# A Molecular Mechanics Study of the Complexation of Metal Ions by Inositols†

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Molecular mechanics calculations have been used to rationalize a previous observation that metal ions of ionic radius less than 0.8 Å adopt the ax-ax-ax mode while those of ionic radius greater than 0.8 Å adopt the ax-eq-ax mode with *cis*-inositol (cyclohexane-1,2,3,4,5,6-hexol). It is found that the different modes adopted are controlled by the need for large metal ions to maximize the number of five-membered chelate rings of which they form a part, while smaller metal ions need to maximize the number of six-membered chelate rings. Molecular mechanics also indicates that the previous observation that metal ions of ionic radius less than 0.6 Å do not co-ordinate with neutral *cis*-inositol is due to van der Waals repulsion between the donor groups at these shorter M–O bond lengths.

The complexing properties of neutral oxygen donors have received considerable attention because of their importance[1] in crown ethers.[2] Much less attention has been paid to other ligands that contain neutral oxygen donors, although recently[1] it has been shown that there are important similarities between the co-ordinating properties of neutral oxygen donors which are part of open-chain ligands and those that are part of macrocyclic ligands. In particular, metal-ion-size preferences are at least partly governed by chelate-ring-size considerations.[1,3] Five-membered chelate rings favour complex formation with large metal ions having ionic radii[4] close to 1.07 Å, while six-membered chelate rings favour very small metal ions having ionic radii closer to 0.17 Å (only ions such as Be$^{II}$ can approach this requirement). This gives rise[1,3] to a rule of ligand design: selectivity of ligands for larger relative to smaller metal ions is enhanced by the presence of five-membered chelate rings, and for smaller relative to larger metal ions is enhanced by the presence of six-membered chelate rings. Thus, virtually all crown ethers for which formation constants are available[5] form five-membered chelate rings on complex formation. Close examination of their co-ordinating preferences reveals that crown ethers co-ordinate best with metal ions having ionic radii in excess of 1.0 Å, rather than displaying 'size match selectivity'.[1,3]

A class of ligands of considerable interest in regard to metal-ion selectivities is the sugars. Angyal[6–8] has studied the complexation of metal ions by sugars and related molecules such as *cis*-inositol (cyclohexane-1,2,3,4,5,6-hexol). *cis*-Inositol illustrates how metal ions may be co-ordinated by sugars in two ways, as seen in Fig. 1(*a*). In the type (i) form (ax-ax-ax), co-ordination is to three axial hydroxyl groups and all three chelate rings formed are six-membered. The second mode of co-ordination, type (ii), involves one equatorial and two axial hydroxyls (ax-eq-ax) and produces one six- and two five-membered chelate rings. Angyal[6] noted that metal ions of ionic radius less than 0.8 Å co-ordinate to *cis*-inositol to give type (i) complexes, while those with ionic radii greater than 0.8 Å give type (ii) complexes. This observation makes excellent sense in terms of the rule[1,3] of ligand design regarding chelate-ring size, since the small metal ions co-ordinate in the type (i) mode so as to maximize the number of six-membered rings present in the resultant complex, and large metal ions co-ordinate in the type (ii) mode so as to maximize the number of five-membered chelate rings. Molecular mechanics calculations have proved a useful tool[9] in co-ordination chemistry, and in this paper we report a molecular mechanics analysis of the co-ordination of metal ions to *cis*-inositol as a model for co-ordination to sugars in general.

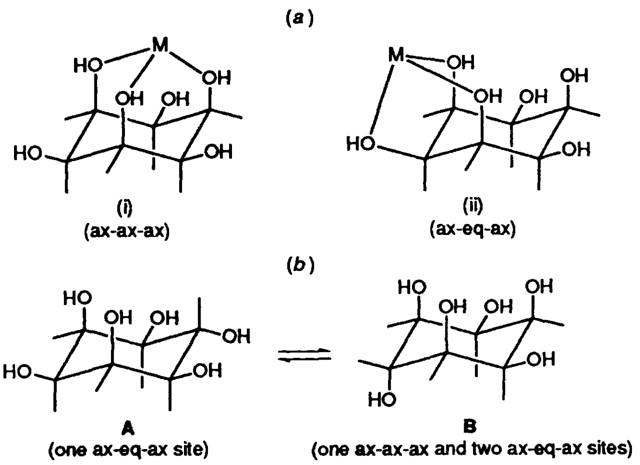

**Fig. 1** The modes of co-ordination of metal ions to *cis*-inositol (*a*) and the conformers of *epi*-inositol observed in aqueous solution (*b*)

## Experimental

*Molecular Mechanics Calculations.*—These were carried out using the commercially available program SYBYL.[10] Scans of strain energy as a function of metal-ion radius were carried out as described previously.[9] The program SYBYL models molecules with a complete description in terms of bond length and angle deformation constants, torsional contributions, out-of-plane contributions, and van der Waals repulsions. Atomic charges can also be included, calculated by empirical or semiempirical molecular orbital (MO) methods. However, SYBYL generates the geometry around the metal ion by use of van der Waals repulsion between the donor atoms, rather than by specifying bond angles and force constants for the metal ion and its donor atoms. The scans were therefore carried out using

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† *Supplementary data available* (No. SUP 56948, 5 pp.): Cartesian coordinates. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1993, Issue 1, pp. xxiii–xxviii.

