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N,N'-BIS(SUBSTITUTED)-4,13-DIAZA-18-CROWN-6 DERIVATIVES HAVING PI-DONOR-GROUP-SIDEARMS: CORRELATION OF THERMODYNAMICS AND SOLID STATE STRUCTURES

Kristin A. Arnold, Anthony M. Viscariello, MinSook Kim,
Richard D. Gandour,+ Frank R. Fronczek,+ and George W. Gokel*
Departments of Chemistry, University of Miami,
Coral Gables, Florida 33124, +Louisiana State University,
Baton Rouge, Louisiana 70803-1804 U.S.A.

Summary: Solution thermodynamic data and solid state structure information are used to show that a series of N,N'-bis(substituted)-4,13-diaza-18-crown-6 (BiBLE) derivatives which lack oxygen or nitrogen donor groups in the sidearms do not utilize the sidearms for binding but show considerable variation in their binding constants.

The nitrogen-pivot, bibracchial lariat ethers (BiBLEs)[1,2] have proved to be an interesting group of compounds both in terms of their cation binding strengths and selectivities. In the studies previously reported, compounds were designed to have "traditional" donor groups, such as ether oxygen, present in the sidearms. As our understanding of the complexation process increased, we became interested to see if such non-traditional donors as alkene or alkyne could, by virtue of enforced proximity, be induced to serve as apical donor groups in bibracchial lariat ether complexes. It is well-known that silver cations interact with pi-bonds[3] but there is, to our knowledge, no evidence that such interactions have ever been detected between alkenes and alkynes and either Na^+ or K^+. We reasoned that if the primary solvation of the cation could be effected by oxygen and nitrogen macroring donors, the pi-donor sidearms might be induced to add the additional solvation required to make the complexes three-dimensional. The sidearms are arranged geometrically so that they would have to compete only with solvent or solvent and counteranion. We report below preliminary results that demonstrate that although the sidearms do not interact directly with the ring-bound cation, they strongly influence the binding by interaction with solvent.

Ligand syntheses. The compounds prepared for use in this study are all based upon the 4,13-diaza-18-crown-6 framework. Their structures are shown in the Table below. The sidearms are: n-propyl, **1**;[4] allyl, **2**;[4] propargyl, **3**;[4] cyanomethyl, **4**; and benzyl, **5**.[1,4] The five compounds were prepared either by the previously reported, single-step synthesis in which R-NH_2 (where R is the incipient sidearm) is allowed to react with triethylene glycol diiodide in the presence of sodium carbonate and acetonitrile,[1] or by the lengthier but higher yielding, two-step process.[4]

Cation binding studies. The affinities of compounds **1-4** for Na^+ and K^+ and **5** for Na^+ were measured in anhydrous methanol solution at 25 °C using ion selective electrode methods as previously described.[5] The thermodynamic components of the binding were determined as previously reported.[6] The results

are shown in Table I.

Table. Equilibrium constants and thermodynamic components of the cation affinities[a]

Compound No.	Sidearm	-----log K_S----- Na^+	K^+	---Sodium cation--- ΔH	$T\Delta S$	--Potassium cation-- ΔH	$T\Delta S$
-	18-Crown-6	4.34	6.09	-7.40±0.11	-1.50±0.09	-11.3±0.02	-3.03±0.04
1	$CH_2CH_2CH_3$	2.86	3.77	-2.82±0.05	1.08±0.04	-6.28±0.27	-1.14±0.30
2	$CH_2CH{=}CH_2$	3.04	4.04	-3.56±0.23	0.59±0.20	-7.34±0.02	-1.84±0.01
3	$CH_2C{\equiv}CH$	3.61	4.99	-4.97±0.04	-0.05±0.12	-4.97±0.04	-0.05±0.12
4	CH_2-CN	2.69	3.91	-4.87±0.08	-1.20±0.10	-9.54±0.11	-4.21±0.09
5	$CH_2C_6H_5$	2.68	ND[b]	-4.53±0.05	-0.82±0.07	ND	ND
-	$CH_2CH_2OCH_3$	4.77	5.52	-7.20±0.05	-0.73±0.08	-8.81±0.03	-1.28±0.02

a. In anhydrous CH_3OH at 15-41 °C as described in reference 6a. Log K_S values in M^{-1}, enthalpy values in kcal/mol; entropies in eu. b. ND means not determined.

