# Oxygen and Nitrogen Crowns

## Macrocyclic complexing agents

Crown ethers[1] are a class of macrocyclic polyethers, the earliest of which, **dibenzo-18-crown-6**, was synthesized by C.J. Pedersen in 1967.[2] The synthetic utility of crown ethers arises from their ability to solvate cations of alkali, alkaline earth and transition metal salts. They thus increase the solubility of ion pairs, providing highly reactive unsolvated anions in nonpolar, aprotic solvents. These unsolvated ("naked")[3] anions show enhanced reactivity as nucleophiles, bases and oxidants, facilitating reactions under much milder conditions than are possible in conventional hydrolytic media. The following examples outline the remarkable synthetic utility of crown ethers.

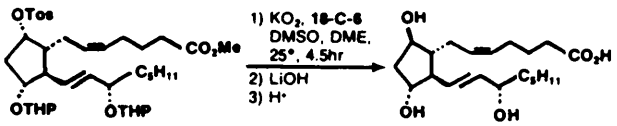
Sterically hindered esters of 2,4,6-trimethylbenzoic acid, which are resistant to hydrolysis by aqueous KOH, are readily saponified by the **dicyclohexyl-18-crown-6** complex of KOH in refluxing aromatic solvents.[4]

It has also been reported that the **dicyclohexyl-18-crown-6** complexes of potassium bromide and potassium iodide in acetone at room temperature convert *n*-butyl brosylate to the corresponding halide in clean, second-order reactions.[5]

$$[KDicy\text{-}18\text{-}C\text{-}6]^+X^- + n\text{-}BuOBs \xrightarrow[25°]{\text{acetone}}$$

$$X = Br, I \qquad [KDicy\text{-}18\text{-}C\text{-}6]^+OBs^- + n\text{-}BuX$$

E.J. Corey and co-workers[6] reported that **18-crown-6** facilitates the dissolution of potassium superoxide in solvents such as DMSO, DMF, DME and ether. This highly reactive superoxide acts as an effective nucleophile, replacing good leaving groups such as mesylate, tosylate and bromide by hydroxyl in high yields. This technique has been applied to the epimerization of a prostaglandin.[6]



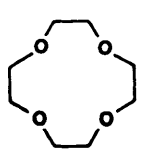

The carboxylate ion is quite nucleophilic in nonpolar solvents when used with crown ethers, and can be used to synthesize phenacyl esters, anhydrides and lactones which are difficult to obtain by classical procedures.[7] Phenacyl esters have found utility in trace fatty acid analysis.[8]

$$RCO_2K \xrightarrow[18\text{-}C\text{-}6]{BrCH_2COPh} RCO_2CH_2COPh$$

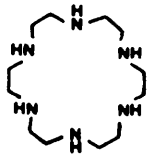
The presence of crown ethers has also enabled the use of mild bases in the Wittig reaction. As a result, a remarkable effect of solvent ($CH_2Cl_2$ *vs.* THF) on the stereochemistry of the products is observed.[9]

$$PhCHO + [Ph_3\overset{+}{P}CH_2R]\,Br^- \xrightarrow[K_2CO_3,\ CH_2Cl_2]{18\text{-}C\text{-}6} Ph\text{-}CH{=}CHR$$

Aldrich is pleased to introduce **12-crown-4** and **hexacyclen** to its existing line of crown ethers.



**12-Crown-4**



**Hexacyclen**

**12-Crown-4** has been shown to solubilize $KMnO_4$ in benzene, and this reagent has been used to oxidize olefins to acids and active methylenes to carbonyl functions in quantitative yields.[10]

$$PhCH{=}CHPh \xrightarrow[KMnO_4]{12\text{-}C\text{-}4,\ PhH} 2\ PhCOOH \qquad 100\%$$

$$PhCH_2Ph \xrightarrow[KMnO_4]{12\text{-}C\text{-}4,\ PhH} PhCOPh \qquad 100\%$$

