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18-CROWN-6: A STRONG COMPLEXING AGENT FOR ALKALI METAL CATIONS

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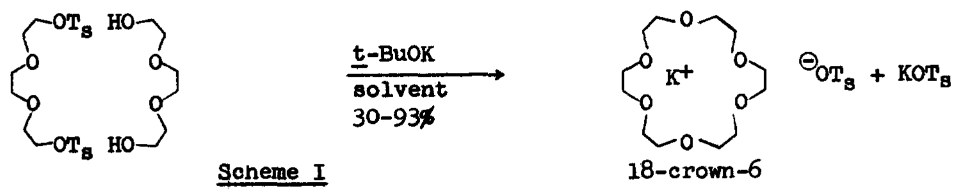
In 1967 C. J. Pedersen reported that macrocyclic polyethers - "Crown" ethers - can complex alkali, alkaline earth and other cations.(1) Pedersen showed that the complexing ability of the crowns could be correlated with the relative sizes of the cation in question and the diameter of the macrocycle. The crowns had benzene or cyclohexane rings fused to the center ring. No data were reported on the one monocyclic crown prepared in 2% yield: 1,4,7,10,13,16-hexaoxacycloöctadecane (18-crown-6(2)). Since that time numerous articles have appeared demonstrating the complexing ability of dibenzo- and especially dicyclohexyl-18-crown-6.(13) The ability of such crowns to effect ion-pair separation of alkali and alkaline earth salts has been convincingly demonstrated.(4) X-ray structures have appeared indicating that cations are enclosed within the cavity of the crown ethers,(5) in a manner similar to that found in naturally occurring macrocyclic antibiotics such as nonactin(6) and valinomycin.(7)

Because of the great potential of crown ethers in organic synthesis and catalysis new monocyclic analogues have been synthesized. We now report the facile synthesis of 18-crown-6, 21-crown-7, 24-crown-8, and 1-aza-4,7,10,13,16-pentaoxacycloöctadecane (aza-18-crown-6). Stability constant measurements on 18-crown-6 indicate that it complexes $Na^{\oplus}$ and $K^{\oplus}$ in MeOH even better than dicyclohexyl-18-crown-6 and that replacement of one of the ether oxygens with nitrogen decreases its complexing ability as does increase in ring size.(8) The accompanying paper(9) gives kinetic data which shows that 18-crown-6 effects ion-pair separation of potassium salts even at high concentrations of the salts.

Since Pedersen's synthesis of 18-crown-6 gave such poor yields,(1) the Williamson ether synthesis was performed in aprotic solvents using the tosylate leaving group.

18-Crown-6 was synthesized in 84%, 30-60% and 93% yields in dimethyl sulfoxide, tetrahydrofuran and dimethoxyethane, respectively. The THF procedure was the most simple, although lower yields were obtained:(10)



Scheme I

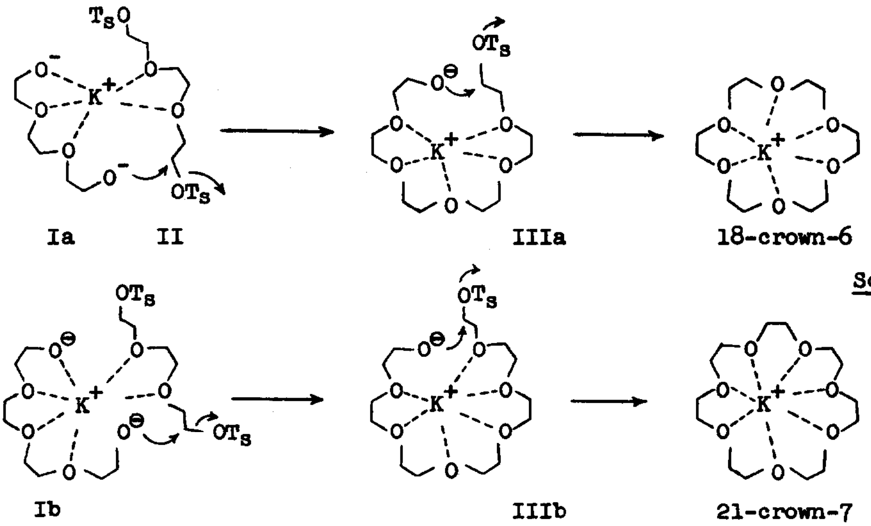
Potassium t-butoxide (0.0200 m) in 100 ml anhydrous THF was added to triethylene glycol (0.019 m) and potassium-t-butoxide (0.0200 m) in 200 ml THF at 35°C at one half the rate of addition of triethylene glycol ditosylate (0.018 m) in 100 cc THF. After stirring 16 hr at 35° the reaction mixture was filtered and reduced in volume to 150 ml. Elution with THF through acid-washed alumina afforded 30-60% pure hygroscopic 18-crown-6 in the first 500 ml of eluate,(11) m.p. 39.5-40.5 (from n-hexane or sublimed at 80°/0.01 mm, Lit. m.p.(1) = 39-40°). Calculated: C, 54.6%; H, 9.17%. Found: C, 55.0%; H, 9.2%; molecular weight (calculated) 264.3, found (mass spectrometry, vapor pressure osmometry) 264. Nmr a singlet at δ 3.67 ($CDCl_3$). 18-Crown-6 was soluble in hydrocarbons, benzene, chloroform, methanol, "Freon-113" and water.

