bis-acylations and hydroxyalkylations[9b]) have not been successful.

In summary, the ready availability of the two bis-stannylated compounds 1 and 2 has opened short pathways to a wide variety of both symmetric and unsymmetric 2,3-disubstituted 1,3-butadienes, many of which would be difficult or impossible to prepare by current methodologies.[11]

Acknowledgment. We thank the donors of the Petroleum Research Foundation, administered by the American Chemical Society, the National Institutes of Health, and the National Science Foundation for support of this work. H. E. Zimmerman and L. W. Linder[13] first prepared compounds 1 and 2 and converted 1 to the mono and disilyl (5) derivatives by treatment with *n*-butyllithium and trimethylsilyl chloride. We thank them for providing details of their work.

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(10) Allylstannanes react with Mannich reagents to give aminomethylated products: Reich, H. J.; Schroeder, M. C.; Reich, I. L. *Isr. J. Chem.* **1984**, *24*, 157.

(11) Of all of the 2,3-disubstituted butadienes reported here, only three have been previously prepared: the 2,3-bis(trimethylsilyl)-,[12a] the 2,3-diiodo-,[12b] and the 2,3-di-*n*-hexyl-1,3-butadienes.[12c]

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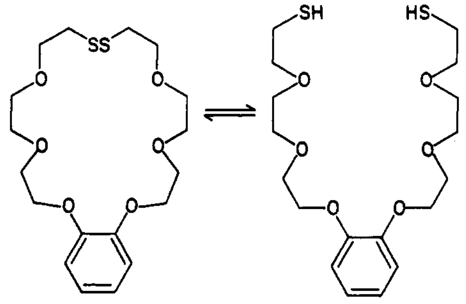
Redox-Switched Crown Ethers. Cyclic–Acyclic Interconversion Coupled with Redox between Dithiol and Disulfide

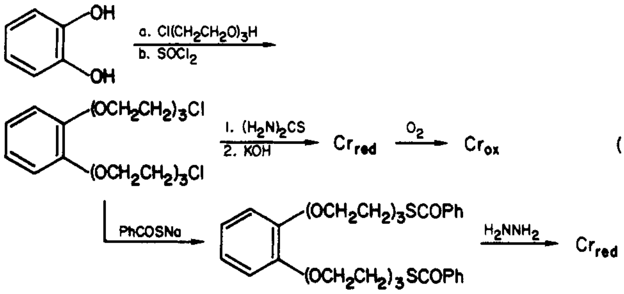
Summary: Synthesis, ion affinity, and redox properties of a pair of "redox-switched" crown analogues with a dithiol group at α,ω-positions ($\mathrm{Cr_{red}}$) and a disulfide bond in the ring ($\mathrm{Cr_{ox}}$) are described.

Sir: Macrocyclic polyethers contain intramolecular cavities delineated by molecular segments and are capable of specific chelation with alkali and alkaline earth metal cations. It is now established that the specificity stems from a host–guest relationship.[1-3] As the ion selectivity is largely governed by the size of the intramolecular cavities, one may expect that if the topological ring shape can be reversibly changed, it would lead to the control of ion-binding ability and ion selectivity. The photo- and pH-responsive crown ethers are typical examples.[4-10] It occurred to us that the most direct change in the cavity shape would be attained by reversible bond formation and bond scission leading to cyclic–acyclic interconversion and the redox reaction of a thiol–disulfide couple would be the most suitable candidate for this.[11,12] We here report a pair of new "redox-switched" crown ether analogues bearing a disulfide bond in the ring and a dithiol group at its α,ω-positions. The oxidized form ($\mathrm{Cr_{ox}}$; 2,3-benzo-1,4,7,10,17,20-hexaoxa-13,14-dithiacyclodocos-2-ene) is a coronand analogue and expected to bind metal ions in the cavity. The reduced form ($\mathrm{Cr_{red}}$: 10,11-benzo-3,6,9,12,15,18-hexaoxaeicos-10-ene-1,20-dithiol) is a podand analogue and expected to show poor ion affinity.



