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The Synthesis of Novel Oxygen-Containing Ligands Derived from Amine Precursors

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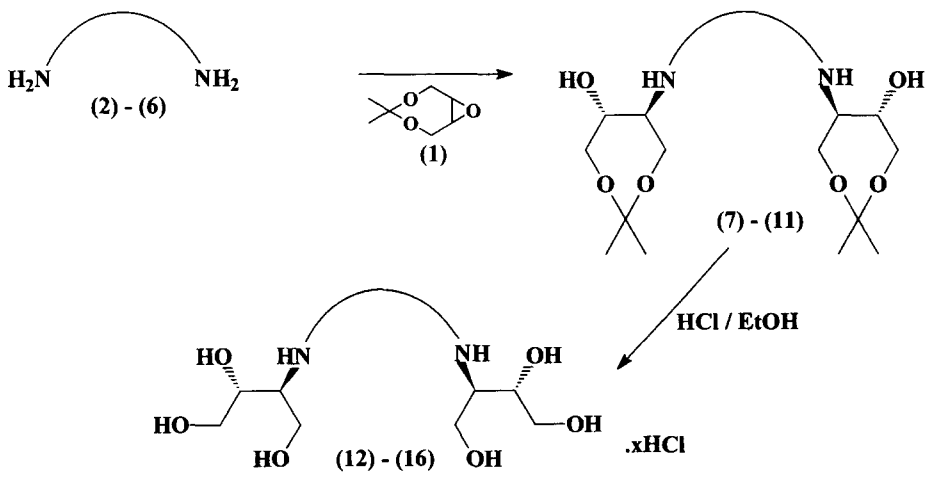
Abstract: The synthesis of novel oxygen-bearing ligands has been achieved by the mono- and di-alkylation of a range of polyamines with 4,4-dimethyl-3,5,8-trioxabicyclo[5.1.0]octane (**1**). Subsequent deprotection of the acetal resulted in the formation of hydroxyl-bearing ligands.

The design and synthesis of ligands for the selective complexation of metal ions is currently of great interest.[2] The use of the neutral oxygen donor has been intensively investigated in the search for selective ligands.[3] Our group has shown that simple 2-hydroxyethyl substituents favour selectivity for large metal ions, whereas the 2-hydroxycyclohexyl substituent promotes selectivity for smaller ions.[4] The use of cyclohexene oxide as an alkylating agent for introducing the latter substituent has proved very successful, as it reacts with high diastereoselectivity with a variety of polyamines to afford exclusively the *trans* products.[5]

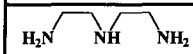
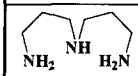
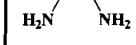
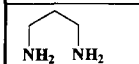
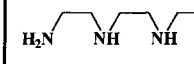
A recent publication[6] has prompted us to report on the synthesis of a number of open chain polyamine ligands with multiple hydroxyl functionalities by using the sterically demanding epoxide 4,4-dimethyl-3,5,8-trioxabicyclo[5.1.0]octane (**1**) as the source of the pendent hydroxy groups. This epoxide has been used before in the monoalkylation of cyclic ligands such as 1,4,7,10-tetraazacyclododecane (cyclen) for producing ligands having use in NMR imaging, radiographic diagnostics and therapeutic applications.[7]



Scheme 1

Initially, we reacted two mole equivalents of the epoxide (**1**) with the amines diethylenetriamine (**2**), dipropylenediamine (**3**), ethylenediamine (**4**), propylenediamine (**5**) and triethylenetetramine (**6**) in ethanol, to yield the dialkylated products (**7**), (**8**), (**9**), (**10**) and (**11**) respectively (**Scheme 1** and **Table 1**).[7] The acetals thus formed were then converted to the corresponding hydrochloride salts of the polyhydroxylated ligands (**12**), (**13**), (**14**), (**15**) and (**16**) in good yield by treatment with ethanolic hydrochloric acid (**Scheme 1** and **Table 1**).[8,9] In each of these reactions, reaction with the epoxide occurred exclusively at the primary amine sites. *Trans* opening of the epoxide is assumed to occur,[10] and each product was formed as a mixture of racemic diastereoisomers.

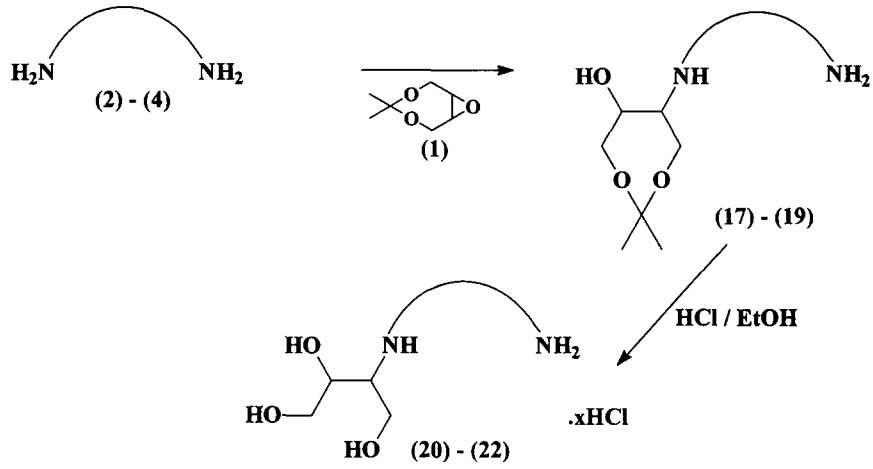
Table 1 : Dialkylation of Polyamines with 4,4-Dimethyl-3,5,8-trioxabicyclo[5.1.0]octane (1)