None of the compounds, **1-5**, contains either an oxygen or nitrogen donor in the sidearm. These compounds thus lack traditional donor groups and we anticipated essentially similar binding behavior from each. Although the binding constants for Na^+ and K^+ are well below the values observed for 18-crown-6 or a BiBLE having sidearm donors, there is considerable variation in the binding strengths. From the gradual increase in binding strength in the series **1, 2, 3**, one might assume that binding is enhanced by a pi-interaction. The crystal structures reported below fail to confirm this interpretation. Alternatively, one may consider that decreasing sidearm size, at least as judged by A values,[7] in this series makes binding more favorable for **1** than for **2** and so on. The latter argument fails as well since the cyanomethyl sidearm of **4** is isosteric to propargyl and the binding constant differs by a power of ten. Indeed, the enthalpy contributions to Na^+ binding are nearly identical in both cases but differences in entropy, due to changes in solvation, account for the variation. The most dramatic example is observed when K^+ binding to **3** and **4** is compared. The K^+ binding differs by a power of ten, but the enthalpies differ by nearly 5 kcal. Moreover, the higher enthalpy is associated with the weaker binder. The lesson is clearly that a simple, enthalpic interpretation of binding constants is, at the least, questionable practice.

Structures of BiBLEs without traditional sidearms and their complexes with K^+. We show ORTEP plots[8] for the solid state structures of N,N'-bis(benzyl)-4,13-diaza-18-crown-6 and its KSCN complex along with the previously reported KSCN complex of N,N'-bis(propargyl)-4,13-diaza-18-crown-6 and the structure of "free" **3**. The latter is actually a remarkable tetrahydrate in which two water molecules bind the macroring from above. These, in turn, bind another water molecule that serves as a relay to the bottom of the next macrocycle. In none of these cases is the sidearm involved in cation binding but in both KSCN complexes, the cations are solvated alternately by one end of the anion and then the

other. In the former case (Figure 1a), the sidearms are turned away from the cation confirming the important role of solvent in the complexation process. In the absence of cation (Figure 1b), the complex is still not "free." Indeed, four molecules of water form what appears to be essentially a molecular channel through the crystal. Again, the sidearms of the host do not interact with the guest.

