CH_3I methylation, together with ketone **3** (27%).

Treatment of **8** with cuprous triflate in benzene according to the method of Kozikowski et al. with analogous selenol esters[5] results in efficient cyclization to tetracyclic diketone **9** (77%). Conversion to the anthracycline derivative **10** can then be achieved in a single operation by reaction of **9** with silver oxide.[6] The yield of 73%[7] from **9** to **10** is reasonable in view of the number of chemical transformations involved (aromatize ring B, oxidize ring C to anthraquinone, desilylate). The overall yield from **1** to **10** is 37% and involves only two isolated intermediates.

For our purpose, the thiol ester is an ideal enolate carboxylation product because it can be cyclized without further activation to give the tetracyclic skeleton. In other applications where a simple ester is preferred, the well-known mercuric ion induced transesterification may be used.[8] Thus, treatment of $C_6H_5COCH(CH_3)COSCH_3$ (see Table I, entry 3) with $Hg(OAc)_2$ in methanol results in complete conversion into the ester, $C_6H_5COCH(CH_3)CO_2CH_3$. This combination of carboxylation/transesterification should allow the synthesis of a variety of β-keto esters from enolates.

Applications of this methodology to 11-deoxyanthracycline synthesis are in progress.

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Registry No. 1, 82293-94-5; 3, 82293-95-6; 4, 82293-96-7; 5, 82293-97-8; 6, 82293-98-9; 7, 82293-99-0; 8, 82294-00-6; 9, 82294-01-7; 10, 82294-02-8; $C_6H_5COCH(CH_3)CO_2CH_3$, 29540-54-3; 3-methyl-2-[(trimethylsilyl)oxy]cyclohexene, 19980-33-7; methyl benzenepropanoate, 103-25-3; 1-phenyl-1-propanone, 93-55-0; 1,3-dithian-2-yl-lithium, 36049-90-8; 2-methyl-6-(methylthiocarbonyl)cyclohexanone, 73067-19-3; methyl 2-(methylthiocarbonyl)benzenepropanoate, 82294-03-9; 2-methyl-3-(methylthio)-1,3-benzenepropanedione, 82294-04-0; 3-(1,3-dithian-2-yl)-2-(methylthiocarbonyl)cyclohexanone, 82294-05-1; 3-(1,3-dithian-2-yl)cyclohexanone, 71491-60-6; 2-methyl-2-(carbomethoxy)cyclohexanone, 7500-91-6; 6-methyl-2-(carbomethoxy)cyclohexanone, 59416-90-9; carbon oxysulfide, 463-58-1; 2-cyclohexen-1-one, 930-68-7.

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(7) It is important to activate commercial AgO by sonication (1 h, THF suspension) to obtain the 73% yield. Some starting material (16%) is recovered in addition.
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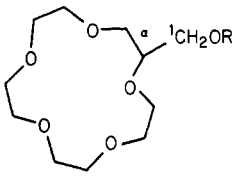
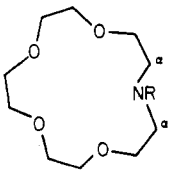
Dynamics of Sodium Cation Complexation by Carbon- and Nitrogen-Pivot Lariat Ethers

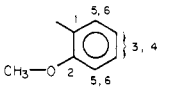
Summary: ^{13}C NMR relaxation time (T_1) measurements for carbon-pivot and nitrogen-pivot lariat ethers indicate that the latter are more dynamic complexers and that in some cases, the side-arm oxygens appear to participate more strongly in the overall binding than do the ring oxygens.

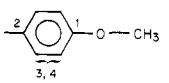
Sir: "Lariat ethers" is the name we have given to the class of crown ethers designed having both a macroring available for cation binding and a side chain bearing a Lewis basic donor group.[2] The crown ring "ropes" the cation and the side-arm donor group further "ties" it up. The expectation is that enhanced binding (compared to simple macrocycles) will be realized, and both the ligands and the complexes will still be highly dynamic as observed with simple crown ethers.[3,4] This would contrast with the cryptands, which are very strong cation binders but essentially static in the complexed (cryptate) form.[3,5] The compounds to which we refer are illustrated as structures **1–6**.