$\mathrm{Cr_{ox}}$ $\mathrm{Cr_{red}}$

$\mathrm{Cr_{ox}}$ and $\mathrm{Cr_{red}}$ were synthesized according to the following reaction sequence and identified by IR, NMR, mass spectrum and elemental analysis.[13] $\mathrm{Cr_{ox}}$ was synthesized



(1)

(2)

by route 1 and finally isolated by a TLC method. On the other hand, purification of $\mathrm{Cr_{red}}$ was very difficult because of ready oxidation either to $\mathrm{Cr_{ox}}$ or to oligomeric materials. We thus developed route 2 in which the final step (H_2NNH_2 treatment) proceeded under reductive atomosphere. As the product was protected from air oxidation, $\mathrm{Cr_{red}}$ could be easily isolated.

The ion-binding ability of $\mathrm{Cr_{red}}$ and $\mathrm{Cr_{ox}}$ was estimated by anaerobic solvent extraction of alkali metal salts of 8-anilinonaphthalene-1-sulfonate (ANS)[14] from water to chloroform and was compared with that of monobenzo-

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(12) A similar idea has recently been offered by M. Rabin et al. (private communication).

(13) $\mathrm{Cr_{red}}$: oil; IR (neat) ν_{SH} 2560 cm^{-1}, ν_{C-O-C} 1130, and 1260 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (2 H, t, SH), 2.68 (4 H, h, SCH_2), 3.74 (16 H, m, $CH_2OCH_2CH_2OCH_2$), 4.18 (4 H, t, $ArOCH_2$), 6.92 (4 H, s, Ar protons). Found: C, 52.06; H, 7.47; S, 15.57. Calcd for $C_{18}H_{30}O_6S_2$: C, 53.18; H, 7.44; S, 15.77. $\mathrm{Cr_{ox}}$: mp 46–49 °C; IR (neat) ν_{C-O-C} 1120 and 1260 cm^{-1}; MS, M$^+$ (*m*/*e*) 404; NMR ($CDCl_3$) δ 2.92 (4 H, t, SCH_2), 3.76 (16 H, m, $CH_2OCH_2CH_2OCH_2$), 4.16 (4 H, t, $ArOCH_2$), 6.87 (4 H, s, Ar protons).

(14) Picrate ion, usually employed for solvent extraction, was not used in the present "redox" system because of its oxidative properties.

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Table I. Extraction of Alkali Metal Salts of ANS with Cr_{red}, Cr_{ox}, and Monobenzo-21-crown-7 (Cr)[a]

metal	Ex%		
	Cr_{red}	Cr_{ox}	Cr
Na^+	0	0	1.9
K^+	0.3	3.3	33.8
Rb^+	0.5	5.6	66.4
Cs^+	1.2	6.7	72.3

[a] 30 °C, N_2. Aqueous phase: [MCl] = 0.05 M, [ANS] = 5.00×10^{-4} M, pH 5.0 with MOH (0.01 M)–phosphoric acid. Organic phase ($CHCl_3$): [crown] = 1.00×10^{-3} M.

21-crown-7 (Cr) in which the disulfide is substituted by an ethereal oxygen. The extractability (Ex%) was determined by the partition of ANS between the aqueous and the organic phase ($CHCl_3$). The pH of the aqueous phase was maintained to 5.0 where ANS is fully dissociated while the thiol groups in Cr_{red} are undissociated. Under these conditions neither Cr_{red} nor Cr_{ox} leaked into the aqueous phase. The results are summarized in Table I, where the details of the extraction conditions are recorded.

