1,2-Dithia-5,8,11,14-tetraoxacyclohexadecane and 1,2-Dithia-5,8,11,14,17-pentaoxacyclononadecane: 'Switched-on' Crown Ethers

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3,6,9,12-Tetraoxatetradecane-1,14-dithiol and 3,6,9,12,15-pentaoxaheptadecane-1,17-dithiol are pro-ionophores which can be converted by Fe^{3+} oxidation into the title compounds which are analogues of 15-crown-5 and 18-crown-6 and which exhibit enhanced ionophoric properties.

The chelation of alkali metal cations by macrocyclic polyethers and the consequent ability of the latter to act as ionophores have been subjects of intensive study during the past decade.[1] While structural modifications are known to affect cation selectivity and ionophoric ability, such structural modifications have been made as permanent structural features of the molecule. In only a few cases have reversible modifications been incorporated.[2–7] In most of these cases photochemical reactions have been used to create thermodynamically unstable forms in which the geometry of the central cavity is changed to produce ionophores which can be 'switched on' or 'switched off' by irradiation.[2–5] In this paper, we report the properties of pro-ionophores which can be 'switched on' by a simple chemical reaction.

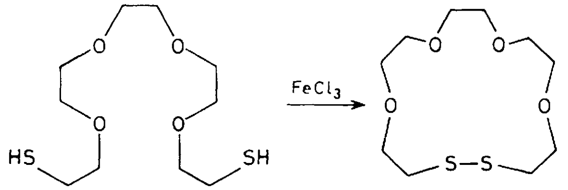
Although changes in the size and shape of the central cavity do affect cation affinity, a potentially more substantial change is associated with the formation of the macrocyclic ring, the macrocyclic effect.[1] We have chosen to construct molecules which can undergo cyclization and ring opening in the presence of appropriate reagents. The ring closure reaction would create a molecule of high ionophoric capability while the ring opening reaction could facilitate cation release, often the slowest step in cation transport.

As the first examples of such molecules, we have chosen to prepare analogues of 15-crown-5 and 18-crown-6 in which one oxygen atom has been replaced by a disulphide unit. The disulphide bond is labile in reducing media and is re-formed on oxidation. Thus, the α,ω-dithiols (**1a**) and (**2a**)[8]

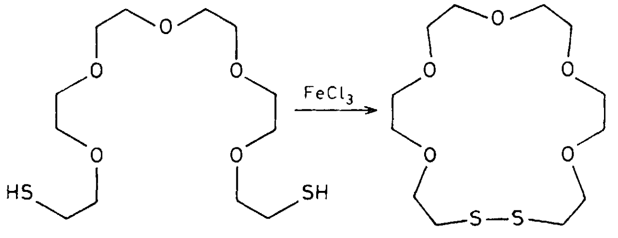
Table 1. Extraction of alkali metal picrates from aqueous solution into methylene chloride.[a]

Compound	% Picrate extracted	
	Na$^+$	K$^+$
(1a)	0.4	0.4
(1b)	1.3	0.7
(2a)	3	4
(2b)	2	17
Dibenzo-18-crown-6	13	80
Hexaethylene glycol	4	7

[a] The aqueous solution contained 1.0 M KOH or NaOH and 2×10^{-4} M sodium or potassium picrate. The methylene chloride was of equal volume and was 1×10^{-3} M in ionophore.



(1a) (1b)



(2a) (2b)

could be converted into the corresponding disulphide-crowns† by oxidation under high dilution with FeCl$_3$.[9] The cation affinities of (**1a**), (**1b**), (**2a**), and (**2b**) were compared with those of crown ethers and their acyclic analogues by extraction of sodium and potassium picrates into methylene chloride (Table 1).

The data in Table 1 indicate that the cyclic disulphide-crowns have considerably more ionophoric activity than the corresponding pro-ionophores (acyclic dithiols) although they are less active than dibenzo-18-crown-6. This is not surprising since the replacement of an oxygen atom by the disulphide-unit removes one of the chelating ligands. The data in Table 1 also indicate that the ion specificities for (**1b**) (Na $>$ K) and (**2b**) (K $>$ Na) parallel those of the crown ether analogues 15-crown-5 and 18-crown-6, respectively.

