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NOVEL SYNTHETIC ACCESS TO 15- AND 18-MEMBERED RING DIAZA-BIBRACCHIAL LARIAT ETHERS (BiBLEs) AND A STUDY OF SIDEARM-MACRORING COOPERATIVITY IN CATION BINDING

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Abstract An extremely practical synthesis of 4,10-diaza-15-crown-5, 4,13-diaza-18-crown-6, and symmetrically N,N'-disubstituted derivatives thereof, is presented along with the first survey of cation binding data for the 15-membered ring systems.

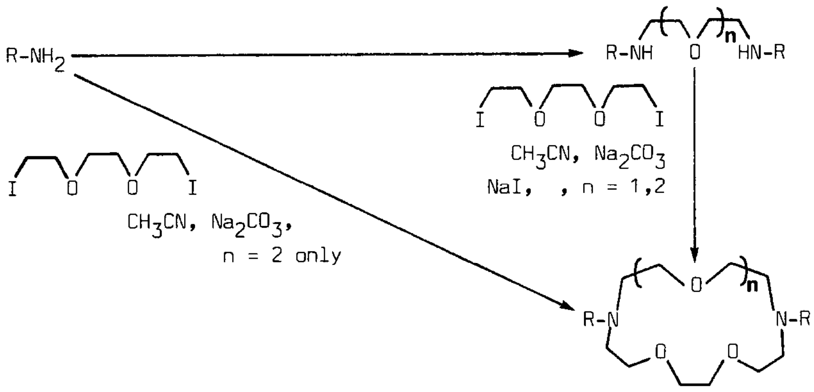
Our recent observation that 4,13-diaza-18-crown-6 derivatives (designated using the compound number and the suffix **B** herein), when substituted by polar sidearms,[1] exhibit Ca^{2+}, rather than the expected[2] K^+, selectivity has encouraged us to extend our studies to the corresponding 15-membered ring systems (designated using the compound number and suffix **A** herein). How these molecules bind cations like Na^+ and K^+ is an especially interesting question since quite different sidearm-macroring arrangements are possible for the 15- and 18-membered ring BiBLEs. Although there is considerable literature available on 4,13-diaza-18-crown-6, **1B**, and its derivatives,[3] relatively little effort has been expended in the synthesis of the 15-membered ring analogs.[4] In addition, relatively few cation binding studies have been reported for 4,10-diaza-15-crown-5, **1A**, or its N,N'-disubstituted derivatives.[5]

We have shown in previous work[2] that the "hole-size" concept does not explain cation binding selectivities in "flexible" macrocycles. We know from crystal structure data previously published for N,N'-bis-(2-hydroxyethyl)-3,14-diaza-18-crown-6 (HO-E-2.2-E-OH) that Na^+ is bound in a basket-shaped cavity created by the macroring and both sidearms.[6] In this case, the ring does not encircle the cation at all. We were interested to see how the smaller ring systems, which are inherently less flexible than the 18-membered ring systems, and the sidearms cooperate to bind cations.

We previously reported[1] that derivatives of **1B** could be prepared by a single step reaction beginning with an aliphatic amine and 1,2-bis-(2-iodoethoxy)ethane, **9.** Stirring an acetonitrile solution of **9** with Na_2CO_3 and $R-NH_2$ at reflux temperature for ca. 24 h, affords N,N'-disubstituted derivatives of **1B** in yields which are typically 20-30%. The convenience of the method makes it attractive even though the yields are not high. This approach is obviously inappropriate to prepare the 15-membered ring compounds. We have therefore developed a method which permits the synthesis of **1A** and its derivatives. This method is also applicable to the 18-membered ring derivatives of 1B and can be used instead of the single-step method noted above.[1] The two approaches for the synthesis of **1B** are shown in Scheme 1 below.

N,*N*-Dibenzyl-4,10-diaza-15-crown-5, **3A**, is obtained in 72% yield by reaction of 1,2-*bis*-(2-iodoethoxy)ethane with 2,2'-*bis*-(benzylamino)diethyl ether, **10**. The former is prepared as shown in Scheme 2 (R = benzyl).

Scheme 1



Scheme 2

$$R\text{-}NH_2 \;+\; Cl\text{-}CO\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CO\text{-}Cl \xrightarrow{C_6H_6,\ Et_3N\ (1\ Eq.)\ 93\%} R\text{-}NH\text{-}CO\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CO\text{-}NH\text{-}R$$

$$\xrightarrow{LiAlH_4\ \text{or}\ BH_3\ \text{in THF},\ 88\%} R\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}R$$

An example of the experimental sequence for *N*,*N*'-dibenzyl-4,10-diaza-15-crown-5, **3A**, the most versatile of the 15-membered ring BiBLEs, is given below.

Preparation of 1,7-Dibenzyl-2,6-dioxo-4-oxa-1,7-diazaheptane, 11. A solution of benzylamine (19.3 g, 0.18 mol) and triethylamine (18.2 g, 0.18 mol) in C_6H_6 (100 mL) was added slowly at 0-8 °C to a stirred solution of diglycoyl chloride (13.0 g, 0.076 mol) in benzene (100 mL). After addition, the mixture warmed to room temperature and was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (200 mL) and washed with 20 mL each of 3*N* HCl, *N* NaOH, and H_2O. The organic phase was dried (Na_2SO_4), concentrated, and the product crystallized (C_6H_6) to give the diamide (22.2 g, 93%) as a white solid, mp 124-125 °C. *Anal*. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.20; H, 6.47; N, 8.97. Found: C, 69.08; H, 6.36; N, 9.00.

