Lariat Ethers. 4. Chain Length and Ring Size Effects in Macrocyclic Polyethers Having Neutral Donor Groups on Flexible Arms[1]

Rose Ann Schultz, Dennis M. Dishong, and George W. Gokel*

Department of Chemistry, University of Maryland College Park, Maryland 20742

Received August 11, 1981

We have recently reported the syntheses and certain binding properties of a class of molecules we call "lariat ethers".[2-4] These compounds are characterized by a macrocyclic polyether ring and a flexible arm extending from the cycle to which are attached electron donor groups. Those compounds having arms joined by a methyleneoxy group appear to be relatively inflexible and exhibit both relatively weak and solvent-dependent cation binding.[2,3] In contrast, when the secondary donor arm is attached to a nitrogen pivot rather than at carbon, binding constants are found to be substantially increased over simple monocyclic systems.[4]

We now wish to report three important findings regarding the cation binding of the highly flexible nitrogen lariat systems. First, the expected ring size–cation diameter correlation does not appear to be as significant for these cases as for others.[5] Rather, binding constants reflect the total number of oxygens present both in the ring and the side arm and seem little affected by the presence of endocyclic nitrogen. Second, the Na^+ binding constants peak when six, rather than five, oxygens are present in the system, further suggesting the insignificance of nitrogen as a donor ligand. Third, after the peak, binding constants decline to a strength similar to or below the binding of corresponding compounds having only a methyl group in the side arm.

Synthesis of the nitrogen lariat ethers reported herein were accomplished in one of three ways. *N*-Methylmonoaza-15-crown-5 (**1**) and *N*-methylmonoaza-18-crown-6 (**8**) were prepared by methylation (Me_2SO_4, Na_2CO_3, THF) of the corresponding secondary nitrogen species. Compounds **2**, **3**, **7**, **9**, **10**, and **14** were prepared from the corresponding N-alkylated diethanolamines as we have previously reported for simpler systems.[4] The latter method proved unsuccessful for the preparation of the remaining half-dozen compounds. When three or more oxygens were present in the intended side chain, the trialkanolamines bound miscellaneous salts so tightly that standard work-up techniques and distillation proved nearly impossible. The appropriate commercially available oligoethylene glycol monomethyl ethers were therefore converted into the corresponding tosylates and then condensed with either monoaza-15-crown-5 or monoaza-18-crown-6 which in turn were obtained by hydrogenolysis of the previously reported *N*-benzyl crowns.[6] All new compounds gave ^1H NMR, IR, and C, H, N combustion analyses (±0.3%) in accordance with expectations. Experimental details are available as supplementary material.

Binding data[7] for the 15-membered-ring (**1–7**)[4,9] and 18-membered-ring (**8–14**) nitrogen lariats[4,9] and 15-membered-ring oxygen lariats (**15–17**)[2] are recorded in Table I and graphed in Figure 1. The similarity for compounds having different ring sizes but equal numbers of oxygens is remarkable. It even extends to the *N*-methyl compounds which have no secondary binding sites in the side arm. It seems likely that nitrogen does not enforce significant conformational restrictions on the system, and the molecules readily adjust to achieve optimum binding orientation. The structures of Na^+-18-crown-6[10] and K^+-30-crown-10[11] complexes both suggest that folding occurs when the ring is apparently too large for the cation.

Although it is clear from an examination of the graph that Na^+ binding peaks when six oxygens are present, the precise shape of the remainder of the line is less certain. There may be an actual

Table I. Sodium Binding Constants for Lariat Ethers Having Varying Ring Sizes and Side-Arm Lengths

	log *K* (Na^+ in MeOH					
	nitrogen lariats				oxygen lariats	
	15-crown-5		18-crown-6		15-crown-5	
n	compd	log *K*	compd	log *K*	compd	log *K*
0	1	3.39	8	3.93	15	3.03
1	2	3.88	9	4.58	16	3.05
2	3	4.54	10	4.33	17	3.13
3	4	4.32	11	4.28		
4	5	4.15	12	4.27		
5	6	4.19	13	4.22		
~8[11]	7	3.52	14	3.44		

