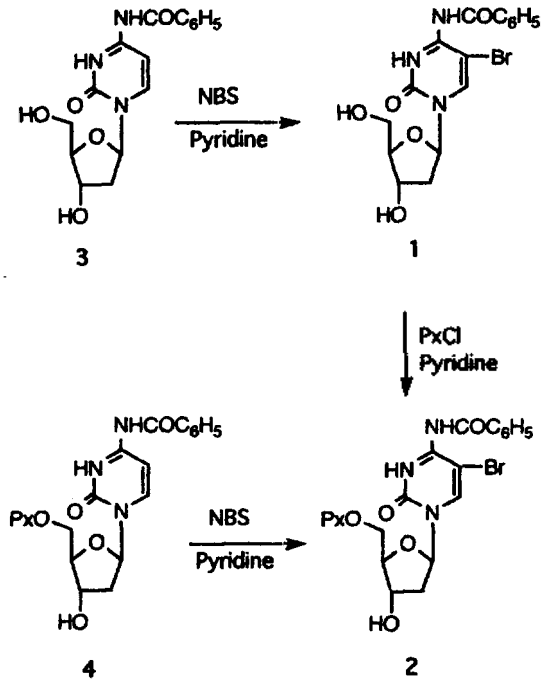

Figure 1. Synthesis of 4-N-Benzoyl-5-Bromo-5'-O-Pixyl-2'-deoxycytidine.

Synthesis of 4-N-benzoyl-5-bromo-2'-deoxycytidine. N-Bromosuccinimide (1.068 g, 6.000 mmol) was added to a solution of 4-N-benzoyl-2'-deoxycytidine (1.657 g, 5.000 mmol) in dry pyridine (40 m*l*) at room temperature. After overnight (16 h),the products were poured into saturated $NaHCO_3$ solution (70 m*l*) and extracted with $CHCl_3$ (2×70 m*l*). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude yellowish product. The product was crystallized from methanol. Yield 1.07 g (52%). R_f 0.24 (10% methanol in chloroform) mp. 154-156℃ (dec).

^{1}H-NMR(DMSO-d_6) δ 2.15-2.32(m, 2H, 2'-H), 3.56-3.72(m, 2H, 5'-H), 3.86-3.90(m, 1H, 4'-H), 4.25-4.32(m, 1H, 3'-H), 5.18-5.26(t, 1H, 5'-OH) 5.26-5.33(d, 1H, 3'-OH), 6.07-6.13(t, 1H, 1'-H), 7.48-7.65(m, 3H, aromatic), 8.10-8.17(m, 2H, aromatic), 8.65(s, 1H, 6-H), 12.80(bs, 1H, NH). Anal. Calcd. for $C_{16}H_{16}N_3O_5Br$: C, 46.85; H, 3.93; N, 10.24. Found: C, 46.71; H, 4.06; N, 10.30.

Synthesis of 4-N-Benzoyl-5-bromo-5'-O-(9-phenyl-9 H-xanthen-9-yl)-2'-deoxycytidine. To the dry pyridine solution (35 m*l*) of 4-N-benzoyl-5-bromo-2'-deoxycytidine (1.657 g, 5.000 mmol) was added pixyl chloride (1.757 g, 6.000 mmol) in dry pyridine (35 m*l*) dropwise over a period of 1 h. The reaction mixture was added to H_2O (4 m*l*). The reaction mixture was stirred for 10 min and $CHCl_3$ was added to it. After cooling with a few chips of ice, the reaction mixture was washed with $NaHCO_3$ solution. Aqueous layer was reextracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The product was purified by short column chromatography over silica gel eluting with 10% ethyl acetate in benzene (60.8% yield).

Alternatively, N-Bromosuccinimide (1.068 g, 6.000 mmol) was added to a solution of 4-N-benzoyl-5'-pixyl-2'-pdeoxycytidine (2.938 g, 5.000 mmol) in dry pyridine (40 m*l*) at room temperature. After overnight (16 h), the products were poured into saturated $NaHCO_3$ solution (70 m*l*) and extracted with $CHCl_3$ (2×70 m*l*). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude yellowish product. The product was purified by short column chromatography over silica gel eluting with 3% ethanol in $CHCl_3$ (68.6% yield): R_f 0.68 (10% methanol in chloroform) ^{1}H-NMR (DMSO-d_6) δ 2.26-2.42(m, 2H, 2'-H), 3.02-3.20 (m, 2H, 5'-H), 3.92-4.04(m, 1H, 4'-H), 4.20-4.30(m, 1H, 3'-H), 5.24(m, 1H, 3'-H), 5.24(bs, 1H, 3'-OH), 6.08-6.20(t, 1H, 1'-H), 7.10-8.20(m, 18H, aromatic), 8.30(s, 1H, 6H), 12.80(bs, 1H, NH). Anal. Calcd. for $C_{34}H_{28}N_3O_6Br$: C, 62.39; H, 4.31; N, 6.43. Found: C, 62.43; H, 4.39; N, 6.40.