Examination of Table I reveals the following results: (i) Cr_{ox} has the highest selectivity for Cs^+ as Cr has, (ii) the absolute Ex% of Cr_{ox} (6.7%) is smaller than that of Cr (72.3%), and (iii) most importantly, Cr_{red} scarcely extracts alkali metal cations into the organic phase. The inspection of Corey–Pauling–Koltun models suggests that the ring size of Cr_{ox} is close to or slightly larger than that of Cr. This is the origin of the Cs^+ selectivity as Cr usually shows.[1-3] Comparison of Ex% of Cr_{ox} with that of Cr indicates, however, that the replacement of an ethereal oxygen with a disulfide bond brings forth a significant decrease in the Cs^+ affinity. This is due to the incorporation of the disulfide bond having no coordination ability. It is surprising that the elimination of only one chelating oxygen of seven causes such a conspicuous change. Previously, Drewes and Riphagen[15] synthesized crown ether analogues in which $-O(CH_2CH_2O)_n-$ (n = 3,4) is linked to –CO–(*o*-phenyl)–SS–(*o*-phenyl)–CO–. They could not find any positive result for binding of alkali metal ions. This means that introduction of the long noncoordinative unit is very unfavorable to ion binding. There is another way to elucidate the Ex% decrease: the azimuthal angle of the disulfide bond is 90° in the lowest energy state,[16] and if this is the case in Cr_{ox}, the ring cannot adopt a planar conformation. This unfavorable conformation may also decrease Ex% of Cr_{ox} relative to Cr.

The finding iii suggests, on the other hand, that the ion affinity of the crown ether analogues would be regulated by redox-switched cyclic–acyclic interconversion. We have found that Cr_{ox} is reduced to Cr_{red} by sodium dithionite, 2-mercaptoethanol, tri-*n*-butylphosphine, or $NaBH_4$, while Cr_{red} is readily oxidized to Cr_{ox} by molecular oxygen, I_2, etc. The more interesting process is the latter oxidation of Cr_{red} to Cr_{ox}, because one may expect the metal template effect for the ring-formation step. Recently, the template effect of metal cations on the ring-formation step of crown ethers has widely been investigated by Mandolini et al.,[17] but the method (carried out in strongly basic solutions) is rather inconvenient. We found that the facile oxidation of Cr_{red} to Cr_{ox} is very useful as a convenient method to evaluate the template effect. Cr_{red} (0.010 M) in water–ethanol (20:80, v/v) solvent containing 0.02 M LiOH was oxidized by molecular oxygen at room temperature. The analysis of the products with a TLC scanner (Shimadzu CS-920) showed that the ratio of Cr_{ox} vs. oligomeric products is 34/66 but is enhanced up to 80/20 in the presence of 0.05 M cesium dodecanoate. The oxidation of Cr_{red} under further diluted concentration gave the cyclic products in almost quantitative yields: Cr_{red} (1.0×10^{-3} M) in methanol containing 0.050 M Et_4NOH was oxidized by I_2 at room temperature and the products were analyzed by gel-permeation chromatography (column: Shimadzu HSG-20). In the absence of the template the products were Cr_{ox} (5.2%), cyclic dimer ($\overline{\mathrm{SS{-}SS}}$, 15%), cyclic trimer ($\overline{\mathrm{SS{-}SS{-}SS}}$, 3.6%), and polymer (MW >2000, 66%).[18] In the presence of the template (0.05 M cesium tosylate), on the other hand, the products were Cr_{ox} (70%) and cyclic dimer (28%) and no polymeric material was detected.

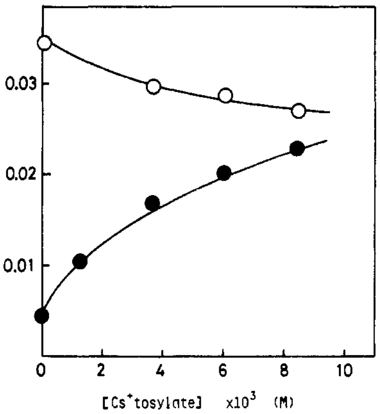
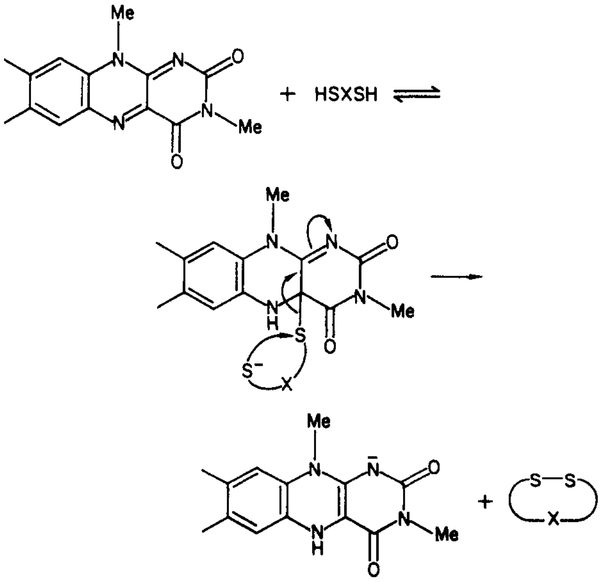


