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Lithium aluminum hydride in tetrahydrofuran is an efficient demethylating reagent combination for mono- and bicyclic polyether compounds which bear intra-annular methoxyaryl groups.

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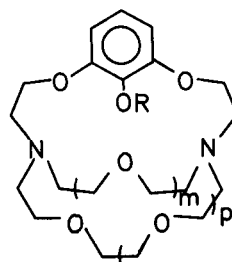
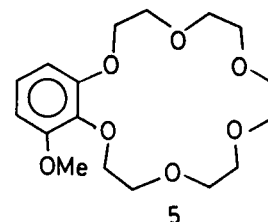
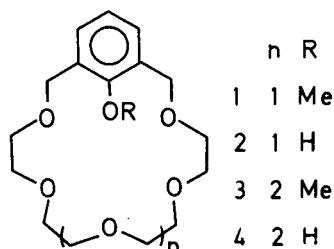
Methods for the protection of inward-facing phenolic groups in macrocyclic polyether compounds have recently received considerable attention. Methoxymethyl [1], methyl [2], allyl [3], and acetyl [4] groups have been utilized for protection of phenolic functions during ring-forming reactions. Subsequent deprotection has been accomplished under a variety of conditions. Particularly effective is the use of anhydrous lithium iodide in pyridine for demethylation of methyl-protected, 1,3-xylyl-based crown ethers [2]. In 1980, McKervey and coworkers [5] noted that lithium aluminum hydride in hydrocarbon solvents could effect demethylation of some substituted methyl phenyl ethers. Use of benzene or heptane, in which lithium aluminum hydride is insoluble and thereby presents a fire hazard, produced demethylation. Similar reactions in the coordinating solvent tetrahydrofuran were found to be much slower [5]. Later Japanese researchers utilized lithium aluminum hydride in benzene or heptane to demethylate macrocyclic ligands with inward-facing [6] or pendant [7,8] anisole units.

We now report efficient demethylation of crown ethers, aza crown ethers, and cryptands which bear intra-annular methoxyaryl groups by lithium aluminum hydride in tetrahydrofuran. For the latter two compound classes, facile reduction of amide linkages and demethylation may be accomplished in a single synthetic step.

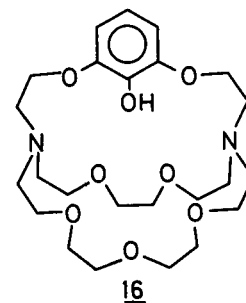
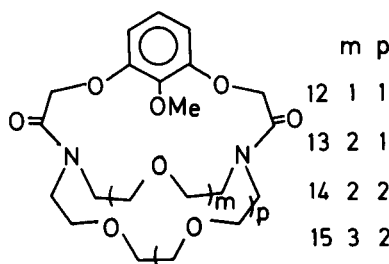
#### Results and Discussion.

When crown ethers **1** and **3** were refluxed with excess lithium aluminum hydride in tetrahydrofuran for 20 hours, crown phenols **2** and **4** were obtained in yields of 76 and 83%, respectively. These yields approximate those reported when anhydrous lithium iodide in pyridine was used for the demethylation of **1** and **3** [2], but there is an important advantage in ease of workup when tetrahydrofuran is the reaction solvent, rather than pyridine.

In contrast to the efficient demethylation of **1** and **3**, treatment of crown ether **5**, in which the methoxyl group is extra-annular, with either lithium aluminum hydride in tetrahydrofuran or lithium iodide in pyridine gave no