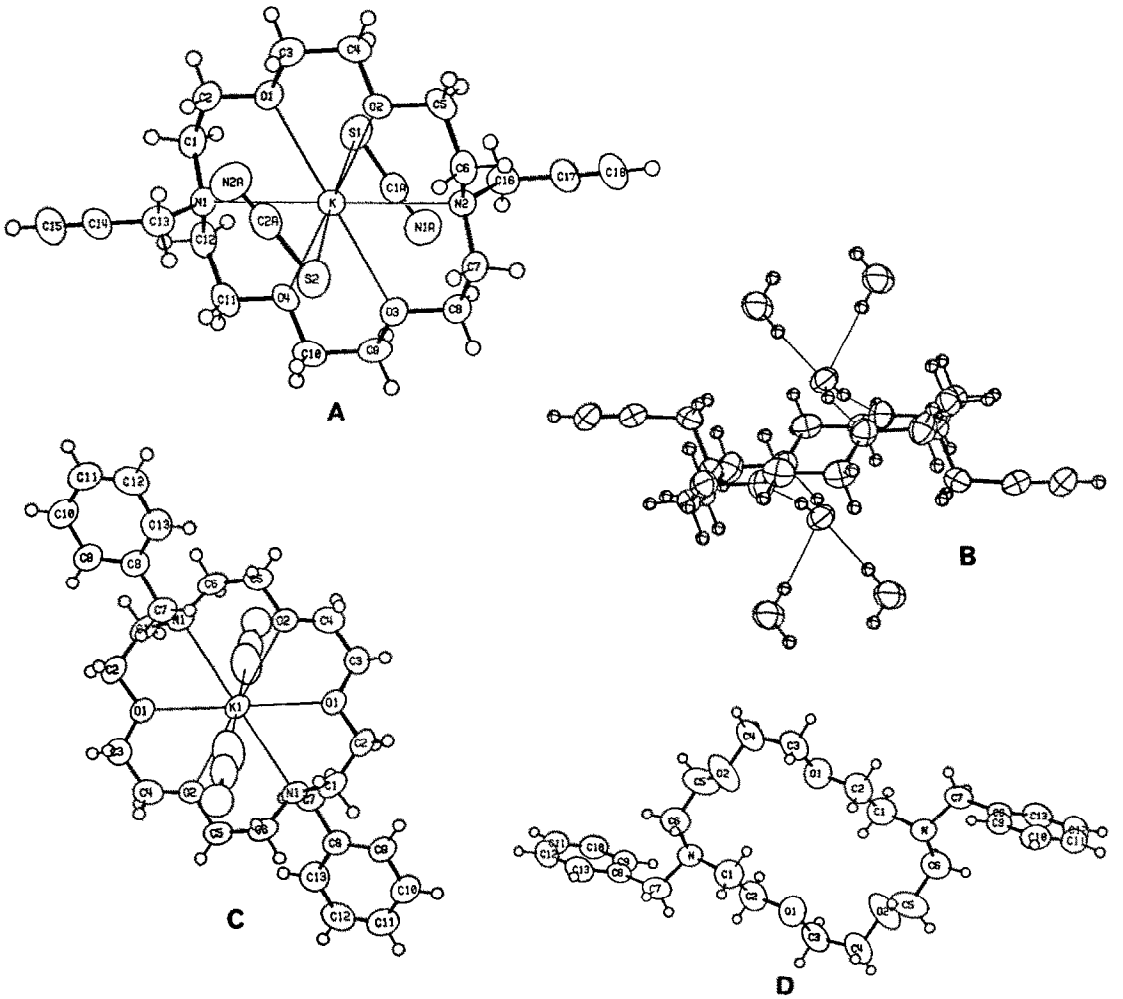

Figure 1. Solid state structures of (a) **3**·KSCN;[4b] (b) **3**·4H_2O; (c) **5**·KSCN; (d) **5.**

The complexation of cations by lariat ethers involves not only contributions from macroring and sidearm, the role of solvent and solvation are crucially important. The extraordinarily large variation in cation binding strengths illustrated by solution thermodynamic studies and X-ray crystallographic information sound an important note of warning for the enthalpic interpretation of cation-macrocycle interactions.

Experimental Section

N,N'-bis(Propyl)-4,13-diaza-18-crown-6, 1, was obtained as previously described[4] (0.51g, 78%) as a transparent oil (bp 130-131 °C/0.06 torr).

N,N'-bis(2-Allyl)-4,13-diaza-18-crown-6, 2, was obtained as previously described[4] (0.44g, 26%) as a white crystalline solid (mp 44-45°C).

N,N'bis(2-Propargyl)-4,13-diaza-18-crown-6, 3, was prepared as previously described.[4] Chromatography (alumina, 0-5% 2-propanol:hexanes) afforded an impure oil which was dissolved in $CHCl_3$ (20 mL). To this solution was added excess (10 g, 0.1 mol) solid KSCN while stirring. After 30 minutes, the solution was filtered and concentrated in vacuo. Recrystallization of this solid afforded **3**·KSCN as white crystalline solid, mp 214-215 °C. Anal. Calcd. for $C_{18}H_{30}N_2O_4$·KSCN: C, 52.38; H, 6.94. Found: C, 52.11; H, 6.97%. The solid thus obtained was dissolved in $CHCl_3$ (200 mL), washed with H_2O (2 x 250 mL), dried ($MgSO_4$), and concentrated in vacuo. Crystallization ($CHCl_3$: hexanes) afforded pure **3** (7.00 g, 22%) as a white solid, mp 41-42 °C. ^1H NMR: 3.6 (m, 20H, propargyl CH_2 and crown CH_2-O-), 2.8 (t, 8H, NCH_2), 2.2 (S, 2H, acetylene-H). IR (KBr): 3140 (s), 2100, 1630, 1450, 1350. Anal. Calcd. for $C_{18}H_{30}N_4O_2$: C, 63.87; H 8.93; N, 8.20. Found: C, 63.94; H, 9.10; N, 8.30.

N,N'-bis(2-Propargyl)-4,13-diaza-18-crown-6·3H$_2$O. Compound **3** (200 mg) was dissolved in $CHCl_3$ (20 mL) and washed with H_2O (2 x 50 mL). The organic phase was concentrated in vacuo. The resulting oil was crystallized from hexanes (10 mL), and then recrystallized (hexanes), mp 41-42 °C. Note that the structure shown is of the tetrahydrate obtained from the sample described above.

N,N'bis(Cyanomethyl)-4,13-diaza-18-crown-6, 4. To a stirred solution of (0.52 g, 2 MM) 4, 13-diaza-18-crown-6, 19, (0.38 g, 5 mM) and chloroacetonitrile in 30 mL of dry acetone was added anhydrous sodium carbonate (0.32 g). The mixture was refluxed with vigorous stirring for 10 h and filtered. The filtrate was evaporated in vacuo, to obtain a dark yellow solid that was decolorized using activated charcoal in benzene (50 mL). Recrystallization from THF (20 mL) gave pure **4** (0.54 g, 75%) as a white solid, mp 105-105.5 °C. ^1H-NMR ($CDCl_3$): 3.92 (s, 4H); 3.60 (m, 16H); 2.75 (t, 8H). IR (KBr): 2260. Anal. calcd. for $C_{16}H_{28}N_4O_4$: C, 56.44; H, 8.30; N, 16.46%. Found: C, 56.50; H, 8.31; N, 16.38%.

N,N'bis(Benzyl)-4,13-diaza-18-crown-6, 5, was obtained as described previously (mp 80-81 °C) and had physical properties identical to those reported.[4]

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8. Full details of these and several related structures will be published shortly.

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