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Cyclitol based metal complexing agents. Preference for the extraction of lithium by *myo*-inositol based crown-4-ethers depends on the relative orientation of crown ether oxygen atoms

Shailesh S. Dixit, Mysore S. Shashidhar* and Subramanian Devaraj

Division of Organic Synthesis, National Chemical Laboratory, Pashan Road, Pune 411 008, Maharashtra, India

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Abstract—*myo*-Inositol derived crown-4-ethers in which two of the oxygen atoms in the crown ether moiety have different relative orientations were prepared. Metal picrate binding studies revealed that the crown ether having 1,3-diaxial orientation shows the highest selectivity for binding to lithium although the crown ether having 1,2-diequatorial orientation exhibited the highest binding constant for lithium picrate. These results suggest that relative binding affinity of metal ions to crown ethers can be tuned by varying the relative orientation of crown ether oxygen atoms. The relevance of these results to the previously observed regioselectivity during the O-substitution of *myo*-inositol orthoesters is discussed.

1. Introduction

The realization of the existence of phosphoinositol based cellular signal transduction mechanisms in eukaryotic cells[1] and the role played by *myo*-inositol in the anchoring of certain proteins to the cell membranes[2] has driven chemists to devise novel methods for the efficient synthesis of cyclitol derivatives.[3–5] These synthetic investigations revealed several unusual reactions of *myo*-inositol derivatives.[5] In particular, the regioselectivities encountered during O-alkylation,[6,7] O-acylation,[8] O-sulfonylation,[9] and trans-esterification[10] reactions of *myo*-inositol 1,3,5-orthoformate and its derivatives, was attributed to their chelation with metal ions. To investigate the extent of the binding of metal ions with inositol derivatives, we carried out lithium and sodium picrate extraction studies of several *myo*-inositol derivatives.[11] Most of the *myo*-inositol derivatives bound lithium picrate better than other alkali metal picrates. Studies on the binding of lithium to inositol derivatives are of potential interest due to the ability of lithium to inhibit the activity of *myo*-inositol-1-phosphate phosphatase.[12–14] This has been implicated for the therapeutic effect of lithium, which is used as a drug for manic depression.[15] Lithium selective ligands[16–18] are also of interest in supramolecular chemistry. The reports[19,20] on the chemistry and biology cited above prompted us to prepare inositol-based crown-4-ethers to investigate their ability to bind lithium selectively. Although several carbohydrate derived crown ethers have been reported in the literature as tools for asymmetric Michael addition,[21–23] asymmetric hydrogenation,[24] O-alkylation of carbohydrates and nucleosides,[25] other enantioselective reactions[26–28] and molecular recognition,[29,30] there are only a few reports on inositol derived crown ethers.[31,32] Earlier work in our laboratory had shown that some *myo*-inositol based podands[33] and crown ethers[32] bind silver ions preferentially. The present work deals with the preparation and metal ion binding study of *myo*-inositol derived crown-4-ethers.

2. Results and discussion

The *myo*-inositol-derived crown ethers (Scheme 1) were prepared by the reaction of the diols **1**, **3** and **5** with triethyleneglycol ditosylate, in the presence of sodium hydride. The crown ethers **7**, **8** and **9** could not be easily separated from the ditosylate by column chromatography. Hence the crude product obtained was refluxed with sodium methoxide in methanol to convert the unreacted triethyleneglycol ditosylate to the corresponding dimethyl ether, from which the required crown ethers were separable. In the crown-4-ethers **7**, **8** and **9**, two of the oxygen atoms in the ionophoric ring have varying relative orientations (1,2-diequatorial in **7**, 1,2-axial-equatorial in **8**, 1,3-diaxial in **9**), as they are part of the *myo*-inositol ring. The association

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Keywords: Crown ether; Cyclitol; Inositol; Lithium; Ligand; Metal complex.