Figure 1. Oxidation of Cr_{red} (●) and 1,4-butanedithiol (○) by 3-methyllumiflavin (1.20×10^{-5} M) at 30 °C. Water (pH 9.0 with 0.10 M LiOH–boric acid)–ethanol (20:80), N_2, [dithiol] = 1.01×10^{-3} M.

Another interesting aspect of the template effect is the kinetics for the ring-formation step. It is known that flavin coenzymes oxidize dithiols at room temperature.[19] This is one of the most important coenzymatic reactions and occurs according to eq 3. Therefore, the oxidation rate can be easily followed by monitoring the disappearance



(3)

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(16) Pryor, W. P. In "Mechanisms of Sulfur Reactions"; McGraw-Hill: New York, 1962; p 18.

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(18) The formation of similar cyclic dimer and cyclic trimer has been observed for the air oxidation of polysarcosine bearing sulfhydryl groups at its chain ends: Sisido, M.; Tamura, F.; Imanishi, Y.; Higashimura, T. *Biopolymers* **1977**, *16*, 2723.

(19) Hemmerich, P.; Nagelschneider, G.; Veeger, C. *FEBS Lett.* **1970**, *8*, 69.

of the absorption band of flavin. We carried out the oxidation of Cr_{red} and 1,4-butanedithiol by 3-methyllumiflavin (λ_{max} 445 nm) in water-ethanol (20:80, v/v) at 30 °C. The pseudo-first-order rate constants (k_1) are plotted as a function of the template (cesium tosylate) concentration in Figure 1. Interestingly, the k_1 values for the oxidation of Cr_{red} increased with increasing cesium tosylate concentration. In contrast, the k_1 values for the oxidation of 1,4-butanedithiol decreased gradually. The rate decrease is probably attributed either to the effect of ionic strength or to the formation of tight ion pairs. The data in Figure 1 imply, therefore, that the "kinetic" template effect is also operative on the ring-formation step in eq 3.

In conclusion, the present study established that the redox reaction between dithiol and disulfide is useful to give a switch function to crown ether analogues and that the ring-formation step is significantly subjected to the template effect. Although the "reversibility" and "response speed" of the present redox-switched crown ethers should be further improved, we believe that the concept is applicable more fruitfully to ion extraction, ion transport, selective metal recognition, etc. The investigations are currently underway in this laboratory.

Acknowledgment. Support of this research by the Ministry of Education of Japan is gratefully acknowledged.

Registry No. Cr_{red}, 91295-69-1; Cr_{ox}, 91295-70-4; Cr, 67950-78-1; K^+ANS, 76402-43-2; Rb^+ANS, 91295-71-5; Cs^+ANS, 91295-72-6; 1,4-butanedithiol, 1191-08-8; 3-methyllumiflavin, 18636-32-3.

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Acidity Measurements with Lithiated Amines: Steric Reduction and Electronic Enhancement of Acidity

Summary: A study of 15 secondary amines having either two alkyl, or an alkyl and a silyl, or two silyl substituents of differing bulk reveals acidities which vary by more than 10 p*K* units. Use of their lithio derivatives permits measurement of acidities in tetrahydrofuran in the p*K* range of 27-43. The most hindered amines show potentially useful selectivity in their preference for methyl proton abstraction.