Pure 21-crown-7 and 24-crown-8 were prepared analogously from the appropriate diols and ditosylates in 18% and 15% yields, respectively. In both cases crude mixtures of 24-crown-8, 21-crown-7 and 18-crown-6 were obtained (these are separated by TLC on unactivated silica gel G eluting with 12 ether/3 MeOH/2 NH_3 (30%) and R_f values are 0.53, 0.36 and 0.12, respectively, visualizing with iodine or Dragendorff reagent (permanent orange spots). These were separated by distillation and/or preparative layer chromatography.

Using a mode of addition patterned after Cornforth,(12) N-trityl-aza-18-crown-6 was prepared in 43% yield from tetraethylene glycol ditosylate and N-trityldiethanolamine and cleaved with 1 N HCl at 25° to aza-18-crown-6 in 65% yield.

The cyclization of a diol and a ditosylate in THF in the presence of potassium t-butoxide to form crown and two moles of potassium tosylate gives a precipitate of one mole of potassium tosylate in the case of 18-crown-6 and of two moles of potassium tosylate in the case of 21-crown-7, 24-crown-8 or N-trityl-aza-18-crown-6. These results possibly indicate that in the synthesis of 18-crown-6 one mole of $K^{\oplus}$ is enveloped during cyclization. 18-Crown-6 is readily isolated in the form of its potassium tosylate complex. On increasing the final concentration of 18-crown-6 from 0.04 M to 0.09 M in DMSO, the yield of 18-crown-6 only drops from 84% to 75%. All of these data indicates that the potassium cation is helping yields by forming a template about which molecules cyclize.

Do the high yields ascribed by us to a "template effect"(13) indicate that in a competitive reaction the most strongly complexing crown would be formed? When a mixture of one mole each of tri- and tetraethylene glycol is allowed to compete for one mole of triethylene glycol ditosylate in the presence of KO-t-Bu in THF equal amounts of 18-crown-6 and 21-crown-7 are formed. With tetra-n-butylammonium hydroxide equal amounts of the two crowns are again formed in a slower reaction in greatly decreased yield, the majority of starting material polymerizing.



Scheme II

Scheme II gives a possible a priori mechanism. The high yields in the presence of K^+ indicate that cyclization of III is faster than the first displacement whether the first displacement involves complexed or uncomplexed I and II. If I and II were uncomplexed they would react to give equal amounts of the two crowns; if complexed, they would give different amounts of the two crowns unless their complexing abilities were identical. Since Smid has shown that the complexing ability of glymes increases with the number of oxygen atoms(4c) (although their stability constants are orders of magnitude smaller than those of the crowns(8)), and since prior complexation of I and II would involve a severe decrease in entropy, it is likely that the first displacement is between uncomplexed I and II. Clearly the template effect involves a cation that is not too bulky guiding together the termini of III, thus increasing the rate of cyclization with respect to polymerization.

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