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The Remarkable Indifference of Alkali Metal Cation Binding Constants to Sidearm Thioether and Sulfoxide Donors in Azalariat Ethers

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Abstract. The first example of a lariat ether containing a sulfur sidearm donor is reported here along with a comparison of cation binding strengths to Na^+ and K^+. The binding strength differs remarkably little from analogs completely lacking a sidearm donor group and similar results are observed for the novel sulfoxide analog.

Key words. Cation binding, complexation, crown ether, lariat ether, sulfur donor, sulfoxide donor.

1. Introduction

Almost as soon as Pedersen reported the syntheses of crown ethers [1] the search for relatives having non-oxygen heteroatoms began. Indeed, Pedersen himself prepared a number of sulfur-containing macrocycles [2] and these and others were the basis of early cation binding studies by the group of Izatt, Christensen, Bradshaw, and others [3]. Exchange of an oxygen heteroatom was an early variant of the original cryptands [4]. Great attention and interest has also focused on the polythiamacrocycles as a result of their ability to bind copper [5] and a number of other coinage or transition metal cations [6]. After the initial interest in sulfur as a substitute for a macroring oxygen atom, little new information has emerged.

A major goal of our program in lariat ether chemistry [7] is to develop a general understanding of alkali and alkaline earth cation binding strengths and affinities by synthesizing and comparing a number of systematically varied structures. After an initial effort to prepare carbon-pivot lariat ether compounds [8] we focused our attention on the more flexible and versatile nitrogen-pivot systems [9]. Much is now known about the cation binding strengths and selectivities of systems containing sidearm oxygen(s) but a comparison of this information with corresponding data for sulfur and sulfoxide has, until now, been unavailable.

2. Experimental

Melting points (Thomas-Hoover apparatus, open capillaries) are uncorrected. Infrared spectra were recorded on a Perkin Elmer 281 spectrophotometer as neat samples unless otherwise noted. Spectral bands are reported in cm^{-1} and calibrated

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against the 1601 cm^{-1} band of polystyrene, ^{1}H-NMR spectra were recorded at 60 MHz as approximately 15 wt. % solutions in $CDCl_3$ unless otherwise specified. Chemical shifts are reported in ppm downfield from internal Me_4Si and are reported in the order: chemical shift, spin multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and integration. Combustion analyses (C,H,N) were performed by Alantic Microlabs, Atlanta, GA.

2.1. SYNTHESIS OF COMPOUNDS

All reagents were the best grade commercially available and were used without further purification unless otherwise specified. All solvents were distilled prior to use and tetrahydrofuran (THF) was distilled from $LiAlH_4$ or Na-benzophenone. Benzene and dioxane were dried by distillation from Na-benzophenone under a dry N_2 atmosphere immediately prior to use. Dimethylformamide was distilled from CaO prior to use. Oven temperatures are given for bulb-to-bulb distillations conducted in a Kugelrohr apparatus. Preparative chromatography columns were packed with MCB activated Al_2O_3 (80–300 mesh, chromatographic grade). Precoated sheets (aluminum oxide 60 F-254 neutral-Type E or silica gel 60 F-254) 0.2 mm thick were used for t.l.c. analyses.

2.1.1. *N-Benzylaza*-15-*crown*-5

Benzyl chloride (557.0 g, 4.4 mol) was allowed to react with diethanolamine (420.0 g, 4.0 mol) to afford *N*-benzyldiethanolamine after vacuum distillation (609 g, 78%): bp 143–146°C (0.1 torr). *N*-Benzylaza-15-crown-5 was prepared by cyclization of *N*-benzyldiethanolamine (195 g, 1.0 mol) as described in [9]. The crude mixture was distilled [Kugelrohr, 125°C (0.1 torr)] to give the macrocyclic polyether (142.0 g, 46%) as a colorless oil.

2.1.2. *Aza*-15-*crown* 5, **1**

Was prepared by hydrogenolysis of *N*-benzylaza-15-crown-5, as described previously [9]. The title compound [6.5 g, 98%, bp 76°C (0.05 torr)] was isolated as a colorless oil, which solidified to a soft, white hygroscopic solid (mp 30–32°C).

2.1.3 *N-Butylaza*-15-*crown*-5, **2**

Was obtained as described previously [9].

2.1.4. *N*-(2-*Methylthioethyl*)*aza*-15-*crown*-5, **3**

Was obtained by a procedure similar to that described below for **5**. The product was obtained (0.38 g, 40%) as a pale yellow oil after chromatography over alumina (chloroform eluent). ^{1}H NMR ($CDCl_3$): 2.10 (s, 2H); 2.80 (t, 8H); 3.63 (m, 12). *Anal.*: calcd for $C_{13}H_{27}NO_4S$: C, 53.24; H, 9.21%. Found: C, 53.26; H, 9.31.