* Corresponding author. Tel.: +91 20 2590 2055; fax: +91 20 2590 2132; e-mail: ms.shashidhar@ncl.res.in

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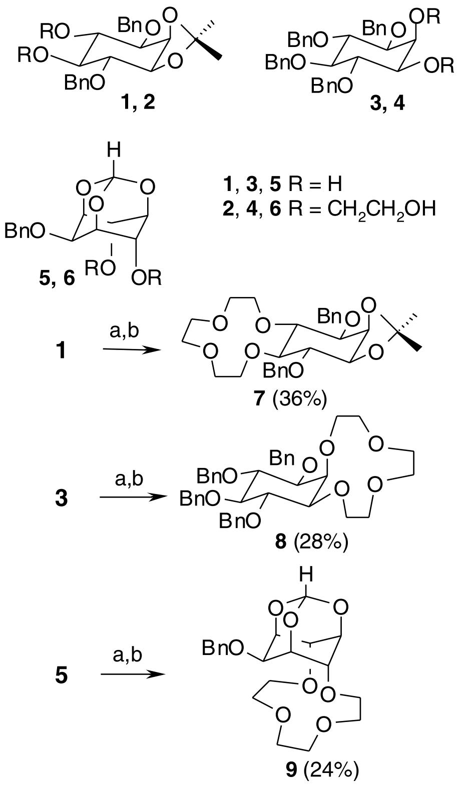


Scheme 1. (a) $TsO(CH_2CH_2O)_3Ts$, NaH, THF, reflux, 24 h; (b) NaOMe, MeOH, reflux, 8 h.

constants (Table 1) of these inositol based crown ethers with alkali metal picrates as well as ammonium and silver picrates, were evaluated by Cram's picrate method.[34] For the calculation of the association constants shown in Table 1 we have assumed the formation of 1:1 complexes with all metal ions.

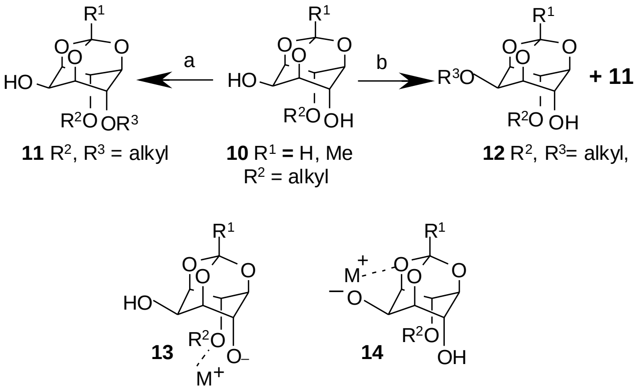
Table 1. Association constants ($Ka \times 10^{-4}$ dm^3 mol^{-1}) in $CDCl_3$, for the binding of crown-4-ethers **7–9** (27 °C) with metal picrates

Crown	Li^+	Na^+	K^+	Cs^+	NH_4^+	Ag^+
7	100	25.4	6.27	20.2	2.96	14.4
8	19.9	3.95	0.97	2.12	3.97	15.9
9	27.2	2.96	0.69	0.62	0.21	0.9
			$Ka_{(Li^+)}/Ka_{(M^+)}$			
7		4	16	5	34	7
8		5	20	9	5	1
9		9	40	44	130	30

From Table 1, it is seen that all three crown-4-ethers exhibit the highest binding constant for lithium picrate (among the picrates tested) as expected. Lithium picrate binds better to inositol based crown-4-ethers when compared to 12-crown-4-ether ($Ka = 1.6 \times 10^4$).[35] Among the three crown ethers, the crown ether **7** derived from the diequatorial diol **1** binds lithium picrate best. Comparison of the association constants for the extraction of lithium picrate for the crown-4-ethers with inositol derived crown-5 and crown-6-ethers[32] shows that as expected, crown-4-ethers bind lithium picrate more effectively than the larger crown ethers. We had earlier reported[33] the metal picrate binding characteristics of a few *myo*-inositol-derived podands, which are open chain analogs of crown-4-ethers. An increase in the value of the association constants on going from podands to crown ethers (ratio of Ka's = 4 to 43; Ka for podands:[33] 2.3×10^4, 5.3×10^4 and 2.3×10^4, respectively, for the diols **2**, **4** and **6**) indicates the contribution of the ionophoric ring towards the binding of metal picrates.