The role of lithium ion in lithium organocuprate complexes is better understood as a result of reactivity studies performed in the presence of **12-crown-4**. Lithium ion solvated by **12-crown-4** was found to *inhibit* the reactivity of lithium organocuprates in reactions involving enones, acid chlorides and $\beta$-keto esters.[11]

**Hexacyclen** is the nitrogen analog of **18-crown-6** in which the secondary amines act as excellent electron donors to transition metal cations exhibiting Lewis acidity.[12] The macrocyclic polyamines related to **hexacyclen** form complexes with transition metals which are less stable to acids than are regular amine-metal complexes. These metal-polyamine complexes have found utility as thermally activated curing agents for epoxy resins.[13]


**References:** (1) Reviews: C.J. Pedersen, *Aldrichimica Acta*, **4**, 1 (1971); G.W. Gokel and H.D. Durst, *ibid.*, **9**, 3 (1976); G.W. Gokel and H.D. Durst, *Synthesis*, 168 (1976); J.J. Christensen *et al.*, *Chem. Rev.*, **74**, 351 (1974). (2) C.J. Pedersen, *J. Amer. Chem. Soc.*, **98**, 2495 (1967). (3) C.L. Liotta and H.P. Harris, *ibid.*, **96**, 2250 (1974). (4) D.J. Sam and H.E. Simmons, *ibid.*, **94**, 4024 (1972). (5) D.J. Sam and H.E. Simmons, *ibid.*, **96**, 2252 (1974). (6) E.J. Corey *et al.*, *Tetrahedron Lett.*, 3183 (1975); *Chem. Commun.*, 658 (1975). (7) D. Dehm and A. Padwa, *J. Org. Chem.*, **40**, 3139 (1975); H.D. Durst, *Tetrahedron Lett.*, 2421 (1974); *J. Chromatogr.*, **112**, 673 (1975). (8) H.D. Durst *et al.*, *Anal. Chem.*, **47**, 1797 (1975); C.L. Liotta *et al.*, *Tetrahedron Lett.*, 4205 (1975). (9) R. Boden, *Synthesis*, 784 (1975). (10) F.D. Cima *et al.*, *J. Chem. Soc., Perkin Trans. 2*, 55 (1973). (11) C. Quannes *et al.*, *Tetrahedron Lett.*, 815 (1977). (12) Ger. Offen. 2,447,279 (1975); *Chem. Abstr.*, **83**, 43400*m* (1975); U.S. Patent 3,930,867 (1976); *Chem. Abstr.*, **84**, 158011*y* (1976). (13) U.S. Patent 4,001,212 (1977).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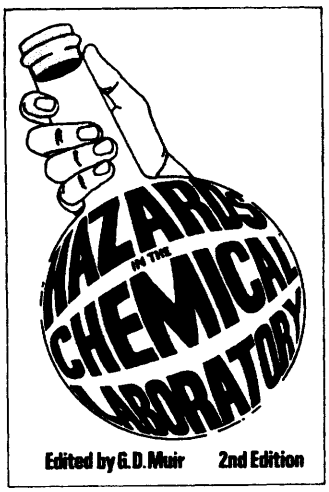


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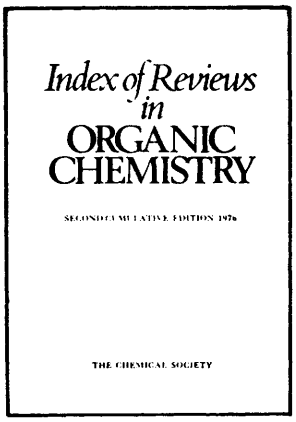


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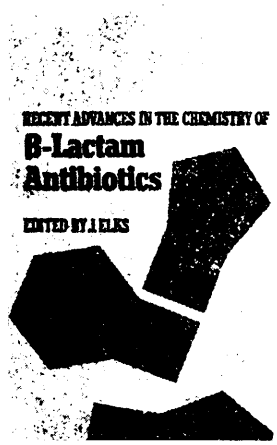


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