

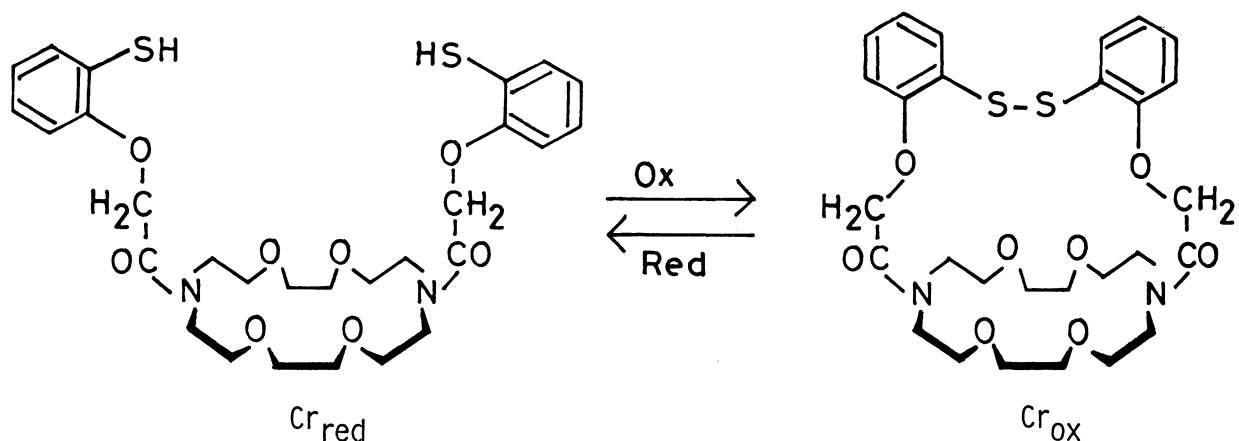
REDOX-SWITCHED CROWN ETHERS.
CROWN-CRYPTAND INTERCONVERSION COUPLED
WITH REDOX OF THIOL GROUPS

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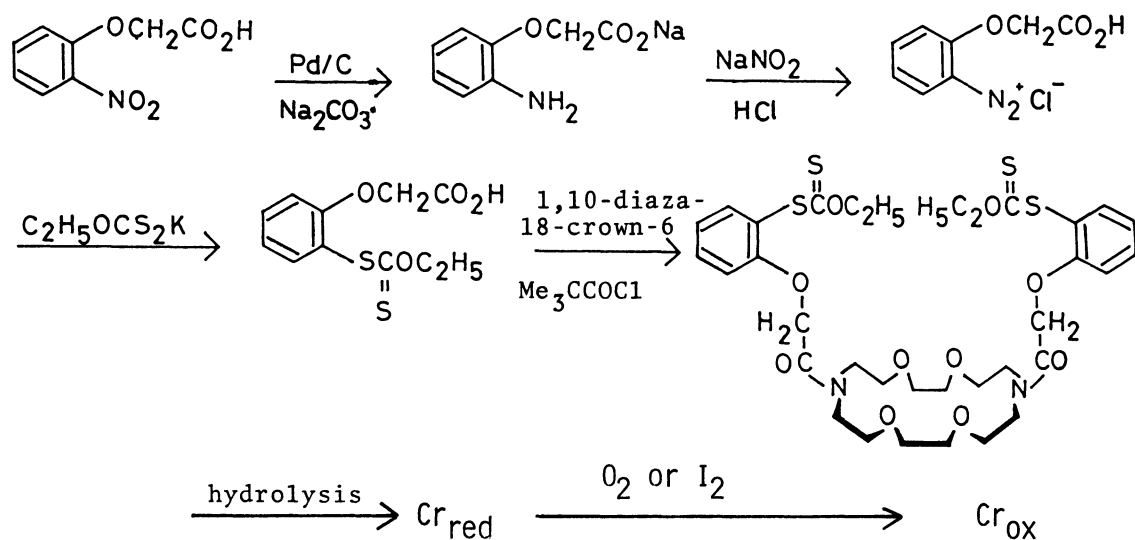
A crown ether capped with a redox-functionalized thiol-disulfide couple was synthesized. The oxidized form with an ionophoric cap binds K^+ , Rb^+ , and Cs^+ more efficiently than the reduced form with two lariat-type groups. This is the first example of the redox-switched interconversion between crown and cryptand.

Macrocyclic polyethers contain intramolecular cavities delineated by molecular segments and are capable of specific chelation with alkali and alkaline earth metal cations. The specificity in the chelation stems from a host-guest relationship^{1,2)}: that is, the ion-selectivity is primarily governed by the size and shape of the intramolecular cavities. One may thus expect that if the ring conformation or the topological ring shape can be reversibly changed in response to some input energy, it would lead to the "control" of ion-binding ability and ion-selectivity by an on-off switch. Furthermore, this is important in relation to the membrane transport phenomenon mediated by some antibiotic carriers where the reversible interconversion between the cyclic and the acyclic form of the antibiotics plays the crucial role.³⁾

We considered that the interconversion between the cyclic and the acyclic form is realized in an artificial system by utilizing the reversible bond-formation and bond-scission. The most suitable candidate for this purpose is the redox reaction of a thiol-disulfide couple. Here, we wish to report an example of "redox-switched crown ethers", Cr_{ox} and Cr_{red} which exhibit a crown-cryptand interconversion coupled with redox of a thiol-disulfide bond. The oxidized form (Cr_{ox}) has two coordinative oxygens in the disulfide cap and is expected to act as a cryptand analogue. On the other hand, the reduced form (Cr_{red}) is a simple crown ether (or at most, a lariat crown ether)^{4,5)} and is expected to have the ion-binding ability inferior to that of Cr_{ox} . Thus, the redox-mediated interconversion would play the role of a "lock" to put on and off a thiol cap containing two ionophoric oxygens.