Polyamine	Product (Yield)	Product (Yield)
 (2)	(7) (58%)	(12) (64%)
 (3)	(8) (51%)	(13) (84%)
 (4)	(9) (56%)	(14) (90%)
 (5)	(10) (100%)	(15) (51%)
 (6)	(11) (58%)	(16) (96%)

There are reports in the literature of successful monoalkyation of both acyclic and macrocyclic amines with epoxides.[11] However, a serious drawback in these previous syntheses is that they have often required the use of laborious protecting steps to mask other reactive sites in the amine. A further problem is that some of these protecting groups involve the use of complexes of hazardous metals, *e.g.* chromium or molybdenum.[11] These drawbacks are especially undesirable in the case of industrial pharmaceutical synthesis. However, as sterically demanding epoxides have been used for specific monoalkylation of cyclic amines,[5] it seemed reasonable to expect that open chain amines would also undergo monoalkylation with the oxirane (**1**).

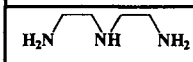
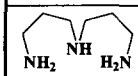
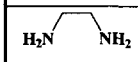
When one mole of the epoxide (**1**) was reacted with the open-chain amines diethylenetriamine (**2**), dipropylenetriamine (**3**) and ethylenediamine (**4**), the monoalkylated products (**17**), (**18**), and (**19**) were produced respectively (**Scheme 2** and **Table 2**).[12] The epoxide (**1**) had to be added carefully dropwise over one hour to an ethanolic solution of the amine as rapid combination of molar equivalents of open chain amine and epoxide (**1**) resulted in a mixture of mono- and di-alkylated products as well as unreacted amine. Examination of the ^{13}C NMR spectra of the products (**17**), (**18**) and (**19**) showed doubling of a number of the peaks. This was clearly not evident when any of the same ligands were dialkylated. At present this apparent

anomaly is being investigated. The acetals (**17**), (**18**) and (**19**) were then converted into the corresponding hydrochloride salts of the trihydroxylated ligands by treatment with ethanolic hydrochloric acid, as described previously.



Scheme 2

Table 2. : Monoalkylation of Polyamines with 4,4-Dimethyl-3,5,8-trioxabicyclo[5.1.0]octane (1)

Polyamine	Product (Yield)	Product (Yield)
 (2)	(**17**) (67%)	(**20**) (87%)
 (3)	(**18**) (92%)	(**21**) (80%)
 (4)	(**19**) (98%)	(**22**) (86%)

Complexation studies using these ligands are now under way and will be reported in full later. Some of the metal-containing complexes are crystalline and hence X-ray crystallography studies will be performed in order to determine the stereochemistry of the mono and dialkylated ligands.

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8. *Dialkylation of polyamines (typical procedure)*: The amine (19.4 mmol) was dissolved in anhydrous ethanol (50 ml), and epoxide (**1**) (38.8 mmol, 2 mol equiv.) was added to the solution in one portion. The mixture was heated under reflux for 48 h. The solvent was removed *in vacuo* to afford products as oils. Characteristic NMR and mass spectral data of product (**7**): δ_H ($CDCl_3$) 3.68-3.33 (10H, m); 2.88-2.38 (10H, m); 1.28 (6H, s); 1.26 (6H, s); δ_C ($CDCl_3$) 101.04; 72.36; 62.59; 59.93; 48.74; 48.68; 46.38; 24.54; 24.49; Found M^+, 391.2663. $C_{18}H_{37}N_3O_6$ requires 391.2682.
9. *Deprotection of acetals (typical procedure)* : The acetal (0.29 mmol) was dissolved in a solution of HCl and absolute ethanol (50 ml, 3 % v/v). After the solution was vigorously shaken for 3 minutes a finely divided precipitate appeared. The mixture was cooled for 18 h and a solid white deposit was formed on the bottom of the round bottomed flask. The solvent was decanted and the solid was dried *in vacuo*. Characteristic NMR and mass spectral data of product (**14**): δ_H (D_2O) 4.02-3.45 (m); δ_c (D_2O) 70.44; 65.30; 64.00; 59.26; 44.22; Found M^+, 268.1618. $C_{10}H_{24}N_2O_6$ requires 268.1634.
10. Epoxides are normally subject to *anti* ring opening. Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B.M.; Ed.; Pergamon Press: Oxford, 1991, pp. 733-734.
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12. *Monoalkylation of polyamines (typical procedure)* : Epoxide (**1**) (9.70 mmol) was dissolved in anhydrous ethanol (10 ml) and added dropwise over 1 h to a heated solution (70°C) of the amine (9.69 mmol) in anhydrous ethanol (25 ml). The reaction mixture was boiled under reflux for 18 h, after which the solvent was removed *in vacuo* to yield a clear oil. Characteristic NMR and mass spectral data of product (**17**): δ_H ($CDCl_3$) 3.69-3.38 (6H, m), 2.88-2.43 (8H, m), 1.33 (3H, s), 1.31 (3H, s); δ_C ($CDCl_3$) 100.83; 72.11; 62.64; 62.60; 59.84; 51.87 and 51.57 (*Two peaks of equal intensity); 48.74; 46.48; 41.32 and 41.16 (*Two peaks of equal intensity); 24.39 (two overlapping signals); Found M^+,– $CH_2{=}NH_2$, 217.1561. $C_9H_{21}N_2O_3$ requires 217.1552.

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