The magnitude of the preference of individual crown ethers for binding to a metal ion (MI) among a group of '*n*' metal ions can be estimated by the ratio of association constants (K_{MI}/K_{Mn}), for binding to the same crown ether. The ratio of the binding constant for lithium picrate to that of other metal picrates shows that the crown ether **9**, having 1,3-diaxial orientation exhibits the highest selectivity for lithium as compared to other metal picrates. It is pertinent to note that although all the crown ethers have four oxygen atoms in the ionophoric ring, in the diequatorial (**7**) and axial-equatorial (**8**) crown ethers all the oxygen atoms are separated by two carbon atoms, whereas, in the diaxial crown ether (**9**), oxygen atoms attached to the inositol ring (at C-4 and C-6) are separated by three carbon atoms, but are closer to each other due to their diaxial disposition. Interestingly, these differences lead to better selectivity for binding to lithium picrate. A comparison of the ratio of association constants between crown-4-ethers having different relative orientations of the two of the oxygen atoms (attached to the inositol ring) reveals that this difference matters most for the binding of cesium ions ($K_{a(\mathbf{7})}/K_{a(\mathbf{9})} = 33$).

The observed trend in the extraction of the metal picrates by inositol-derived crown-4-ethers, especially for lithium, is interesting with regard to the experimentally observed regioselectivity for the alkylation of *myo*-inositol orthoesters assisted by sodium hydride and butyllithium (Scheme 2). Reaction of triols (**10** $R^2 = H$) with alkyl halides[6] in the presence of 1 equiv of sodium hydride resulted in exclusive reaction at the C4(6)–O-position to yield the monoether **10** (R^2 = alkyl); further reaction of these diols with alkyl halides in the presence of sodium hydride resulted in the formation of a mixture of diethers **11** and **12** (Scheme 2).



Scheme 2. (a) LiH or BuLi, R^3X; (b) NaH, R^3X.

The use of butyllithium or lithium hydride[11] instead of sodium hydride for the same reaction resulted in better regioselectivity, with the exclusive formation of the 4,6-di-*O*-substituted derivatives **11**. Reaction of the monoether (such as **10**, R^2 = alkyl) with alkyl halides in the absence of metal ions provided the unsymmetrical diether **12** as the major product.[36] The fact that the reaction assisted by butyllithium gave the diaxial diether **11** as the major product was attributed to the better chelation of lithium ions (as compared to sodium ions) by the 4,6-diaxial oxygen atoms resulting in relatively higher stability of the chelate **13** (as compared to **14**). The observed metal ion selectivity in picrate extraction studies (Table 1), that is, better selectivity for the binding of lithium exhibited by the 1,3-diaxial crown-4 **9** as compared to crown-4-ethers with other orientations, now strongly supports this possibility.

3. Conclusions

A comparison of the metal picrate binding characteristics of inositol derived crown-4-ethers shows that although the strength of binding of metal picrates to these crown ethers could depend on various factors, the selectivity of binding of metal ions can be modulated by reducing the flexibility of the crown ether oxygen atoms.[37–40] These results also complement the observed regioselectivity for the O-substitution reactions of *myo*-inositol 1,3,5-orthoesters in the presence of metal ions and support the involvement of chelates during these reactions. We are presently investigating the possibility of modulation of metal ion binding to inositol derived crown ethers by tuning the protecting groups on the hydroxyl groups (not involved in crown ether formation) in inositol derived crown ethers.

4. Experimental

4.1. General methods

For details on general methods see Ref. 32. Flash column chromatographic separations were carried out using ethyl acetate–light petroleum mixtures. The racemic isopropylidine derivative **1**,[41] the tetrabenzyl ether **3**,[42] and the orthoformate **5**[9] were prepared according to the literature procedures. Metal picrate–crown ether binding constants were estimated by the method of Cram.[34]

4.2. Synthesis of crown ethers. General procedure

A solution of triethyleneglycol ditosylate (1.2–1.3 mmol) in dry THF (50 mL) was added dropwise over 2 h to a refluxing solution of the required *myo*-inositol derived diol (1 mmol) and sodium hydride (4 mmol) in dry THF (100 mL), in an atmosphere of nitrogen. Refluxing was continued for another 24 h, after which the reaction mixture was cooled to ambient temperature and the solvent was evaporated under reduced pressure. The residue was extracted with chloroform and washed successively with water and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to give a gum. The crude product was dissolved in dry methanol (7–10 mL) and heated under reflux with sodium methoxide (5–10 mmol) for 8–12 h (to convert unreacted triethyleneglycol ditosylate to triethyleneglycol dimethyl ether, which is easily separable from crown ethers). Methanol was evaporated under reduced pressure to get a gum, which was purified by column chromatography on silica gel using ethyl acetate and light petroleum (gradient elution) as eluent to obtain the crown ether as a gum.