2.1.5. *N*-(2-*Methylsulfoxyethyl*)*aza*-15-*crown*-5, **4**

Was prepared as follows: *N*-(2-Methylthioethyl)aza-15-crown-5 (**3**, 1.0 g, 3.4 mmol) was added to a 15 mL one-necked round bottom flask containing a mixture of sodium metaperiodate (0.763 g, 3.57 mmol) and water (8 mL) previously cooled to 0°C. After 30 minutes, a new spot developed on t.l.c. After 16 h, the reaction was stopped leaving only a trace of starting material unreacted (t.l.c.). The solid was separated by filtration and the solvent removed by evaporation *in vacuo* to afford crude **4** (1.27 g) as a yellow oil. This material was chromatographed (alumina, 0–2% 2-PrOH/hexanes) to afford pure **4** (0.60 g, 56%) as well as recovered starting material (0.1 g). ^{1}H-NMR 2.64 (s, 3H), 2.85 (m, 8H), 3.66 (m, 16H); IR 2860, 1350, 1120 cm^{-1}.

2.1.6. *N-(2-Phenylthioethyl)aza-15-crown-5*, **5**

Was prepared as follows: Aza-15-crown-5 (1.53 g, 7 mmol) was placed in a 100 mL, round bottomed, N_2-flushed flask and Na_2CO_3 (0.85 g, 8 mmol) and MeCN (50 mL) were added. The mixture was brought to gentle reflux. Phenyl 2-chloroethyl sulfide (1.20 g, 7 mmol) was added dropwise and reflux continued for 48 h. Unreacted aza-15-crown-5 was detected by t.l.c. and an additional 7 mmol of sulfide was added. Reflux was continued for 5 more days. NaI (0.2 g, 1 mmol) was added and reflux continued until a total of 10 d had elapsed. The mixture was allowed to cool, and the reaction mixture was filtered and reduced to minimum volume *in vacuo*. Water (25 mL) was added and the product extracted with chloroform (4 × 20 mL). The residue was chromatographed over Al_2O_3 (chloroform eluent) and distilled [Kugelrohr, 126–129°C (0.003 torr)] to give the product 0.90 g, 36%) as a pale, yellow oil. ^{1}H NMR ($CDCl_3$, ppm): 2.8 (t, 8H); 3.65 (m, 12H); 7.25 (s, 5H). IR (neat); 3020, 2820, 1570, 1110 cm^{-1}. *Anal.*: calcd for $C_{18}H_{29}NO_4S$: C, 60.87; H, 8.16%. Found: C, 60.48; H, 7.99%.

2.1.7. *N-(2-Methoxyethyl)aza-15-crown-5*, **6**

Was obtained as previously described [9].

2.1.8. *N-[2-Methoxy(2-ethoxy)ethyl]aza-15-crown-5*, **7**

Was obtained as previously described [9].

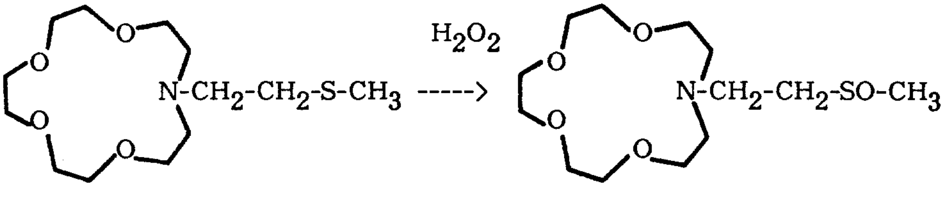
2.2. CATION BINDING CONSTANTS

Potentials to within ±0.1 mV were measured using an Orion Model 701 voltmeter. Sodium activity was determined by using a sodium ion selective electrode (ISE, Corning model no. 476210). Potassium cation activities were determined using Corning monovalent cation electrode model no. 476220. A Corning Ag/AgCl reference electrode (476029) was used with each of the ion selective electrodes. A water bath, placed on a magnetic stirrer, was maintained at the desired temperature using a Cole Parmer circulator heater (model 125200). Sample cells were prepared and electrodes were conditioned as previously described [10]. The standard measurement techniques were also recently described [10].

3. Results and Discussion

The macrocycles required for the study described here were generally obtained by methods we have previously published. Some additional manipulation was required for the syntheses of the sulfur compounds since the activity of the :ZCH_2CH_2X unit is generally high due to electron donation by —Z: as X^- departs. Such anchimeric assistance is important when Z is N, O, or S. Thus, the synthetic approaches required consideration of this property.

Aza-15-crown-5 was prepared by previously reported conditions [9] and alkylated with commercially available 2-chloroethyl methyl ether in the presence of sodium carbonate and acetonitrile to afford the methylthioethyl lariat ether, **3**. This was oxidized to the corresponding sulfoxide by treatment with hydrogen peroxide in acetone solution. The phenylthioethyl derivative, **5**, was prepared in a fashion similar to that used for methylthioethyl lariat ether **3**. The syntheses of **6** and **7** were also acomplished by alkylation as previously described [9]. Compounds **3** and **4** are illustrated below.



