Strongly Binding, Rapidly Complexing, Ion Selective Spherands

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Cyclic urea units bound to anisyl or methylene units have been incorporated into 20-membered ring hosts whose complexation of alkali metal and ammonium ions show high binding free energies, high extraction rates, and high ion selectivities.

The spherands, of which (**1**) is a prototype, are the strongest known binders of Li^+ or Na^+.[1] They owe this property to their organization of oxygen ligating sites during synthesis, rather than during complexation.[2] Although spherands complex Li^+ or Na^+ ions in $CDCl_3$ with rate constants in the 10^4 to 10^6 l mol^{-1} s^{-1} range, such ions are extracted very slowly from water by chloroform solutions of these hosts.[3] The urea oxygen is less sterically hindered, and is intrinsically a much better hydrogen bonding site than an anisyl oxygen.[4] These facts suggested the present study of the hosts (**2**—**5**), in which cyclic urea and anisyl units intermingle in 20-membered ring systems. Owing to their complexity, the compounds will be referred to in terms of combinations of letters whose identities are indicated.

Alkylation of HAh-Ah-AhH[2] with benzyl bromide and base gave HAh-Ab-AhH† (74%, amorphous), bromination of which with 2,4,4,6-tetrabromocyclohexadienone gave BrAh-Ab-AhBr† (60%, m.p. 144—147 °C). Methylation (MeI, K_2CO_3) of this diphenol produced BrA-Ab-ABr† (91%, m.p. 122—123 °C), which was metallated and carbonated to give HO_2CA-Ab-ACO_2H† (68%, m.p. 195—197 °C). The two carboxy-groups were subjected to the Curtius rearrangement ($SOCl_2$, NaN_3, toluene, heat) to give the corresponding bisisocyanate, which was treated with $Br[CH_2]_3NH_3$-Br and base to give Ab($ANHCONHCH_2CH_2CH_2Br)_2$† (79% overall, m.p. 228 °C, decomp.). When mixed with Bu^tOK–

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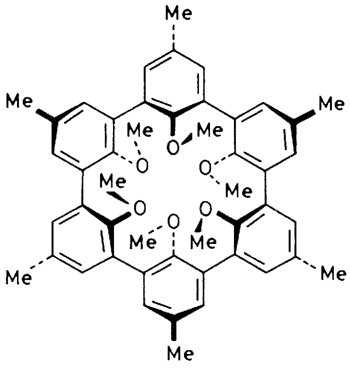
† These new compounds gave C and H (N when present) analyses within 0.30% of theory and ^1H n.m.r. and mass spectra compatible with their assigned structures.



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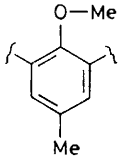

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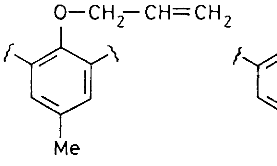

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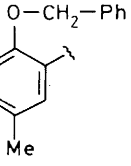

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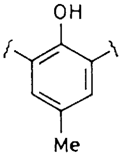

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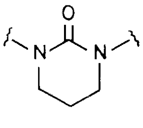

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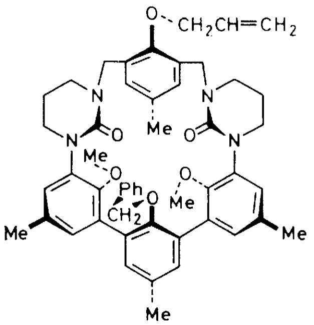

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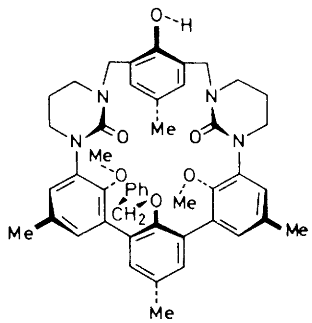

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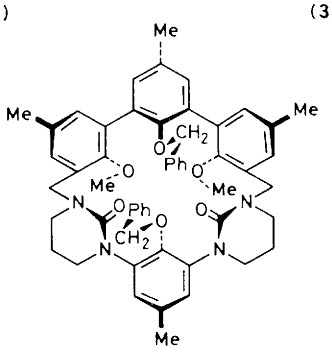