1, R = $\overset{2}{C}H_2\overset{3}{C}H_2OCH_3$

2, R = 

3, R = 

4, R = $\overset{1}{C}H_2\overset{2}{C}H_2OCH_3$

5, R = $\overset{1}{C}H_2\overset{2}{C}H_2O\overset{3}{C}H_2\overset{4}{C}H_2OCH_3$

6, R = $\overset{1}{C}H_2\overset{2}{C}H_2\overset{3}{C}H_2\overset{4}{C}H_3$

We report herein an NMR study[6–9] of carbon-13 relax-

(1) (a) University of Puerto Rico. (b) University of Maryland. (c) Direct correspondence concerning the NMR aspects of this work to L.E. and correspondence concerning the synthesis and properties of these compounds to G.W.G.
(2) (a) Gokel, G. W.; Dishong, D. M.; Diamond, C. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1053. (b) Dishong, D. M.; Diamond, C. J.; Gokel, G. W. *Tetrahedron Lett.* **1981**, 1663. (c) Schultz, R. A.; Dishong, D. M.; Gokel, G. W. *Tetrahedron Lett.* **1981**, *2623*. (d) Schultz, R. A.; Dishong, D. M.; Gokel, G. W. *J. Am. Chem. Soc.* **1982**, *104*, 625. (e) Schultz, R. A.; Schlegel, E.; Dishong, D. M.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.* **1982**, 242.
(3) Binding is measured[2b,c] as K_s, the equilibrium constant for the reaction ligand + cation $\rightleftarrows$ complex; $K_s = k_f/k_r$. Cation binding rates for 18-crown-6, a typical, highly dynamic system, are k_f = ca. 10^8 M^{-1} s^{-1} and k_r = ca. 10^7 M^{-1} s^{-1}.[4] Cryptands are much less dynamic: typical k_f and k_r values for [2.2.2]-cryptand (Na^+, H_2O) are ca. 10^5 M^{-1} s^{-1} and ca. 10 M^{-1} s^{-1}, respectively.[5]
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(6) The relaxation time experiments were performed in $MeOH/D_2O$ solutions (9:1 by weight) on 0.5 M solutions of the ethers. Stoichiometric (1:1) ratios of lariat ethers/$NaClO_4$ were utilized for the complexation studies. All solutions were prepared and sealed under vacuum after careful degassing of the samples by freeze–pump–thaw cycles. The solvents were carefully dried and purified before use. All spectra were recorded with a JEOL-FX-90Q spectrometer operating at 22.5 MHz for C-13 analysis and 23.71 MHz for Na-23 analysis. Relaxation time experiments were accomplished by inversion-recovery methods,[7] with pulse delay times of 70 s. Each T_1 value reported is the average value of at least three independent measurements. Nuclear Overhauser enhancement (NOE) factors were measured for all samples by comparing the relative intensities of all resonances under full-decoupling conditions with their respective values obtained under gated-decoupling conditions during data acquisition. All NOE values are those expected for a predominantly dipole–dipole relaxation mechanism (2.7–2.9 s). The relaxation time of the C-13 resonance of methanol was used as an internal standard for the T_1 experiments. These values oscillated between 13 and 13.6 s, in good agreement with literature values.[7]
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(9) NMR studies of various types have been conducted previously. See for example the following reviews and references therein: (a) Izatt, R. M.; Christensen, J. J. "Synthetic Multidentate Macrocyclic Compounds"; Academic Press: New York, 1978. (b) Izatt, R. M.; Christensen, J. J. *Prog. Macrocyclic Chem.* **1979**, *1*; **1981**, *2*.

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Table I. Sodium-23 Line Width Measurements[a]

temp, °C	Na line width ($\Delta\nu_{1/2}$), Hz	
	1	4
25	96	58
0	202	87
−25	587	190
−50	~2500	490
−75	>2500	~1300

[a] Ratio (ether/Na^+) = 0.5; solvent = MeOH/D_2O, 9:1 by weight.

ation times (T_1) and sodium-23 linewidths directed at answering two questions. First, is there unequivocal evidence that in solution the side-arm donor group participates in the binding phenomenon? If the side arm is involved, reduced molecular mobility in those carbon atoms relative to the ring carbons should be observed. Second, what are the comparative dynamics of the C-(1–3) vs. N-pivot (4–6) molecules, especially compared to simple crowns and cryptands?

The second of these questions is answered by the data shown in Table I. When the ^{23}Na line widths were determined[6] in 90 wt % MeOH/D_2O, it was found that the nitrogen lariat complex of **5** exhibited relatively sharp lines, even when the temperature was lowered to −75 °C, the experimental limit (due to solvent viscosity) of the measurement. The corresponding carbon-pivot lariat complex (Na^+·**1**), in which noninvertible carbon is the attachment point, exhibited relatively broad lines, indicating slower cation exchange than that observed for the Na^+·**5** complex.