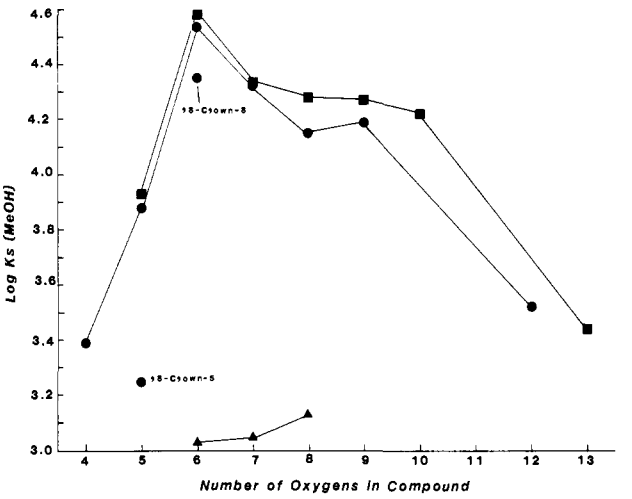
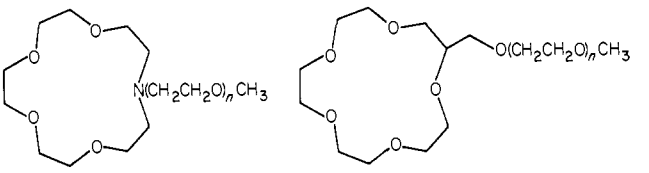


Figure 1. Sodium cation binding by 15- and 18-membered lariat ethers. (●) 15-membered nitrogen lariats (**1–7**); (■) 18-membered nitrogen lariats (**8–14**); (▲) 15-membered oxygen lariats (**15–17**).



1–14 **15–17**

(1) Crown–Cation Complex Effects. 17.

(2) Gokel, G. W.; Dishong, D. M.; Diamond, C. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1053.

(3) Dishong, D. M.; Diamond, C. J.; Gokel, G. W. *Tetrahedron Lett.* **1981**, 1663.

(4) Schultz, R. A.; Dishong, D. M.; Gokel, G. W. *Tetrahedron Lett.* **1981**, 2623.

(5) (a) Lamb, J. D.; Izatt, R. M.; Christensen, J. J.; Eatough, D. J.; "Coordination Chemistry of Macrocyclic Compounds"; Melson, G. A., Ed.; Plenum Press: New York, 1978; Chapter 3 p. 45. (b) Lamb, J. D.; Izatt, R. M.; Swain, C. S.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 475.

(6) Gokel, G. W.; Garcia, B. J. *Tetrahedron Lett.* **1977**, 317.

(7) Binding constants were determined in anhydrous methanol at 25 ± 1.0 °C using a Corning 476210 electrode and Orion model 501 or 701 "Ionalyzer" meter. Measurements were conducted in a water-free dry box under a nitrogen atmosphere. Constant temperature was maintained with a bath of circulating di-*n*-butyl phthalate. The error in such measurements has been placed at ±10%.[8] Our values of *K* for 15-crown-5 and 18-crown-6 are 3.25 and 4.35, respectively. These compare with literature[5b] values of 3.48 and 4.36, respectively.

(8) (a) Frensdorff, H. K. *J. Am. Chem. Soc.* **1971**, *93*, 600. (b) Pedersen, C. J.; *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 46.

(9) The side arms on **7** and **14** were derived from the corresponding oligoethylene glycol monomethyl ether tosylate. The alcohol, $CH_3(OCH_2CH_2)_nOH$, was purchased from the Aldrich Chemical Co. (cat. no. 20 247-9) and had a specified *M*, of 350 g/mol. The average value of *n* should therefore be 7.2. Integration (^1H NMR) of the methyl resonance and methylenes allowed a value of $n = 7.8$ to be calculated. The molecular weight of this alcohol was determined independently (triplicate) by Galbraith Microanalytical Laboratory who found a value of $M_r = 400$ g/mol; therefore, $n = 8.4$. The value of *n* is rounded to 8 in Table I.

(10) Dobler, M.; Dunitz, J. D.; Seiler, P. *Acta Crystallogr., Sect. B* **1974**, *B30*, 1741.

(11) Bush, M. A.; Truter, M. R. *J. Chem. Soc., Perkin Trans. 2* **1972**, 345.

0002-7863/82/1504-0625$01.25/0

plateau from 6-9 or 10 oxygens, or the plateau may reflect experimental uncertainty in a downward decline from 6-13 oxygens. In the latter case, least-squares fits of the lines should confirm the approximate linearity.[12] The calculated slopes, intercepts, and correlation factors suggest a straight-line relationship and that the plateaus are artifacts. It seems reasonable, however, to presume that side-chain oxygen atoms positioned in a range of distances from the ring might be useful for secondary binding but, beyond a certain point, be inaccessible.