m	p	R
6	1	Me
7	1	H
8	2	Me
9	2	H
10	3	Me
11	3	H



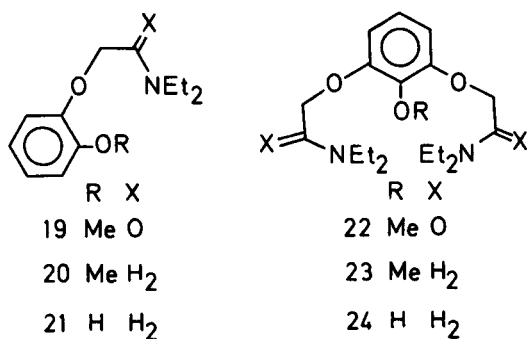
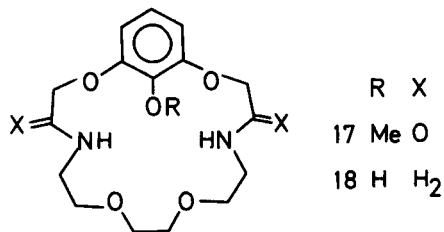
demethylation. Thus the importance of an intra-annular methoxyl group for facile demethylation is established. Reaction of **5** with lithium aluminum hydride in benzene at reflux resulted in rupture of the polyether ring.

Reactions of cryptands **6**, **8**, and **10**, which possess inward-facing anisole units, with lithium aluminum hydride in tetrahydrofuran at reflux gave good-to-excellent yields of phenolic cryptands **7** (85%), **9** (75%), and **11** (96%). For comparison the demethylation of **8** was

also conducted with lithium iodide in pyridine and found to produce a 70% yield of **9**.

#### Concurrent Demethylation and Reduction.

Immediate precursors to cryptands **6**, **8**, and **10** are the corresponding cryptand diamides **12**, **13**, and **15**, respectively. Cryptand diamides without inward-facing anisole units have ordinarily been reduced to cryptands with diborane [9]. Reduction of such compounds with lithium aluminum hydride is reported to proceed slowly and often result in destruction of the bicyclic structure [9]. When **12**, **13**, and **15** were refluxed with excess lithium aluminum hydride in tetrahydrofuran, the reaction products were cryptand phenols **7** (90%), **9** (68%), and **11** (91%) which resulted from both demethylation and diamide reduction. Similarly cryptand diamide **14** gave cryptand phenol **16** in 85% yield. Thus concurrent demethylation and diamide reduction in a one-pot reaction with lithium aluminum hydride in tetrahydrofuran is demonstrated to be a viable synthetic alternative to a two-reaction sequence in which a cryptand diamide, such as **13**, is first treated with diborane to reduce the amide groups and, after workup, reacted with lithium iodide in pyridine to effect demethylation [10].



Facile demethylation and diamide reduction were also accomplished in a monocyclic system. Thus aza crown diamide **17** was transformed into aza crown phenol **18** in 74% yield by lithium aluminum hydride in refluxing tetrahydrofuran.

To examine the relative propensities for demethylation and amide reduction for acyclic analogs, monoamide **19**

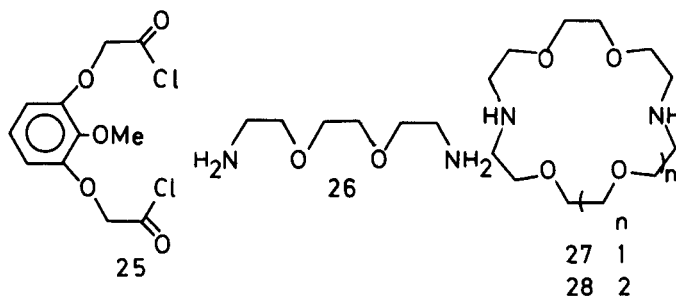
and diamide **22** were prepared. Reaction of monoamide **19** with excess lithium aluminum hydride in refluxing tetrahydrofuran for 20 hours gave 70% of amide reduction product **20**, but only traces of the amino phenol **21** for which both demethylation and amide reduction had occurred. Under similar conditions diamide **22** produced an 83% yield of **23** and 5% of **24**. Such sluggish demethylation of acyclic anisole derivatives by lithium aluminum hydride in tetrahydrofuran is in agreement with results reported by McKervery [5]. When equimolar quantities of the anisole diamine derivative **23** and the crown ether 18-crown-6 were refluxed with excess lithium aluminum hydride in tetrahydrofuran for 20 hours, no demethylation was observed and 80% of **23** was recovered. This result reveals that some type of lithium aluminum hydride complexation within an encompassing monocyclic or bicyclic polyether cavity is required to produce the smooth demethylation of inward-facing anisole units which has been observed in this work.

