthorhombic, space group *Pbca*, CCDC 189432. See http://www.rsc.org/suppdata/cc/b2/b204321c/ for crystallographic data in CIF or other electronic format.

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