One way to account for the difference in ^{23}Na line widths without involving a flexibility argument is to attribute the difference to the presence of N in **4** compared to **1**. The homogeneous equilibrium binding constant (K_s) determined potentiometrically in 90% MeOH for Na^+ and 15-crown-5 is about 1000.[2b] The respective binding constant for **6** is less than half that.[2c] Since the binding constant for **6** is an order of magnitude higher than that for **4**/**6**,[2c] the binding enhancement must be due to some combination of side-arm flexibility and donor groups and not simply to replacement of CH by N. A greater flexibility for N-pivot molecules was anticipated since N is an inherently more flexible atom (due to nitrogen inversion) than C.

The first question posed above concerns whether or not the side arm participates in the binding phenomenon. We have previously reported evidence which we believe unequivocally implicates the intramolecular side arm of 18-membered-ring nitrogen-pivot lariats in ammonium ion binding.[2e] The situation should be similar for sodium cation and the 15-membered rings, but this is not certain.

A comparison of the C-13 relaxation times allows one to assess changes in molecular mobility as circumstances alter. In Table II, we compare various ligands in the presence and absence of Na^+, for which each ligand presumably has an affinity. Also included in Table II are independently determined binding constants[2] (K_s for the equilibrium: ligand + Na^+ ⇌ complex), measured in the same solvent mixture by standard electrochemical methods.[2b,c] When 15-crown-5 complexes sodium, T_1 for the ring carbons changes from 3.60 to 2.10 s (a 42% decrease). The same loss of carbon mobility is noted for the ring carbons in **1**. Remarkably, nitrogen lariats **4** and **5** show virtually no change in ring-carbon mobility as judged by the C-13 T_1's. The average ring relaxation times for free and complexed **4** and **5** are respectively 2.24, 2.21 and 1.46, 1.34 s. These differ by less than 10% in each case. The conclusion one might draw from this is that **4** and **5** are poor Na^+ binders. On the contrary, K_s values for these compounds are respectively 4587 and 14630 (compared to less than 1000 for 15-crown-5).[2]

The poor Na^+ binder **6** is identical with **4** except that there is no oxygen in the side chain of **6**. Because no donor group is present in the side arm, whatever complexation occurs must be due to the ring donor atoms. As with 15-crown-5 and **1**, the T_1 values diminish considerably (over 40%) when Na^+ is added to the ligand-containing solution.

As suggested in our first question (see above) concerning binding by these compounds, side-arm mobility must also diminish if binding takes place. Although it is not possible to assign all of the side-chain carbon resonances unequivocally, wherever comparative data are available (see Table II), relaxation times for these atoms either remain unaltered or fall.

We conclude from this evidence that the nitrogen lariats are indeed dynamic cation complexers and that the secondary donor group(s) on the side arms contributes very significantly to the overall complexation strength. Our current view of the complexation is that in the poor binders like 15-crown-5, **1**, and **6**, the cation is completely enveloped by the ring donors (submerged in the ring), whereas when good donors are present on a flexible side arm, the arm contributes more to the binding, the ring retains more mobility (i.e., is less strongly involved in the complexation), and the cation is not immersed so deeply in the macroring.

Table II. Relaxation Times (T_1)[a] for Several Macrocyclic Polyethers[i]

compd	K_s[b]	equiv of Na^+[c]	side-chain carbons					ring carbons		
			C-1	C-2	C-3	C-4	CH_3	Cα[d]	other (av)[e]	range[f]
15-crown-5	na	0	na	na	na	na	na	3.60	na	na
15-crown-5	927	1	na	na	na	na	na	2.10 (42%)[g]	na	na
1	na	0	una	una	2.61	na	9.06	1.72	1.46	1.07-1.80
1	669	1	una	una	1.62	na	7.18	0.99	0.65 (55%)[g]	0.39-0.66[h]
4	na	0	2.62	2.84	na	na	8.40	2.96	2.24	2.05-2.46
4	4587	1	2.35	2.65	na	na	7.87	2.17	2.21 (1%)[g]	2.16-2.34
5	na	0	1.07	una	una	2.96	8.79	0.99	1.46	1.21-1.74
5	14630	1	1.17	una	una	1.68	7.19	1.18	1.34 (8%)[g]	1.18-1.65
6	na	0	1.48	1.60	2.43	na	2.98	1.63	1.47	1.43-1.54
6	414	1	0.62	0.93	1.39	na	2.65	0.47	0.54 (63%)[g]	0.51-0.56

Notes: [a] ±10%, see ref 6. [b] In 90% (wt/wt) MeOH/H_2O. [c] As the ClO_4^- salt for the NMR measurements. [d] Refers to the tertiary C in **1** and to the C adjacent to N in the N lariats (**4**–**6**), i.e., average of all observed ring-carbon T_1 values. [f] Inclusive range of all observed ring-carbon T_1 values exclusive of Cα unless otherwise noted. [g] Percentage decrease in T_1 from noncomplexed state. [h] Range of a single unassigned ring-carbon T_1 value of 1.43 s. [i] Abbreviations: na = not applicable; una = unassigned.