#### Synthesis.

Cyclic diamide **17** was synthesized by high dilution cyclization of diacid chloride **25** and diamine **26** in 37% yield. Cyclization of **25** with diamines **27** and **28** under similar conditions produced cryptand diamides **14** and **15** in 54 and 48% yields, respectively. Crown ether **5** was prepared by cesium fluoride-catalyzed cyclization [11] of 3-methoxycatechol with pentaethylene glycol ditosylate in acetonitrile. Acyclic monoamide **19** and diamide **22** were obtained by treatment of the corresponding acid chlorides with diethylamine.

#### Conclusion.

Due to high yields, safety of reaction conditions, and simplicity of workup, demethylation of inward-facing anisole units by lithium aluminum hydride in tetrahydrofuran offers an attractive alternative to known demethylation methods which have been employed in crown ether and cryptand chemistry.



#### EXPERIMENTAL

The ir spectra were obtained on neat samples with a Nicolet MX-S spectrometer. The nmr spectra were recorded with Varian EM360A or

EM360 spectrometers and chemical shifts are determined in parts per million ( $\delta$ ) downfield from tetramethylsilane. Elemental analysis was performed by Galbraith Laboratories, Inc. of Knoxville, Tennessee.

Unless specified otherwise reagent grade reactants and solvents were obtained from chemical suppliers and used as received. Tetrahydrofuran was purified by distillation from lithium aluminum hydride under nitrogen. Methoxycrown ethers **1** and **3** [2], anisole cryptands **6** and **8** [10], anisole cryptand diamides **12** and **13** [10], diacid chloride **25** [10], 1,8-diamino-3,6-dioxaoctane (**26**) [12], cyclic diamines **27** and **28** [9], pentaethylene glycol ditosylate [13], and [(2-methoxy)phenoxy]acetyl chloride [14] were prepared by literature methods.

### 3'-Methoxybenzo-18-crown-6 (**5**).

Under nitrogen, 3-methoxycatechol (0.84 g, 6.0 mmoles), cesium fluoride (4.56 g, 30 mmoles), and 75 ml of acetonitrile were combined and stirred for 1 hour. Pentaethylene glycol ditosylate (3.30 g, 6.0 mmoles) in 40 ml of acetonitrile was added and the reaction mixture was stirred and heated at 65° for 36 hours. The mixture was filtered and the filtered material was washed with dichloromethane. The washings and filtrate were combined and evaporated *in vacuo* to give a residue which was chromatographed on alumina with cyclohexane-ethyl acetate as eluent to provide 1.29 g (64%) of **5** as a hygroscopic, colorless oil; ir (neat): 1114 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  3.5-4.4 (m, 23H), 6.4-7.2 (m, 3H).

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{30}\text{O}_6 \cdot 0.75\text{H}_2\text{O}$ : C, 66.41; H, 7.63. Found: C, 66.23; H, 7.38.

### Cryptand Diamides **14** and **15**.

Cryptand diamides **14** and **15** were prepared by high dilution cyclization of acid dichloride **25** and cyclic diamines **27** and **28**, respectively, in toluene according to a published procedure for the synthesis of the smaller analogs **12** and **13** [9]. Compound **14** was prepared in 54% yield as a very viscous, colorless oil; ir (neat): 1651 (C=O), 1114 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  2.5-5.35 (m, 35H).

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{38}\text{N}_2\text{O}_{10} \cdot 0.2\text{CHCl}_3$  [15]: C, 54.99; H, 6.88. Found: C, 55.25; H, 6.72.

Compound **15** was obtained in 48% yield as a viscous, colorless oil; ir (neat) 1647 (C=O), 1114 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  2.6-6.3 (m, 39H), 6.5-7.0 (m, 3H).

*Anal.* Calcd. for  $\text{C}_{27}\text{H}_{42}\text{N}_2\text{O}_{11}$ : C, 56.83; H, 7.43. Found: C, 56.49; H, 7.52.