There are at least two obvious explanations for the eventual decline in binding constants. One is that as the number of oxygens in the side arm increases, hydrogen bonding by the medium decreases its flexibility (a ponderal effect) and thereby its effectiveness in binding. Another possibility is coiling of the side arm limiting access by the cation. This might be due to a hydrophobic effect (i.e., a lipophilic-lipophilic interaction) or water-bridged hydrogen bonds between ring and sidearm. Further work is in progress to clarify this observation.

Acknowledgment. We thank the NIH for a grant (GM 29150) which supported this work.

Supplementary Material Available: Measurement of binding constants for **1-17** and preparation of lariat ethers (4 pages). Ordering information is given on any current masthead page.

(12) The slopes, intercepts, and correlation factors (r) calculated for the 15-membered and 18-membered nitrogen lariats are as follows: slopes -0.16, -0.15; intercepts 5.50, 5.48; r = -0.975, -0.938. The slopes are calculated from the peak toward the higher values of n, rendering the intercepts meaningless except for comparative purposes.

Soret-Excited Resonance Raman Spectrum of (Carbon monoxy)leghemoglobin: Assignment of ν_{Fe-CO}

R. S. Armstrong,* M. J. Irwin, and P. E. Wright

Department of Inorganic Chemistry, University of Sydney Sydney, N.S.W. 2006, Australia

Received July 1, 1981

Many resonance Raman spectra in the low-frequency region (<700 cm^{-1}) have been reported recently for hemeproteins.[1-12] The intensities of Raman bands in this region have been enhanced by laser excitation into or near the Soret absorption band[1-10] or into charge-transfer absorptions.[11,12] Bands have been assigned to Fe-L(axial) stretching vibrations either by inference or by direct isotopic substitution in the ligands. For example, vibrations due to Fe-OH^-, Fe-N_3^-, and Fe-F^- in derivatives of ferric myoglobin have been observed by Asher et al.[11,12] using laser excitation in the range 600-630 nm. Desbois et al.[1] have assigned similar bands in the resonance Raman spectra of the same myoglobin derivatives by using excitation (441.6 nm) near the Soret absorption band. In the ferrous form of oxygen binding hemeproteins, bands have been assigned to ν_{Fe-O_2} in oxyhemoglobin[2] (HbO_2), oxymyoglobin[1,3] (MbO_2), and oxyleghemoglobin[4] (LbO_2) and to Fe-N_ϵ (proximal histidine) in deoxyhemoglobin,[2,5,6] deoxymyoglobin,[1,7] and deoxyleghemoglobin.[4] To date, only one report of a resonance Raman spectrum, in the low-frequency region, of a carbon monoxide complex of a hemeprotein has appeared.[8] No attempt was made to assign ν_{Fe-CO} in that work. We report here excellent spectra of soybean CO-leghemoglobin. From isotopic substitution ($^{12}C^{16}O \rightarrow {}^{13}C^{18}O$) we are able to assign, for the first time, $\nu_{Fe-^{12}C^{16}O}$ (505 cm^{-1}). Our results also suggest that the excitation wavelength which most favors photodissociation of bound carbon monoxide is distinct from that which gives rise to the resonance enhancement of the ν_{Fe-CO} Raman band.

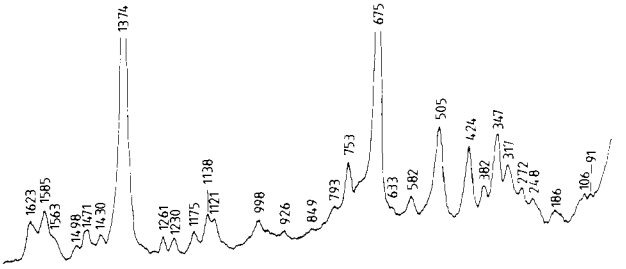


Figure 1. Single scan resonance Raman spectrum of CO-leghemoglobin (50 μM). Laser excitation 413.1 nm; 45 mW at sample; 1-cm^{-1} s^{-1} scan; 1-s time constant; 7.5-cm^{-1} resolution. Ferric soybean Lb, purified as in ref 15, was introduced into a sample spinning cell sealed with a septum, flushed with argon, and a twofold excess of dithionite was added to give deoxyleghemoglobin. The CO complexes were formed by injection of $^{12}C^{16}O$ (Matheson Gas Products) or $^{13}C^{18}O$ (Prochem, B.O.C. Limited; 92% ^{13}C, 98.5% ^{18}O) such that the samples were under a 1:1 mixture of carbon monoxide and argon at atmospheric pressure. All samples were in 10 mM phosphate buffer (pH 7.0) containing 0.1 mM EDTA.