Cr_{ox} (mp 172-175°C) and Cr_{red} (mp 165-168°C) were synthesized according to the following reaction sequence and identified by IR, NMR, mass spectrum, and elemental analysis. Cr_{ox} was reduced to Cr_{red} by sodium dithionite, 2-mercaptoethanol, or sodium borohydride, while Cr_{red} was oxidized to Cr_{ox} by molecular oxygen or iodine.⁶⁾



The binding ability of Cr_{ox} and Cr_{red} was estimated by preliminary solvent extraction of alkali metal salts of 1-anilinonaphthalene-8-sulfonate (ANS) from water to organic phase (o-dichlorobenzene: butyl alcohol = 80:20 by volume).⁷⁾ The extractability (Ex%) was estimated by the partition of ANS between the aqueous and the organic phase. The pH of the aqueous phase was buffered to 4.0 where ANS is fully dissociated while the thiol groups of Cr_{red} are undissociated. The results are summarized in Table 1.

The inspection of CPK model of Cr_{ox} suggests that two phenolic oxygens can be directed toward the crown ring, indicating the coordination ability to metal ion complexed in the crown ring. The oxygens are apparently far from the crown ring

Table 1. Extraction of alkali metal salts of
1-anilinonaphthalene-8-sulfonate with Cr_{ox} and
 Cr_{red} .^{a)}

Crown	Ex% of			
	Na^+	K^+	Rb^+	Cs^+
Cr_{ox}	40.2	53.3	46.7	35.6
Cr_{red}	39.9	39.0	31.6	26.5

- a) 30°C. Organic phase: $[\text{Cr}_{\text{ox}} \text{ or } \text{Cr}_{\text{red}}] = 4.00 \times 10^{-3} \text{ M}$
in o-dichlorobenzene(80): n-butyl alcohol (20).
Aqueous phase: pH 4.0 with H_3PO_4 (0.0114M)–MOH(0.0100M),
[MC1]=0.10M, [ANS]= $5.00 \times 10^{-5} \text{ M}$.

plane as compared with those of cryptand[2.2.2] which exhibits a high affinity with Na^+ and K^+ .¹⁾ The expansion of the intramolecular cavity is due to six atoms (two sulfurs and four carbons) present between the two oxygens in the disulfide cap. The examination of Table 1 reveals that (i) Cr_{ox} and Cr_{red} have the similar Ex% values for Na^+ , whereas Cr_{ox} is capable of extracting K^+ , Rb^+ , and Cs^+ more efficiently than Cr_{red} and (ii) the maximum extractability is attained for the extraction of K^+ with Cr_{ox} . No difference in the extractability of Na^+ suggests that the two oxygens in the disulfide cap of Cr_{ox} do not contribute to the metal-binding. Conceivably, small Na^+ ion is deeply bound to the diaza-18-crown-6 ring, so that the two oxygens are too far to coordinate to the complexed Na^+ ion. In contrast, other alkali metal ions with relatively large ion-radii would be able to interact with the oxygens owing to the large ion-radii and the "shallow-binding" to the crown ring. Based on the extraction method,⁸⁻¹⁰⁾ we estimated the complexation constants in a mixed solvent of o-dichlorobenzene-butyl alcohol(80:20 by volume): K_c for Cr_{ox} , $771 \text{ M}^{-1}(\text{Na}^+)$, $2250 \text{ M}^{-1}(\text{K}^+)$, $1370 \text{ M}^{-1}(\text{Rb}^+)$, and $635 \text{ M}^{-1}(\text{Cs}^+)$; K_c for Cr_{red} , $756 \text{ M}^{-1}(\text{Na}^+)$, $697 \text{ M}^{-1}(\text{K}^+)$, $416 \text{ M}^{-1}(\text{Rb}^+)$, and $284 \text{ M}^{-1}(\text{Cs}^+)$. These values indicate again that the complexation constants of Cr_{ox} for K^+ , Rb^+ , and Cs^+ are greater by 3-4 fold than those of Cr_{red} , while there is no difference in the complexation constants for Na^+ . The extractability is affected not only by the binding ability but also by the lipophilicity of ionophores. At present, we consider that the difference in the complexation constants should be ascribed mainly to the structural difference, because the similar association constants observed for Na^+ cannot be explained by the lipophilicity.

Previously, we and others have reported "photoresponsive crown ethers" which change the ion-binding ability in response to photoirradiation.¹¹⁻¹⁴⁾ Rebek et al.¹⁵⁾ reported a crown ether, the binding ability of which is controlled by metal complexation to the incorporated 2,2'-bipyridyl unit. These systems are all based on an idea to induce the conformational changes in the crown ring by the structural change in the subunits. One can expect a much more substantial change in the binding ability and the selectivity for the direct cyclization and ring-opening of the delineating molecular segments. The present results indicate that such reversible interconversion between the cyclic and the acyclic form can be realized by using a redox reaction of a thiol-disulfide couple. Application to ion transport driven by redox reactions is now in progress in this laboratory.

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- 6) The oxidation by molecular oxygen gave Cr_{ox} almost quantitatively, whereas that by iodine gave a mixture of Cr_{ox} and the polymeric analogue.
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