Reduction of 11 to 10. Solid **11** (3.7 g, 12 mmol) was added to a stirred, 0 °C solution of $BH_3 \cdot THF$ (96 mL, 1.0M). The reaction was stirred at room temperature for 2 days. Excess BH_3 was destroyed by addition of H_2O and the mixture was concentrated *in vacuo*. Hydrochloric acid, (6N, 50 mL) was added, the solution was heated at reflux for 4h, cooled, adjusted to pH 9 with NaOH, diluted (H_2O) until all salts dissolved and then extracted with $CHCl_3$ (3 x 100 mL). The $CHCl_3$ extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Bulb-to-bulb distillation (Kugelrohr apparatus, 150-155 °C/0.2 torr) gave diamine **10** (3.0 g, 88%) as a colorless oil. ^1H-NMR ($CDCl_3$): 1.69 (s, 2H); 2.77 (t, 4H); 3.55 (t, 4H); 3.77 (s, 4H); 7.31 (s, 10H). *Anal.* calcd for $C_{18}H_{24}N_2O$: C, 76.00; H, 8.42; N, 9.85. Found: C, 75.93; H, 8.68; N, 9.66.

Cyclization. A solution of 1,7-dibenzyl-4-oxa-1,7-diazaheptane, **10**, (4.30 g, 15 mmol), diiodide 9 (7.4 g, 20 mmol), Na_2CO_3 (10.6 g, 100 mmol), and NaI (1.5 g, 10 mmol) in MeCN (400 mL) was heated at reflux for 19 h. The reaction was cooled, filtered, and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (100 mL), and extracted with HCl (6N, 2 x 50 mL). The combined aqueous phases were adjusted to pH 8-10 with Na_2CO_3 and then extracted with $CHCl_3$ (2 x 100 mL) and concentrated *in vacuo*. Column chromatography (alumina) 10% EtOAc/hexanes, gave 4.3 g (72%) of **3A** as a transparent oil. ^1H-NMR ($CDCl_3$): 2.65-2.90 (m, 8H), 3.47-3.63 (m, 16H), 7.28 (s, 10H). *Anal.* Calcd for $C_{24}H_{34}N_2O_3$: C, 72.31; H, 8.62; N, 7.03. Found: C, 72.64; H, 8.70; N, 7.07.

The compounds prepared by this method and their Na^+ and K^+ binding constants are reported in the Table. For the two-armed systems, steric factors and three-dimensional structure are important in determining the overall binding properties. Molecular models (CPK) of **7** and **8** suggest that binding from the same side of the macroring as observed for the Na^+ complex of HO-E-2.2-E-OH[6] would be very sterically hindered. The furan oxygen of 7 (contained in a five-membered ring and two carbon atoms away from the macroring) is more sterically accessible than the methoxy oxygen of **8** (three carbons away from the macroring). Consequently, Na^+ and K^+ binding constants for **8** are uniformly lower than for 7 even though both use sp^2 oxygen donor sidearms. Note also that when the macrorings are smaller, the steric influence of the sidearms is magnified. The sidearms in **6A** and **B** can bind Na^+ or K^+ respectively from the same or opposite sides of the macroring. This versatility should increase the net stability of the cation complexes. We suspect that 6A forms a basket-shaped complex with Na^+ and the stability of this complex in MeOH solution exceeds that of any previously studied complex utilizing only ether and amine donor groups.

We suggest that the magnitude of binding in these BiBLE complexes is determined by: (i) The type of oxygen donor group (sp^2 vs. sp^3); (ii) The steric accessibility of the donor group to the macroring bound cation; and (iii) The number (and stability) of the three-dimensional geometries the complex can adopt. The latter is related to steric accessibility because a basket-shaped complex should form more readily when the sidearm is less bulky. Studies are currently underway to confirm these assertions.

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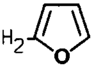
Table: Cyclization Yields, Sodium, and Potassium Cation Binding Data^a

Sidearm	Cpd. No.^{b}	Yield of 15	Log Ks		Cpd. No.^{b}	Yield of 18^c	Yield of 18^d	Log Ks	
			Na$^+$	K$^+$				Na$^+$	K$^+$
H^e	**1A**	66^f	<1.5	<1.5	**1B**	27^f	63^f	1.50	1.80
n-butyl	**2A**	--	--	--	**2B**	--	77	2.84	3.82
$CH_2C_6H_5$	**3A**	72	2.59	2.12	**3B**	29	68	2.72	3.38
$(CH_2)_5CH_3$	**4A**	--	--	--	**4B**	7	32	2.89	3.78
$(CH_2)_8CH_3$	**5A**	--	--	--	**5B**	11	--	2.95	3.70
CH_2CH_2-O-CH_3	**6A**	38	5.09	4.86	**6B**	--	43	4.75	5.46
CH_2- 	**7A**	67	3.99	3.87	**7B**	27	62	3.77	4.98
CH_2-C_6H_4-2-OMe	**8A**	52	3.59	3.13	**8B**	30	--	3.65	4.94

Notes (a) Yield data are for isolated, purified compounds; binding data were determined in anhydrous MeOH solution at 25 °C using ion selective electrode techniques as described in reference 2. (b) The compound number plus **A** refers to 4,10-diaza-15-crown-5 and its derivatives; **B** refers to the symmetrical 18-membered ring BiBLE. (c) Prepared by previously reported single-step method. (d) Prepared by two-step method described here. (e) Obtained by hydrogenolysis of the corresponding bis-benzyl derivative. (f) Yield corresponds to cyclization followed by hydrogenolysis.

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