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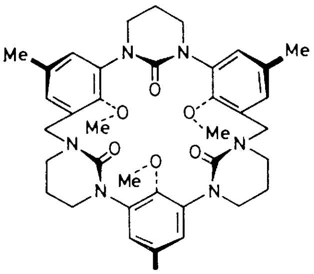

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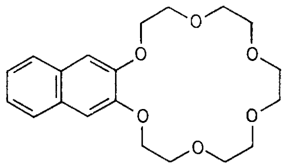

(6)

Bu^{t}OH, this compound gave HU-A-Ab-A-UH† (89%, m.p. 269—271 °C). Allylation of $HOCH_2AhCH_2OH$ with $CH_2{=}CHCH_2Br{-}K_2CO_3$ gave $HOCH_2AaCH_2OH$† (10%, m.p. 95—97 °C), which with PBr_3 gave $BrCH_2AaCH_2Br$† (54%, m.p. 77—79 °C). Condensation of HU-A-Ab-A-UH with $BrCH_2AaCH_2Br$ (high dilution, NaH, tetrahydrofuran, −78 °C to reflux) gave the macrocycle $Ab(AUCH_2)_2Aa$† (**2**, 41%, m.p. 249—255 °C), purified by direct crystallization and also through its crystalline NaBr complex. This macrocycle was deallylated with 10% Pd–C, EtOH, *p*-$MeC_6H_4SO_3H$ to give $Ab(AUCH_2)_2Ah$† (**3**, 25%, m.p. > 265 °C, decomp.).

Reduction of $HO_2CA{-}Ab{-}ACO_2H$ (see above) through its dimethyl ester (CH_2N_2) with $LiAlH_4$ gave $HOCH_2A{-}Ab{-}ACH_2OH$† (91%, m.p. 124—125 °C), treatment of which with PBr_3 gave $BrCH_2A{-}Ab{-}ACH_2Br$† (65%, amorphous). Benzylation of BrAhBr[5] with $PhCH_2Cl$ (K_2CO_3, KI, acetone) gave BrAbBr† (65%, m.p. 75—76 °C), which was lithiated (Bu^{s}Li, tetrahydrofuran) and carbonated to give HO_2CAbCO_2H† (72%, m.p. 134—135 °C). This diacid, when submitted to the Curtius rearrangement ($SOCl_2$, NaN_3, toluene, heat), gave OCNAbNCO, which with $Br[CH_2]_3NH_3Br$ and base gave $Ab(NHCONHCH_2CH_2CH_2Br)_2$† (38%, m.p. 174 °C). When treated with Bu^{t}OK–Bu^{t}OH, this compound yielded HU-Ab-UH† (83%, m.p. 276—278 °C). Condensation of $BrCH_2A{-}Ab{-}ACH_2Br$ with HU-Ab-UH (NaH, tetrahydrofuran, high dilution, −78 °C to reflux) produced $Ab(ACH_2U)_2Ab$† (**4**, 41%, m.p. 272—275 °C), purified by direct crystallization as well as through its NaBr complex.