### Methoxycryptand **10**.

Cryptand diamide **15** was reduced with diborane in tetrahydrofuran according to the literature procedure reported for the reductions of cryptand diamides **12** and **13** [10] to give methoxycryptand **10** in 80% yield as a very viscous, colorless oil; ir (neat): 1113 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  2.3-3.2 (m, 12H), 3.2-4.3 (m, 31H), 6.3-6.9 (m, 3H).

*Anal.* Calcd. for  $\text{C}_{27}\text{H}_{46}\text{N}_2\text{O}_9 \cdot 0.1\text{CHCl}_3$  [15]: C, 58.69; H, 8.38. Found: C, 58.59; H, 8.56.

### Cyclic Diamide **17**.

Solution A [0.88 g (6.0 mmoles) of **26** and 1.64 g (16.2 mmoles) of triethylamine in 30 ml of toluene] and Solution B [1.76 g (6.0 mmoles) of **25** in 30 ml of toluene] were simultaneously added to 100 ml of vigorously-stirred toluene at 0-5° during a 4-hour period. After the addition was completed, the reaction mixture was stirred overnight at room temperature and filtered. The filtrate was evaporated *in vacuo* and the residue was chromatographed on alumina with ethyl acetate-methanol (20:1) as eluent to give 0.82 g (37%) of **17** as a white solid with mp 109-111°; ir (neat): 3420, 3300 (N-H), 1689, 1662 (C=O), 1172, 1128 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  3.3-3.75 (m, 12H), 4.00 (s, 3H), 4.65 (s, 4H), 6.55-7.3 (m, 3H), 7.85 (br s, 2H).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_7$ : C, 55.43; H, 6.57. Found: C, 55.25; H, 6.66.

### Diethyl [(2-Methoxy)phenoxy]acetamide (**19**).

Into a solution of 4.00 g (20 mmoles) of [(2-methoxy)phenoxy]acetyl chloride in 30 ml of tetrahydrofuran was added 1.46 g (20 mmoles) of diethylamine. The reaction mixture was refluxed for 20 hours, filtered, and evaporated *in vacuo*. The residue was chromatographed on alumina with petroleum ether-ethyl acetate (2:1) as eluent to provide 2.80 g (59%) of **19** as an extremely hygroscopic, pale yellow oil; ir (neat): 1664, 1643 (C=O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  0.94-1.37 (overlapping t, 6H), 3.42 (q, 4H), 3.88 (s, 3H), 4.70 (s, 2H), 6.97 (s, 4H).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{19}\text{NO}_3 \cdot 0.3\text{H}_2\text{O}$ : C, 64.28; H, 8.14. Found: C, 64.07; H, 8.06.

### Acyclic Diamide **22**.

To a solution of diethylamine (1.82 g, 25 mmoles) in 30 ml of benzene was added dropwise a solution of **25** (1.32 g, 4.5 mmoles) in 20 ml of benzene. The mixture was stirred overnight at room temperature, filtered, and evaporated *in vacuo*. The residue was chromatographed on alumina with ethyl acetate-petroleum ether (1:1) as eluent to give 1.00 g (61%) of **22** as a colorless oil; ir (neat): 1655, 1640 (C=O), 1110 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  0.8-1.5 (m, 12H), 3.43 (q, 8H), 3.93 (s, 3H), 4.74 (s, 4H), 6.5-7.1 (m, 3H).

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}_5$ : C, 62.27; H, 8.25. Found: C, 62.05; H, 7.97.

### General Procedure for Demethylation or Demethylation-Diamide Reduction with Lithium Aluminum Hydride in Tetrahydrofuran.

A solution of the substrate (1.8-2.0 mmoles) in 20 ml of tetrahydrofuran was added dropwise to a suspension of lithium aluminum hydride (13.5-16.0 mmoles) in 20 ml of tetrahydrofuran and the mixture was refluxed for 20 hours. After cooling, 2.5 ml of 5% aqueous sodium hydroxide was added and the mixture was stirred overnight. The inorganic precipitate was filtered and washed several times with hot tetrahydrofuran. The combined filtrate and washings were evaporated *in vacuo* and the residue was chromatographed on alumina.