The difference in ionophoric activities of acyclic dithiols and cyclic disulphides could also be assessed by the rate of transport of alkali metal salts (picrates or thiocyanates) from one aqueous layer to a second aqueous layer through a methylene chloride bridge.‡ The rate of transport was monitored by colorimetric analysis of the picrate in the receiving layer (or of the Fe^{III} complex when the alkali thiocyanates were used). Figure 1 illustrates the transport of Li, Na, and K picrates by (**1a**) and (**1b**), the pro-ionophore and the disulphide-crown related to 15-crown-5. As illustrated, the disulphide-crown is a better ionophore for either metal ion than is the acyclic disulphide. In addition, we note that the rate ratio, (**1b**)/(**1a**), is greater for Na than for K: Na, 5.22; K, 2.07. This is consistent with our notion that the cavity of (**1b**) fits sodium ion better than potassium ion as does 15-crown-5. A different result was obtained for transport of Na and K thiocyanates by (**2b**), the disulphide related to 18-crown-6. Here the rate of transport of KSCN was considerably faster than the transport of NaSCN in accord with the extraction data.

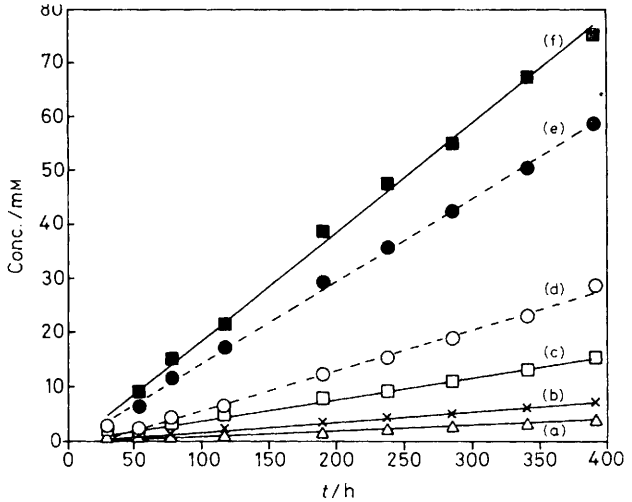


Figure 1. Alkali picrate transport by (**1a**) and (**1b**) as measured by the increase in picrate concentration in the receiving aqueous phase: (a) Li, (**1a**); (b) Li, (**1b**); (c) Na, (**1a**); (d) K, (**1a**); (e) K, (**1b**); (f) Na, (**1b**).

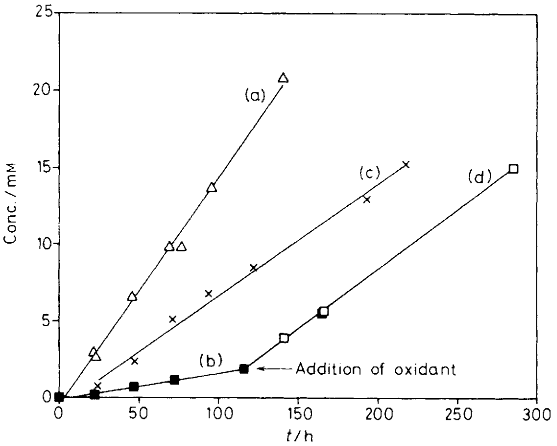


Figure 2. 'Switched on' potassium thiocyanate transport by (**2**): (a) transport by (**2b**); (b) transport by (**2a**); (c) transport by ionophore formed from (**2a**) on addition of potassium ferricyanide after 24 h; (d) transport by ionophore formed from (**2a**) on addition of potassium ferricyanide after 120 h.

Chemically switchable pro-ionophore–ionophore couples can serve as models for biological 'ion gates,' structures in which ion transport is initiated by an external stimulus. In a second set of transport experiments, the ability of (**2**) to act as a switchable ionophore was demonstrated. In these experiments, the pro-ionophore, (**2a**) was introduced into the transport system (Figure 2). The initial rate of transport was very

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† Compound (**1b**) was a liquid. Compound (**2b**) was a low melting solid, m.p. 34 °C. The results of combustion analyses and ^{13}C n.m.r. and mass spectra were in accord with the assigned structures.

‡ These experiments were carried out in U-shaped vessels with 5 ml aqueous solutions (one of which was 1 M in alkali metal picrate or thiocyanate), and an 8 ml methylene chloride bridge, which was 10^{-3} M in ionophore.

slow, as could be inferred from the extraction data. After 24 or 120 h, oxidant [$K_3Fe(CN)_6$, 10^{-2} M] was introduced to 'switch on' the transport, *i.e.*, to convert the pro-ionophore (**2a**) into the ionophore (**2b**).§ As indicated in Figure 2, oxidation leads to greatly enhanced transport, although not as great as that produced by an equivalent amount of (**2b**). Since oxidation *in situ* may not produce quantitative conversion of (**2a**) into (**2b**) the lower rate of transport in the 'switched on' system was not unexpected.

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§ Chemical ionisation mass spectra of disulphide and dithiol both show $(M + H)^{\cdot +}$ peaks. Analysis of the solutions from experiments in which the pro-ionophoric dithiol was 'switched-on' demonstrated the presence of the disulphide as the major volatile product along with traces of unchanged dithiol.

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