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Registry No. 2, 76719-75-0; **3**, 76719-76-1; 15-crown-5, 33100-27-5; sodium, 7440-23-5.

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Mechanistic Probes of the Hydride-Transfer Process in the Reduced Nicotinamide Adenine Dinucleotide Dependent Alcohol Dehydrogenase Reactions

Summary: NADH-dependent alcohol dehydrogenase reductions of several chemically based radical-probe molecules proceed without any indication of the radical anion intermediates.

Sir: Despite the large amount of the structural and kinetic information available on the NADH-dependent alcohol dehydrogenase reactions, a complete understanding of the chemical mechanism of the crucial hydrogen-transfer step and of the transition-state structure has not yet been achieved.[1,2] The key mechanistic question is whether the hydrogen transfer between the coenzyme and the substrate carbonyl occurs in a single step as hydride or in two steps as electron and hydrogen atom. The experimental data obtained from the enzymic studies and the nonenzymic models have been variously interpreted in support of either of the two mechanistic possibilities. The in vitro models have shown that a one-electron redox process is possible between dihydropyridines and some suitable substrates.[2]

We have examined the mechanism of the hydrogen-transfer process in NADH-dependent horse liver alcohol dehydrogenase (HLADH) reactions by means of several chemically based radical probes,[3] and we herein report some of these results. Since cyclopropyl methyl radicals and cyclopropyl ketyl radical anions are known to undergo a rapid ring-opening reaction,[4] the possible ring opening was first examined in the HLADH reduction of nortricyclanone (**1**).[5] Ketone **1** (42 mg, 0.389 mmol, at least 96% pure by GC analysis on 5 ft 10% FFAP) was incubated with NADH (400 mg, 0.51 mmol) and HLADH (4 mg; Sigma) in phosphate buffer (0.1 M, pH 7, 50 mL) at room temperature under Ar in the dark for 11 h. The reduction was virtually complete over this period, and the organic product was obtained by an extractive workup (ether). GC and ^{1}H NMR analyses clearly showed that nortricyclanol (**2**) was the exclusive product and that there was no trace of the possible ring-opened products such as norcamphor or *endo*-norborneol[6] (Scheme I).

Scheme I

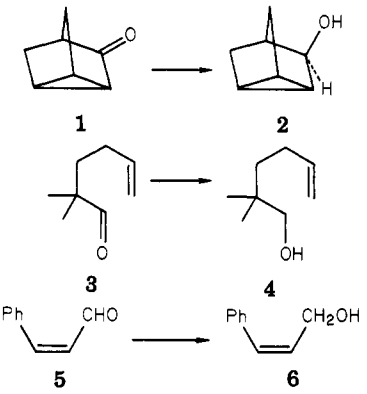

Table I

incubation time, min	cinnamaldehyde, % cis (δ 9.98)	cinnamaldehyde, % trans (δ 9.73)	cinnamyl alcohol, % cis (δ 4.48)	cinnamyl alcohol, % trans (δ 4.33)
0	97	3		
10	84		13	3
30	77		20	3
60	65		32	3
150	14		83	3

Shono et al. reported that electroreduction of nonconjugated olefinic ketones such as 6-hepten-2-one gave the cyclized alcohol products in high yields, thus demonstrating a facile cyclization of the 5-hexenyl ketyl radical anions.[7] Therefore, we next examined the possible ring closure in the HLADH reduction of 2,2-dimethyl-5-hexenal (**3**).[8] When the substrate **3** (50 mg, 0.397 mmol, ca. 90% isomeric purity) was incubated with NADH (310 mg, 0.397 mmol) and HLADH (5 mg; Sigma) in phosphate buffer (50 mL), the reduction was over within 1 h. The exclusive product was identified (GC, TLC, and ^{1}H NMR) to be 2,2-dimethyl-5-hexen-1-ol (**4**).

In view of the successful application of the stereochemical isomerization of enones as a radical anion probe in the reactions involving dialkylcuprates and Grignard reagents,[9] we have also studied the stereochemistry of the HLADH reduction of *cis*- and *trans*-cinnamaldehyde. The trans aldehyde was smoothly reduced by NADH and HLADH to *trans*-cinnamyl alcohol, as reported in the literature.[10] The cis substrate (**5**;[11] 50 mg, 3% (max) contamination by

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