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Reduction of Disulfides to Thiols with Lithium Tris(dialkylamino)aluminum Hydrides

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Lithium tris(dialkylamino)aluminum hydrides[1], such as lithium tris(diethylamino)aluminum hydride (LTDEA), lithium tris(di-*n*-butylamino)aluminum hydride (LTDBA) and lithium tris(di-*n*-hexylamino)aluminum hydride (LTDHA), appear to be attractive selective reducing agents, especially in the conversion of carboxylic acid derivatives into the corresponding aldehydes[2]. In addition to that these reagents readily reduce both aliphatic and aromatic disulfides to the corresponding thiols without any evolution of hydrogen. Consequently, it is now possible to reduce disulfides under the practical con-

ditions with only the calculated amount of reagents. The sulfur-sulfur bond in disulfides plays an important role in biological activity. Hence, the transformation of the sulfur-sulfur bond in disulfides to thiols has been subjected to considerable investigation[3]. This transformation can be achieved most easily by reduction[4]. The reagents utilized include lithium aluminum hydride[5], sodium borohydride[6], sodium borohydride/aluminum chloride[7], Zinc/acetic acid[8], triphenylphosphine[9], potassium triisopropoxyborohydride[10], as well as other miscellaneous reagents[11]. Among these, potassium triisopropoxyborohydride (KIPBH) considered to be the most effective reagent because of its high selectivity in the reduction of organic functionalities[10]. However, KIPBH also possesses a drawback in the disulfide reduction; there is a subsequent evolution of hydrogen during the reduction. Therefore, 2 mole of reagent per mole of compound should be utilized for complete reduction. Accordingly, when a detailed survey of the reducing properties of the lithium tris(dialkylamino) aluminum hydrides revealed that the reagent readily reduce disulfides to thiols without hydrogen evolution, we undertook a detailed study of the reaction.

Results and Discussion

The reaction proceeds with the uptake of one hydride per mole of disulfide **1**, forming equimolar amounts of the product **4** and its lithium salt **3**. Treatment of the product with acid liberates the thiol **4** in essentially quantitative yield (Eq. 1 and 2).

$$\underset{\mathbf{1}}{\text{R-S-S-R}} + \underset{\mathbf{2}}{\text{LiAlH(NR}_2)_3} \longrightarrow \underset{\mathbf{3}}{\text{R-SLi}} + \underset{\mathbf{4}}{\text{R-SH}} + \text{Al(NR}_2)_3 \quad (1)$$

$$\underset{\mathbf{3}}{\text{R-SLi}} + \text{HX} \longrightarrow \underset{\mathbf{4}}{\text{R-SH}} + \text{LiX} \quad (2)$$

Generally, in the reaction of disulfides with metal hydrides[5,7] there is a subsequent evolution of hydrogen from the reaction of thiol **4** produced with reagent. For example, even KIPBH[10], a very mild reducing agent, liberates hydrogen during the reduction (Eq. 3).

$$\text{R-SH} + \text{KBH(OC}_3\text{H}_7\text{-}i)_3 \longrightarrow \text{R-SK} + \text{H}_2\uparrow + \text{B(OC}_3\text{H}_7\text{-}i)_3 \quad (3)$$

However, the reaction with LTDEA, LTDBA and LTDHA at 0℃ or 25℃ do not liberate any hydrogen. Furthermore, there is no hydrogen evolution in the reaction with LTDBA and LTDHA even under reflux. Therefore, no excess reagent is required for complete reduction.

The rates of reaction is in order to LTDEA>LTDBA>LTDHA. The reaction with LTDEA is readily completed at 0℃ and 25℃, whereas LTDBA requires a longer reaction time or drastic reaction condition. However, the reaction with LTDHA proceeds slowly to reach completion in 6 h at 25℃ or in 1 h under reflux.

Experimental

All glassware used was dried thoroughly in a drying oven, assembled hot, and cooled under a stream of dry nitrogen prior to use. All chemicals were commercial products of the highest available purity. THF was distilled from benzophenone-sodium ketyl. Lithium aluminum hydride was used directly as received from Aldrich. GC analyses were carried out using a Hewlett-Packard 3390A integrator/plotter.