4.2.1. Racemic 1,2-*O*-isopropylidine-3,6-di-*O*-benzyl-4,5-(12-crown-4)-*myo*-inositol (7). The diol **1** (0.4 g, 1 mmol), sodium hydride (0.096 g, 4 mmol) and triethyleneglycol ditosylate (0.596 g, 1.3 mmol) were used to obtain the crown ether **7** as a gum (0.188 g, 36%). IR (neat): ν 1497, 1604, 2872, 2924, 3350–3570 cm^{-1}. δ_H (200 MHz; CDCl$_3$): 7.15–7.60 (10H, m), 4.50–5.0 (4H, m), 4.18 (1H, t, $J=4.4$ Hz), 3.55–4.10 (16H, m), 3.16 (1H, t, $J=9$ Hz), 1.48 (3H, s), 1.33 (3H, s). δ_C (50.3 MHz; CDCl$_3$): 138.7, 138.4, 128.4, 128.2, 127.9, 127.7, 127.4, 109.7, 82.7, 82.5, 81.2, 79.1, 74.6, 74.0, 73.3, 72.5, 72.3, 71.0, 70.7, 27.8, 25.9. Anal. Found: C, 63.69; H, 7.41. $C_{29}H_{38}O_8 \cdot 2H_2O$ requires C, 63.25; H, 7.68%.

4.2.2. Racemic 1,2-(12-crown-4)-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (8). The diol **3** (0.541 g, 1 mmol), sodium hydride (0.096 g, 4 mmol) and triethyleneglycol ditosylate (0.550 g, 1.2 mmol) were used to obtain the crown ether **8** as a gum (0.185 g, 28%). IR (neat): ν 1499, 1602, 2867, 2921, 3200–3600 cm^{-1}. δ_H (200 MHz; CDCl$_3$): 7.15–7.50 (20H, m), 4.55–5.0 (8H, m), 3.90–4.20 (5H, m), 3.55–3.85 (10H, m), 3.30–3.45 (2H, m), 3.16 (1H, d, $J=10$ Hz). δ_C (50.3 MHz; CDCl$_3$): 138.9, 138.4, 129.7, 128.1, 127.8, 127.6, 127.5, 127.2, 83.5, 81.6, 81.2, 80.7, 80.6, 75.6, 72.8, 72.6, 72.5, 72.3, 71.9, 70.7, 70.5. Anal. Found: C, 69.33; H, 6.92. $C_{40}H_{46}O_8 \cdot 2H_2O$ requires C, 69.54; H, 7.29%.

4.2.3. 2-*O*-Benzyl-4,6-(13-crown-4)-*myo*-inositol 1,3,5-orthoformate (9). The diol **5** (0.280 g, 1 mmol), sodium hydride (0.096 g, 4 mmol) and triethyleneglycol ditosylate (0.596 g, 1.3 mmol) were used to prepare the crown ether **9** as a gum (0.094 g, 24%). IR (neat): ν 1496, 1604, 2864, 2904, 3006, 3200–3600 cm^{-1}. δ_H (200 MHz; CDCl$_3$): 7.25–7.50 (5H, m), 5.55 (1H, s), 4.75 (2H, s), 4.51 (1H, m), 4.25–4.35 (2H, m), 4.15–4.25 (2H, m), 3.99 (1H, s), 3.35–3.90 (12H, m). δ_C (50.3 MHz; CDCl$_3$): 137.9, 128.4, 128.1, 127.8, 103.2, 74.4, 72.9, 71.2, 70.4, 70.3, 69.7, 67.6, 66.9. Anal. Found: C, 58.60; H, 7.14. $C_{20}H_{26}O_8 \cdot H_2O$ requires C, 58.24; H, 6.84%.

Note: As revealed by spectroscopy and analytical data, crown ethers **7**, **8** and **9** always contain water and furthermore are not stable either as gums or in solution for long periods of time (few weeks). We suspect that some of the benzylic methylene groups undergo oxidation on storage. This was indicated by the infrared and ^{1}H NMR spectra of samples stored over long periods of time.

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