3 **4**

Sodium and potassium cation binding constants for several *N*-substituted aza-15-crown-5 lariat ether compounds are recorded in Table I. All binding constants were determined at 25°C in anhydrous methanol solution. These make them comparable to numerous other constants that have previously been reported from our group.

Table I. Sodium and potassium cation binding (in methanol) by sulfur-containing ligands

Cpd. No.	Macrocycle or Sidearm on Aza-15-crown-5	log K_S				Ref.
		Na^+	K^+	Other		
1	15-Crown-5	3.29	3.43	–	–	11
–	Thia-15-crown-5	–	–	Ag	5.0[a]	12
–	1,4-Dithia-15-crown-5	–	–	Ag	3.3[b]	12
–	1,7-Dithia-15-crown-5	–	–	Ag	2.7[b]	12
–	4,13-Diaza-7,10-dithiaaza-15-c-5	–	–	Ag	8.95[a]	13,14
–	7,10-Diaza-4,13-dithiaaza-15-c-5	–	–	Ag	9.91[a]	14,15
–	Tetrathia-15-crown-4	–	–	Cu^{2+}	3.3[a]	16,17
–	Tetrathia-16-crown-4	–	–	Cu^{2+}	2.2[a]	16,17,18
2	$—CH_2CH_2CH_2CH_3$	3.02	2.90	–	–	This work
3	$—CH_2CH_2SCH_3$	3.18	3.04	–	–	This work
4	$—CH_2CH_2SOCH_3^c$	3.06	2.75	–	–	This work
5	$—CH_2CH_2SC_6H_5$	3.08	2.93	–	–	This work
6	$—CH_2CH_2OCH_3$	3.88	3.95	–	–	9
7	$—CH_2CH_2OCH_2CH_2OCH_3$	4.54	4.68	–	–	9

[a] Data for aqueous solution.
[b] Data for L : Ag : L complex in water.
[c] Racemic.

A number of other sulfur-containing macrocycles have been prepared recently. Reports of the syntheses, structures, complexation behavior, etc. have appeared. A number of these papers are grouped together as reference 6 because the binding data, if any, cannot readily be correlated to the data presented here.

Divalent sulfur is generally regarded as a soft donor and thus effective in providing solvation to coinage or transition metal cations such as copper, silver, or mercury. The lack of any binding data for alkali metal cations and the variety of macrocycles shown above is consistent with this. Sulfoxide, on the other hand, is known to function reasonably well as a hydrogen bond acceptor and ought to be an effective donor for either Na^+ or K^+. The data shown in Table I are somewhat surprising in the latter respect.

It should first be noted that Na^+ binding by the lariat ether series having $>NCH_2CH_2XCH_3$ sidearms in which X is CH_2, S, SO, or O differ only for the latter case. The sodium cation binding strength exhibited by 15-crown-5 is modest and not significantly different from the nitrogen-pivot compound lacking a Lewis basic donor in the butyl sidearm. In such cases, axial solvation must be provided by solvent to a significant extent. Since the binding constants are nearly the same for methylene and thioether, it seems reasonable to assume that the sulfur plays no enthalpic role in the cation binding. Thermodynamic studies of lariat ether systems [19] have, however, shown that significant enthalpic differences can often by offset by changes in entropy. The enthalpic interpretation must therefore remain speculative.

Although statements have appeared in the literature suggesting that divalent sulfur and CH_2CH_2 are isosteric, this is not supported by modern structural studies and is certainly not apparent from an examination of CPK molecular models. Molecular models of *N*-substituted aza-15-crown-5 lariat ethers have a donor group spaced three, rather than two, methylene units from the nitrogen appear to have the donor atom more centrally located above the macroring cavity. Thus, the sulfoxide oxygen atom should enjoy this favored position. Remarkably, the Na^+-cation binding of all three systems is only a little outside of experimental error from being identical. We have no direct data to support the postulate that enthalpies differ and are compensated by entropic changes but the fact that CH_2, S, and SO do not differ in cation binding strength is suspicious. Despite this interesting possibility, the cation binding strengths are weak by any standard, so a more detailed examination of the cation binding was not undertaken.

4. Conclusion

From the data shown in Table I, it is clear that while macroring nitrogen and sulfur substantially enhance cation binding to coinage or transition metal cations, sulfur contributes little to the overall binding constants observed with nitrogen-pivot lariat ethers. One is tempted to say that sulfur makes no enthalpic contribution to the binding but the similarity in binding constants makes this interpretation suspect. Because the overall binding of these compounds is poor, no detailed thermochemical study was undertaken. The indifference of the cation binding strengths of these molecules to the presence of thioether or sulfoxide residues is, in itself, notable.

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