Crown phenols **2** and **4** [2] were obtained by demethylation of methoxycrowns **1** and **3** in yields of 76 and 83%, respectively.

Cryptand phenol **7** was produced in 85% yield from **6** and in 90% yield from **12** as a mushy, yellow solid; ir (neat): 3367 (OH), 1118 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  2.2-3.1 (m, 12H), 3.2-4.6 (m, 16H), 6.70 (s, 3H), 8.1 (br s, 1H).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_6$ : C, 60.59; H, 8.14. Found: C, 60.32; H, 8.01.

Cryptand phenol **9** [10] was isolated in 75% yield from **8** and in 79% yield from **13** as white crystals with mp 73-75° [16]; ir (neat): 3396 (OH), 1099 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  2.78 (t, 12H), 3.4-3.9 (m, 16H), 4.08 (t, 4H), 6.65 (s, 3H), 9.50 (br s, 1H).

Cryptand phenol **11** was obtained in 96% yield from **10** and in 90% yield from **15** as a colorless, extremely hygroscopic oil; ir (neat): 3502, 3358 (OH), 1113 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  2.65-3.2 (m, 12H), 3.4-4.4 (m, 28H), 6.68 (s, 3H), 9.40 (br s, 1H).

*Anal.* Calcd. for  $\text{C}_{26}\text{H}_{44}\text{N}_2\text{O}_9 \cdot 0.75\text{H}_2\text{O}$ : C, 57.60; H, 8.46. Found: C, 57.60; H, 8.65.

Cryptand phenol **16** was formed in 85% yield from **14** as an extremely hygroscopic, colorless oil; ir (neat): 3380 (OH), 1090 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  2.2-3.1 (m, 12H), 3.1-4.4 (m, 24H), 6.67 (s, 2H), 7.42 (s, 1H), 9.57 (br s, 1H).

*Anal.* Calcd. for  $\text{C}_{24}\text{H}_{40}\text{N}_2\text{O}_8 \cdot \text{H}_2\text{O}$ : C, 57.35; H, 8.42. Found: C, 57.70; H, 8.32.

Diazacrown phenol **18** was isolated in 79% yield from **17** as a colorless oil; ir (neat): 3300 (OH + NH), 1101 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  2.6-3.0 (m, 8H), 3.35-3.85 (m, 12H), 4.55 (s, 7H), 6.6-7.25 (m, 3H).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{30}\text{N}_2\text{O}_5$ : C, 61.00; H, 8.53. Found: C, 60.74; H, 8.49.

### Reaction of Acyclic Monoamide **19** with Lithium Aluminum Hydride.

Monoamide **19** was treated with lithium aluminum hydride in tetrahydrofuran according to the general procedure to produce, after chromatography on alumina with diethyl ether-ethanol (50:1) as eluent, a 76%

yield of the anisole amine **20** [17], but only a trace of the phenolic amine **21**.

Reaction of Acyclic Diamide **22** with Lithium Aluminum Hydride.

Reaction of **22** with lithium aluminum hydride in tetrahydrofuran was carried out as described in the general procedure. The crude reaction product was chromatographed on silica gel with chloroform-ethanol (5:1) as eluent to afford an 83% yield of **23** and a 5% yield of **24**. Compound **23** was obtained as a colorless oil; ir (neat): 1105 (C-O)  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  1.10 (t, 12H), 2.4-3.2 (m, 12H), 3.87 (s, 3H), 3.9-4.3 (m, 4H), 6.4-7.25 (m, 3H).

*Anal.* Calcd.  $\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}_3$ : C, 67.42; H, 10.12. Found: C, 67.19; H, 9.80.

Compound **24** was isolated as a colorless oil; ir (neat): 3600-2100 (br OH), 1080, 1060 (C-O); nmr (deuteriochloroform):  $\delta$  1.09 (t, 12H), 2.45-3.0 (m, 12H), 4.07 (t, 4H), 6.67 (s, 3H).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_3$ : C, 66.63; H, 9.94. Found: C, 66.51; H, 9.80.

Acknowledgement.

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