Addition of H_2NANH_2 to $ClCH_2CH_2CH_2NCO$[6] gave $A(NHCONHCH_2CH_2CH_2Cl)_2$, which was directly converted (NaH–tetrahydrofuran) into HU-A-UH (23% overall, m.p. >270 °C). When $HANH_2$ was mixed with $COCl_2$ in tetrahydrofuran, HANHCONHAH† was produced (60%, m.p. 185 °C), which with $BrCH_2CH_2CH_2Br$ and NaH–tetrahydrofuran gave HA-U-AH† (89%, m.p. 185 °C). Demethylation of HA-U-AH with HBr–AcOH gave HAh-U-AhH† (77%, m.p. 245—247 °C, decomp.). This diphenol was brominated with 2,4,4,6-tetrabromohexadienone to produce BrAh-U-AhBr† (95%, m.p. 237—239 °C, decomp.), which was methylated (CH_2N_2) to give BrA-U-ABr† (70%, m.p. 181—183 °C). This compound was lithiated (Bu^{t}Li-tetrahydrofuran, −78 °C) and carbonated to provide $HO_2CA{-}U{-}ACO_2H$† (90%, m.p. 225—232 °C). Through its ester (CH_2N_2), the substance was reduced ($LiAlH_4$, tetrahydrofuran) to $HOCH_2A{-}U{-}ACH_2OH$† (83% overall, m.p. 201—203 °C), which with PBr_3 gave $BrCH_2A{-}U{-}ACH_2Br$† (76%, m.p. 192—195 °C). Condensation of $BrCH_2A{-}U{-}ACH_2Br$ with HU-A-UH (NaH, tetrahydrofuran, −78 °C to reflux, high dilution) produced the macrocycle $A(UCH_2A)_2U$† (**5**, 60%, m.p. 255 °C, decomp.), purified through its NaBr complex. Decomplexations of the NaBr complexes of (**2**), (**4**), and (**5**) were accomplished by dissolving them in $MeOH{-}H_2O$, heating the mixture to reflux for 2 h, and then allowing the MeOH to evaporate. The free hosts crystallize from the aqueous solution, thus providing a driving force for decomplexation. The ^1H n.m.r. spectra of the complexes and hosts are consistent with single or rapidly equilibrating entities being present.

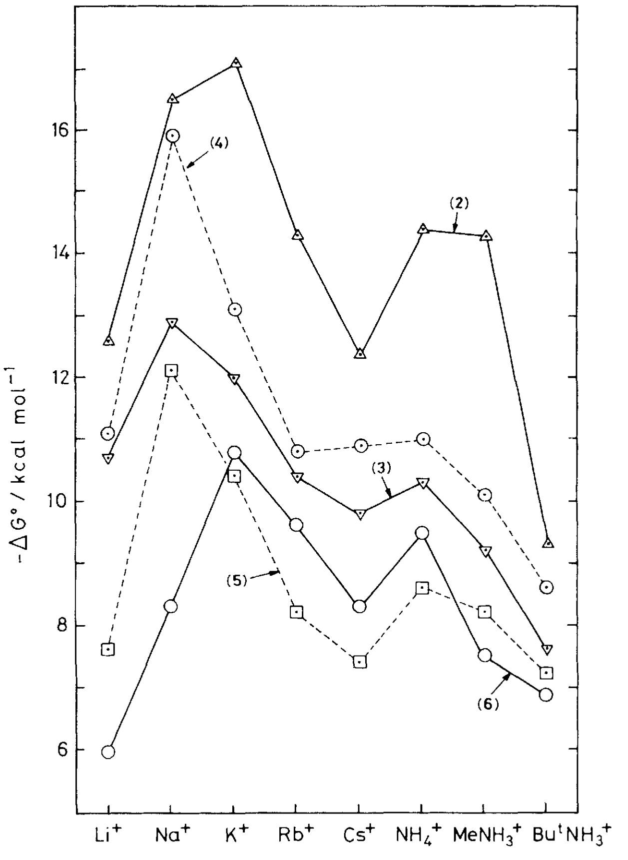

Figure 1. Complexing profiles for the hosts (2)—(6) with alkali metal and ammonium cations.

The binding free energies ($-\Delta G^\circ$ values) of the hosts (**2**)–(**5**) were determined at 25 °C by extracting alkali metal or ammonium picrate salt solutions in D_2O (0.050 or 0.001 M) with $CDCl_3$ solutions of (**2**)–(**5**).[3] Figure 1 provides a complexing profile for each of these hosts as well as one for 2,3-naphtho-18-crown-6 (**6**).[7]