The resonance Raman spectrum[13] (50-1700 cm^{-1}) of soybean CO-leghemoglobin obtained with 413.1-nm laser excitation is shown in Figure 1. An obvious feature of the spectrum is the strong polarized band at 505 cm^{-1} which has not appeared in other Soret-excited resonance Raman spectra of myoglobin,[1,3] hemoglobin,[2,5,6] or leghemoglobin[4] derivatives. Figure 2 shows the resonance Raman spectra of $Lb^{12}C^{16}O$ and $Lb^{13}C^{18}O$ excited with 441.6- and 457.9-nm laser irradiation. The only band that shifts significantly ($\Delta\nu$ = 13 cm^{-1}) upon isotopic substitution is the band at 505 cm^{-1}. The frequency shift calculated from a change in the reduced mass, upon substitution of $^{13}C^{18}O$, for an isolated Fe-CO stretch is 16.5 cm^{-1}. We attribute the 505-cm^{-1} band to the Fe-CO vibration. The difference between the calculated and observed shift upon isotopic substitution may reflect a constraint on the CO mobility or nonlinearity of the Fe-C-O moiety. A similar band has been observed by Rimai et al.[8] in the resonance Raman spectrum of HbCO at 506 cm^{-1}. From the position, intensity, and polarization of this band we assign it to ν_{Fe-CO}.

Other features of the spectra are also of interest. First, the absence of any band near 220 cm^{-1} is noted. Desbois et al.[1] observed bands in this region for the fully ligated ferrous low-spin derivatives of MbO_2 and MbNO. Tsubaki et al.,[3] on the other hand, did not observe such a band for a variety of oxymyoglobins and suggested that the bands observed by Desbois and co-workers arose from a photodissociated deoxymyoglobin component. Our spectra support such a view.

In the present Raman studies of LbCO, spectra were obtained with excitation at different wavelengths. The quality of the spectra varied markedly and provided some insight into the excitation wavelength dependence of photodissociation. The spectrum in Figure 1 was obtained with 45 mW from a tightly focused laser beam (413.1 nm). To obtain spectra without significant photodissociation using 457.9- and 441.6-nm excitation (Figure 2) it was necessary to defocus the laser beam as well as to use lower powers. The plasma lines in the spectra are an unfortunate

(13) Raman spectra were obtained by using the apparatus described in ref 4. Experimental conditions are described in the figure captions. The spectrometer was calibrated with carbon tetrachloride and individual spectra were checked against plasma lines. All peaks are accurate to ±1 cm^{-1}.

(1) Desbois, A.; Lutz, M.; Banerjee, R. *Biochemistry* **1979**, *18*, 1510-1518.
(2) Nagai, K.; Kitagawa, T.; Morimoto, H. *J. Mol. Biol.* **1980**, *136*, 271-289.
(3) Tsubaki, M.; Nagai, K.; Kitagawa, T. *Biochemistry* **1980**, *19*, 379-385.
(4) Irwin, M. J.; Armstrong, R. S.; Wright, P. E. *FEBS Lett.* **1981**, *133*, 239-243.
(5) Nagai, K.; Kitagawa, T. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2033-2037.
(6) Kincaid, J.; Stein, P.; Spiro, T. G. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 549-552 (correction **1979**, *76*, 4156).
(7) Kitagawa, T.; Nagai, K.; Tsubaki, M. *FEBS Lett.* **1979**, *104*, 376-378.
(8) Rimai, L.; Salmeen, I.; Petering, D. H. *Biochemistry* **1975**, *14*, 378-382.
(9) Teraoka, J.; Kitagawa, T. *Biochem. Biophys. Res. Commun.* **1980**, *93*, 694-700.
(10) Campbell, J. R.; Clark, R. J. H. *Inorg. Chim. Acta* **1980**, *39*, 1-8.
(11) Asher, S. A.; Vickery, L. E.; Schuster, T. M.; Sauer, K. *Biochemistry* **1977**, *16*, 5849-5856.
(12) Asher, S. A.; Schuster, T. M. *Biochemistry* **1979**, *18*, 5377-5387.

0002-7863/82/1504-0626$01.25/0