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DISSOLVING METAL REDUCTION BY CROWN ETHER
---HYDROGENOLYSIS OF ALKYL FLUORIDES

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Summary : A black-blue solution of potassium and dicyclohexyl-18-crown-6 in toluene or diglyme has been proved to be effective in the reductive cleavage of the unactivated carbon-fluorine bond.

Cyclic polyethers are known to form stable complexes with various salts and, since alkali metals can be regarded as a sort of salts ($M^+ M^-$ or $M^+ e^-$),1) it will be reasonable to assume the possibility of the complexation of crown ether with metal itself. In fact, several papers on the solubilization of alkali metals by cyclic polyethers have been issued and Dye reported the first isolation of a crystal of 2Na-cryptand 2,2,2 complex, the structure being determined by X-ray crystallography.1)

Enhancement of the solubility of metal by crown ethers in rather non-polar organic solvents and the generation of species as M^- or e^-, whatever in a naked form or contact ion pair, might provide a new aspect of dissolving metal reduction since the active entity of common dissolving metal reduction has been regarded as the solvated electrons.2)

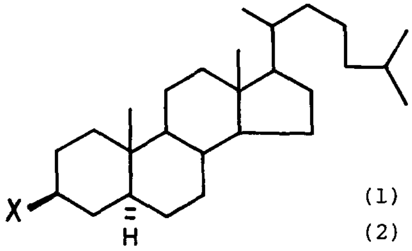
In order to estimate the reactivity of metal-crown ether system as a reductant, alkyl halides, especially fluorides, have been chosen as the substrates, because carbon-fluorine bond is known to strongly resist the usual reduction conditions.

Standard reduction procedure is set up as follows: to a mixture of alkyl halide (0.5 mmol) and dicyclohexyl-18-crown-6 (1.0 mmol) in toluene or diglyme, alkali metal [K or Na-K (44:56 w/w) alloy, >> 1.0 mmol] was added. The reaction mixture was stirred at ambient temperature for 3 hr in nitrogen atmosphere, followed by quenching with iPrOH (1 ml). In some experiments, iPrOH (0.5 ml) was added at the beginning of the reaction as a proton source. The product was isolated by TLC on silica gel.

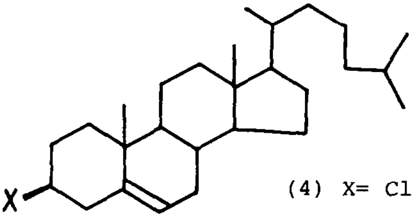
Preliminarily, chlorinated hydrocarbons, 3β-chlorocholestane (1) and 3β-chlorocholest-5-ene (4) were treated with K/dicyclohexyl-18-crown-6 in diglyme to afford cholestane (3) and cholest-5-ene (6) in 96 and 84% yield, respectively.

Unsaturated fluorine compound, 3β-fluorocholest-5-ene (5), whose C-F bond is in the homoallylic position of Δ^5-double bond, was also successfully hydrogenolyzed to cholest-5-ene (6) in 88% yield.

Being encouraged with these data, reduction of fully saturated fluorinated hydrocarbons were investigated. The results of the experiments on 3β-fluorocholestane (2) in various conditions were shown in Table 1.



(1) X= Cl
(2) F
(3) H



(4) X= Cl
(5) F
(6) H

Table 1 Effect of the Reaction Condition on the Reductive Defluorination of 3β-fluorocholestane (2)[a]

Entry	Solvent[b]	Metal	Crown ether[c]	iPrOH[d]	Yield %[e] (3)	(2)
1	DG	K	-	-	11	87
2	"	"	-	+	18	81
3	"	"	+	-	33	65
4	"	"	+	+	19	74
5	"	Na-K[f]	+	-	62	28
6	"	"	++	-	76	--
7	MePh	K	-	-	14	83
8	"	"	-	+	11	83
9	"	"	+	-	74	24
10	"	"	++	-	88[g]	7
11	"	"	+	+	16	84

a) 0.5 mmol of (2) was reduced at ambient temperature for 3 hr.
b) DG = diglyme; MePh = toluene.
c) +, ++ = dicyclohexyl-18-crown-6 (2 or 4 mol equiv), respectively; - = no crown ether.
d) + = iPrOH (0.5 ml); - = no alcohol.
e) isolated yield by TLC on silicagel.
f) Na-K (44:56 w/w) alloy.
g) averaged value; maximum was 99%.

It will be reasonable to draw the following conclusion from these data: i) crown ether can be an effective co-reagent in alkali metal reduction in aprotic solvent. ii) toluene is superior to diglyme as a solvent. iii) addition of proton source as iPrOH lowers the yield of the reduction. iv) Na-K alloy is better than K. vi) an excess of crown ether is required for the completion of the reduction.

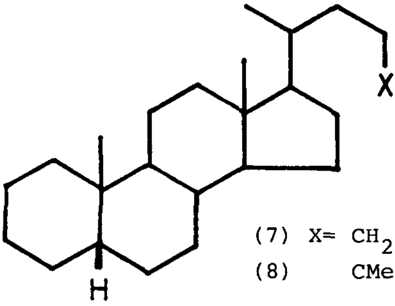
For the comparison, the reductive defluorination of (2) by other reagent systems[3),4),5)] was examined and the results were summarized in Table 2. The maximum yield by these methods was only 58%, which clearly shows that the present method to give 99% yield at its maximum is much superior to other methods.

Table 2 Reductive Defluorination of 3β-Fluorocholestane (2) by Other Systems

Entry	System	Metal	Yield %[a)] (3)	(2)
1	liq NH_3[b)]	Li	4	85
2	THF-HMPT-tBuOH[c)]	K	8	92
3	THF-HMPT	K	22	45
4	HMPT	K	58	41
5	naphthalene-DME[d)]	Na	7	80

a) isolated yield by TLC on silicagel.
b) see ref. 3.
c) see ref. 4.
d) see ref. 5.

Also the unactivated primary and tertiary alkyl fluorides, (7), (8), and (9), were successfully reduced to hydrocarbons by K in toluene in the presence of crown ether, as is shown in Table 3.



(7) X= CH_2F
(8) CMe_2F

(9) $nC_{22}H_{45}F$

The experiment using d_8-toluene as solvent (Table 3, entry 2) shows that one third of the incoming hydrogen comes from toluene, and D^+ (D_2O) used for quenching was not incorporated into the product (entry 3). Moreover, the fact that the better results were obtained in toluene than in diglyme (Table 1) strongly suggests that the unstable radical anion liberated by the aid of crown ether is playing an important role in the former solvent.[6)]

Table 3 Reductive Defluorination of Primary and Tertiary Alkyl Fluorides by K and Dicyclohexyl-18-crown-6 in Toluene and d_8-Toluene[a)]

Entry	Alkyl Fluoride	Yield of Hydrocarbon %[b)]	m/e330/m/e331[f)]
1	(7)	97[c)]	100/27
2	(7)	81[d)]	100/92
3	(7)	82[e)]	100/28
4	(9)	87[c)]	---
5	(8)	100[c)]	---

a) all reactions were carried out at ambient temperature for 3 hr.

b) isolated yield by TLC on silicagel.

c) in toluene. d) in d_8-toluene. e) in toluene, followed by quenching with D_2O. f) m/e 330 (M^+) for $C_{24}H_{42}$; m/e 331 (M^+) for $C_{24}H_{41}D$.

Further experiments are now in progress to clarify the mechanism and stereochemistry of the present reduction. The applicability of the present method to the reduction of other functional groups,[7)] including conjugated dienes and sulfonamides will be reported in other papers.

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