The hosts decrease in their general binding ability toward most guests in the following order: Ab(AUCH$_2$)$_2$Aa (**2**) > Ab(ACH$_2$U)$_2$Ab (**4**) > Ab(AUCH$_2$)$_2$Ah (**3**) > A(UCH$_2$A)$_2$U (**5**) ~2,3-naphtho-18-crown-6 (**6**). This order correlates with conclusions based on Corey–Pauling–Koltun (CPK) molecular model examination of these compounds. In models of the five hosts, only Ab(AUCH$_2$)$_2$Aa (**2**) and Ab(ACH$_2$U)$_2$Ab (**4**) contain *enforced cavities* lined by the unshared electron pairs of potentially ligating oxygens. These compounds are clearly spherands.[1–3] In models of Ab(AUCH$_2$)$_2$Aa (**2**), each oxygen of the U–A–Ab–A–U units must be *anti*- to its flanking oxygen, whereas the three oxygens of the UCH$_2$AaCH$_2$U unit are probably *syn* to one another. This arrangement is found in the crystal structures of complexes of A′(A′UCH$_2$)$_2$A, in which A′ equals A minus the aryl methyl.[8] The binding profiles of Ab(AUCH$_2$)$_2$Aa and A′(A′UCH$_2$)$_2$A closely resemble one another.[8] Two isomeric models of Ab(ACH$_2$U)$_2$Ab (**4**) can be constructed. In the more likely structure, the two PhCH$_2$O oxygens are *syn* to one another and the other four oxygens are all on the opposite side of the macro-ring. Only this isomeric structure provides binding sites at all complementary to RNH$_3^+$ ions, whose free energies of binding to (**4**) range from 8.6 to 11 kcal mol^{-1}.‡ In the less likely structure, the two PhCH$_2$O oxygens are *anti* to one another and each of the six oxygens is flanked by two *anti* oxygens, as in A(AA)$_2$A (**1**). Molecular models of Ab(AUCH$_2$)$_2$Ah (**3**) exist in several conformations in which intramolecular ArOH . . . O hydrogen bonds occupy the cavity and must be broken before guests can enter. Unlike models of (**2**)—(**4**), that of A(UCH$_2$A)$_2$U (**5**) allows the OMe groups to pass through the centre of the macro-ring and the Me groups to occupy the potential cavity. Compound (**5**) is almost as conformationally mobile as chorand (**6**), whose crystal structure shows the complete absence of any cavity.[9] These results illustrate the dominating dependence of high binding free energies on the organization of hosts during synthesis rather than during complexation.

Spherands A(AA)$_2$A (**1**), Ab(ACH$_2$U)$_2$Ab (**4**), and Ab-(AUCH$_2$)$_2$Aa (**2**) differ from one another in ways that correlate with their structures. Thus (**1**) binds Li$^+$, Na$^+$, and K$^+$ with $-\Delta G^\circ$ values (kcal mol^{-1}) of >22, 19, and <6, respectively. This 18-membered ring host forms only capsular complexes, and these only with small ions. Since no electron pairs can face outward to contact either solvent or guest, extractions occur slowly. Spherand Ab(ACH$_2$U)$_2$Ab (**4**) binds Li$^+$, Na$^+$, and K$^+$ with $-\Delta G^\circ$ values of 11.1, 15.9, and 13.3, respectively, and extractions occur rapidly. In this 20-membered ring host, the urea oxygens are exposed to solvent and guest prior to the formation of capsular, nesting, or perching complexes. Although all three types are possible, the capsular complex with Na$^+$ is the most stable since the enforced cavity possesses a diameter complementary to that of Na$^+$. Spherand Ab-(AUCH$_2$)$_2$Aa (**2**), whose macro-ring is also 20-membered, binds Li$^+$, Na$^+$, and K$^+$ with $-\Delta G^\circ$ values of 12.6, 16.5, and 17.1, respectively, and extractions occur rapidly. This host and its analogues also form capsular, nesting, or perching complexes,[8] the capsular complexes of Na$^+$ and K$^+$ being the most stable.[8] The striking difference of 5 kcal mol^{-1} in structural recognition of MeNH$_3^+$ over Bu^{t}NH$_3^+$ by (**2**) is obviously due to steric effects.

These results further demonstrate that molecular design and synthesis can provide hosts whose binding cavities are organized prior to complexation, and which display different ion selectivities, extraction rates, and binding free energies.

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‡ 1 cal = 4.184 J.