Sir: More than 10 years have elapsed since Olofson and Dougherty[1] described the superior properties of lithium tetramethylpiperidide (LTMP) as a proton-specific base, as indicated by a comparison of yields for the conversion of benzyl chloride to phenylcarbene and conversion of *o*-chloroanisole to its benzyne using a variety of bases. Its proton selectivity, coupled with its ready availability, suggested the preferential use of LTMP for the lithiation of weak carbon acids. As a result, LTMP has become widely used in organic reactions as has lithium bis(trimethylsilyl)amide and perhaps most frequently, lithium diisopropylamide (LDA). Another very potent "superbase", the potassium salt of 1,3-diaminopropane[2] (KAPA) has also proven useful and appears to possess a basicity comparable to that of LDA.[3]

We have recently undertaken the measurement of acidities of weak carbon acids in tetrahydrofuran (THF) using ^{13}C NMR[4,5] to determine the position of the equilibrium [1]. The classes studied have included aromatic,

$$R_3CH + LiNR_2 \rightleftharpoons R_3CLi + HNR_2 \qquad [1]$$

heterocyclic,[5] and heteroallylic[6] and, most recently, a series of monosubstituted benzenes.[7] The number of compounds amenable to study has been restricted by the lack of bases having significantly different p*K*'s, yet adequate proton specificity.[8] Thus, the p*K* values for diisopropylamine and tetramethylpiperidine, 35.7 and 37.3, respectively, confines the measurements to the p*K* range of 33 to 40 units. We now describe the synthesis of a variety of dialkylamines and alkylsilylamines whose acidities vary over a range of almost 11 p*K* units. Use of their lithiated derivatives significantly enhances our ability to measure acidities in THF. In addition, the most basic of these new lithiated amines show considerable regioselectivity in abstracting only very unhindered protons.[9]

All new amines have been prepared by standard methods.[10] Their p*K* values have been determined as described previously, by measurement of the equilibrium analogous to [1] vs. LDA or another suitable standard.[12] The p*K* values are reported relative to diisopropylamine previously determined to be 35.7 relative to 2-methyl-1,3-dithiane.[5] As seen in Table I, there is a consistent correlation between the size of the alkyl substituents on the nitrogen and the acidity of the amine.

However, dialkylamines having a p*K* below 35 are not suitable for p*K* measurements. For example, the ^{13}C signals for *N*-2-butyl-*N*-1-propylamine in the presence of its lithium salt are quite broad as a result of the diminished hindrance to Li-H exchange. Still less bulky amines have more rapid exchange, giving only time averaged signals at room temperature.[4] Fortuitously, we have found that alkyl(trimethylsilyl)amines maintain the slow Li-H interchange yet possess appreciably greater acidity (4-6 p*K* units) than dialkylamines,[13] thereby providing the capa-

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(7) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790.

(8) Streitwieser's group has recently reported "Cesium Ion Pair Acidities" of several delocalized aromatic hydrocarbons. With use of the UV method, to measure the equilibrium between two carbon acids, p*K*'s as low as 20 have been determined: Streitwieser, A., Jr.; Sors, D. A.; Kaufman, M. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1394.

(9) In two very recent papers, Corey and Gross describe the synthesis of a new hindered base *tert*-octyl-*tert*-butylamine whose lithio derivative exhibits enhanced selectivity in the formation of *E* vs. *Z* enolates; Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 491, 495.

(10) Those dialkylamines not previously reported in the literature have been prepared by addition of *n*- or *tert*-butyllithium to the appropriate aldimine. The neopentyl(trimethylsilyl)amine was prepared by reacting bis(trimethylsilyl)amine with 2 equiv of neopentylamine.[11] A detailed description of their preparation and properties is given in the supplementary material section.

(11) Fessenden, R.; Fessenden, J. *Chem. Rev.* **1961**, 361.

(12) All equilibrium measurements have been made as described previously[7] using ^{13}C NMR. Each amine's acidity was confirmed by determination vs. a second standard. In all cases agreement was within experimental error (±0.2 p*K* unit). The more accurate value, derived from the *K* closer to unity, appears in Table I.

(13) The increase in acidity of an amine upon replacement of a carbon by a silicon atom is consistent with the known ability of silicon to stabilize an adjacent carbanion; see: Colvin, E. "Silicon in Organic Synthesis"; Butterworths: London, 1981; Chapter 2.

0022-3263/84/1949-3442$01.50/0