Table 1. Reduction of Disulfides with LTDEA, LTDBA and LTDHA in Tetrahydrofuran[a]

Compound	Temp. (℃)	Time (h)	Yield (%)[b]		
			LTDEA	LTDBA	LTDHA
Di-*n*-butyl disulfide	0	6	99	85 (98)[c]	10
	25	3	98	99	76 (94)[d]
	Reflux	1	–	98	93
Diphenyl disulfide	0	6	98	86 (96)[c]	25
	25	3	96	97	74 (96)[d]
	Reflux	1	–	98	92
Dibenzyl disulfide	0	6	97	(97)[c]	–
	25	3	94	98	(93)[d]
	Reflux	1	–	99	96
Bis(*p*-chlorophenyl)disulfide	0	6	89[c]	(87)[c,e]	–
	25	3	91[c]	91[c]	(86)[d,e]
	Reflux	1	–	90[c]	89[c]

[a]10% excess reagents utilized, [b]GC yields, [c]In 12 h, [d]In 6 h, [e]Isolated yields.

Reduction of Di-*n*-butyl Disulfide with LTDEA. To a 50 ml, oven-dried, round-bottom flask fitted with a sidearm and capped with a rubber septum was added di-*n*-butyl disulfide (1.78 g, 10 mmol) under nitrogen. To this was added freshly distilled THF (5 ml) and dodecane as an internal standard. The flask was then immersed in an ice-water bath. To the reaction mixture was slowly added 7.4 ml of 1.5 M solution of LTDEA in THF (11 mmol) and the mixture was stirred for 6 h at 0℃. The reaction mixture was hydrolyzed with 4 N HCl. The product was then extracted with diethyl ether. The organic layer was dried with anhydrous magnesium sulfate. The GC analysis showed a 99% yield of 1-butanethiol.

Reduction of Bis(*p*-chlorophenyl) Disulfide with LTDBA. Into a usual set-up, bis(*p*-chlorophenyl) disulfide (5.75 g, 20 mmol) was added under nitrogen. To this was then added THF (10 ml) and the mixture was kept at room temperature by using a water bath. To the mixture was added 14.8 ml of 1.5 M solution of LTDBA in THF (22 mmol) and the mixture was stirred for 3 h. The mixture was hydrolyzed with 4 N HCl solution, saturated with NaCl, and then filtered. The organic layer was washed with 2 N HCl solution thrice and dried with $MgSO_4$. The ether was then evaporated to give the desired thiol compound, *p*-chlorophenyl thiol, in quantitative yield. The crude product is recrystallized from hot water to give pure product; yield: 5.25 g (91%); mp. 53-54℃.

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NMR Titration, Potentiometry and Extraction Studies of Some Acyclic Polyethers with Aromatic End-Groups

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Acyclic ionophore antibiotics including monensin, nigericine and grisorixin wrap themselves around the cation, in a manner very similar to the cyclic species.[1] The acyclic oligoethers, called podands, can be obtained simply and cheaply; there is no need for high-dilution or template effects in preparation.[2,3] Furthermore, some podands with aromatic end-groups wrap themselves around the cations such as, Na^+ and Rb^+ ions in a helical manner to make pseudo-cycle both in solid[4] and solution[5] states. Vögtle's group has synthesized numerous such open-chain hosts containing nitrogen donors in aromatic end-groups.[6] Inspite of these benifits, less attention was paid to their thermodynamic, structural informations and applications in solution.[7]

Results and Discussion

In this study, we have investigated the cationic interactions of some serial podands (I-VIII) having sulfurs or asymmetric end-groups shown in Figure 1 by means of pmr titrations[8,9] and potentiometry. The stoichiometries and other informations have obtained by plotting the chemical shift changes as a function of host/guest mole ratio shown as in Figure 2. According to Figure 2, all of the cation induced shift varies linearly with the mole ratio until the ratio of 1 : 1 reached and no more shifts were observed above 1. From these breaks, it could be deduced that all of podands in Figure 1 form 1 : 1 complexes with cations.

Since the cation induced shifts of host protons depend mainly on the strength of the interaction between the nearest neighboring donor atoms and guest ions, it is to be expected that the magnitude of chemical shift variation is a sensitive probe of interactions in the same host for a given guest ion.[8,9] For example, by the comparison of slopes in Figure

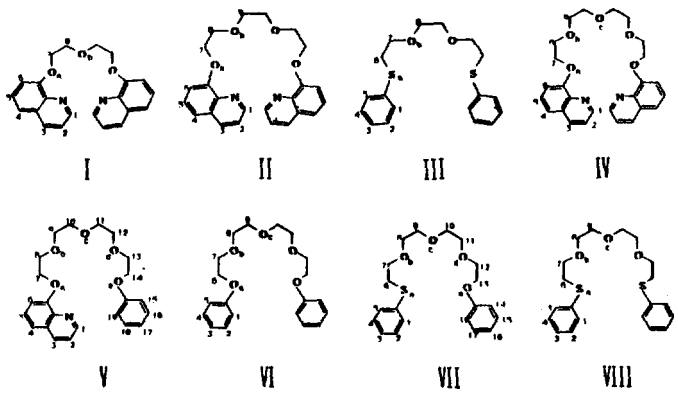

Figure 1. The structures of podands used in this study.