*Non-SI units employed:* cal = 4.184 J, Å = $10^{-10}$ m.

this approach of van der Waals repulsion between the donor atoms to generate the geometry around the metal ion, which has been suggested by Bernhardt and Comba[11] as a modification of our method. All torsional force constants about the metal–ligand bonds were set to zero. An ideal angle of 109.5° and an angle-bending force constant of 0.014 kcal mol$^{-1}$ degree$^{-1}$ were used for the M–O–C angles, and a constant M–O bond-stretching constant of 200 kcal mol$^{-1}$ Å$^{-1}$. The results of the calculations are not[9] particularly sensitive to the value of the M–O force constant. In response to a comment by a referee, it should be pointed out that the preference of small metal ions for six-membered chelate rings, and large metal ions for five-membered chelate rings, arises from bond-angle and torsional requirements within the chelate ring, and so the M–O force constants are not of great importance to the results obtained here, except to constrain the M–O bond to approximately the correct length. The angle-bending constants of the organic part of the chelate ring are standard to the SYBYL force field, and are similar to those in other force fields. The results might be affected by the angle-bending constants involving the metal ion, and here one would say that these constants might be large in metal ions with more-covalent M–O bonding, and smaller in those with less-covalent M–O bonding. This is partly mimicked by the fact that as the M–O bonds get longer, corresponding roughly with more ionic M–O bonds, so the oxygen donor atoms become further apart, and van der Waals repulsions become smaller, equivalent to weaker O–M–O bending constants. The results in Fig. 2 are fairly rugged, and the overall conclusions cannot be altered by variation of the force constants involving the metal ion. All other parameters in the calculations were as contained in the TRIPOS 5.2 force field in SYBYL.[10] A validation of this force field is found in ref. 12. No charges were calculated on the atoms of the metal–inositol complexes. The scans are presented as a function of metal-ion radius. The radius[4] of the metal ions appears from the available data to be related quite well to M–O bond length by the approximation M–O bond length = ionic radius + 1.37 Å. The scans of strain energy *versus* metal-ion radius seen in Figs. 2 and 3 were thus drawn up using this approximation.

In an attempt to eliminate the problem of false energy minima, the molecular dynamics module of SYBYL was used. The structure of a molecule or complex that had been generated by the DRAW model-building module of SYBYL was energy minimized, and then subjected to a 10 000 fs run on the molecular dynamics module DYNAMICS. The file containing the energy of the complex as a function of time was examined, and low-energy structures extracted and energy minimized once more. In many cases this procedure revealed no structures of lower energy than that of the initial structure, although in one or two cases structures of considerably lower energy were located. The energies of unco-ordinated *cis-* and *epi*-inositol were calculated to see whether the reported[6] differences in complex stability could be accounted for in terms of the relative stability of different conformers of the unco-ordinated molecules. To enable hydrogen bonding to be taken into account, the charge distribution on the atoms was calculated using the SYBYL module CHARGES, which makes use of the Marzili–Gasteiger[13] approach to calculate charges on individual atoms in the molecule.

## Results and Discussion

In Fig. 2 is seen the relationship between strain energy and radius of the co-ordinated metal ion for the type (i) and (ii) forms of the *cis*-inositol complex. The calculations were carried out without any additional water molecules co-ordinated to the metal ion, which as a result has a co-ordination number of three. This was done so as to examine first the steric properties of the ligand when co-ordinated to the metal ion alone. The results of the calculation are in good agreement with the observation of Angyal[6] that metal ions of ionic radius above 0.8 Å prefer the type (ii) mode of co-ordination with *cis*-inositol, while those with ionic radii less than 0.8 Å prefer the type (i) mode. The cross-over point, at ionic radii below which the energy of the type (i) complex is lower for smaller metal ions, and above which the energy for type (ii) complexes is lower for larger metal ions, occurs in Fig. 2 at 0.84 Å, in excellent agreement with Angyal's empirical observation. Angyal noted that the best metal ion for co-ordinating in the type (ii) mode with *cis*-inositol appears to have an ionic radius of about 1.0 Å. The strain-energy curve for type (ii) *cis*-inositol complexes flattens out at about 1.0 Å, and there is no sharp rise in strain energy at larger ionic radii. An interpretation that one may put on Angyal's observation that stability is at a maximum with metal ions of ionic radius about 1.0 Å is that the M–O bond strength decreases with increasing ionic radius, and that a radius of 1.0 Å represents an optimum balance between decreasing M–O bond strength with increasing ionic radius and strain energy that begins to increase for type (ii) complexes quite strongly below an ionic radius of 1.0 Å.

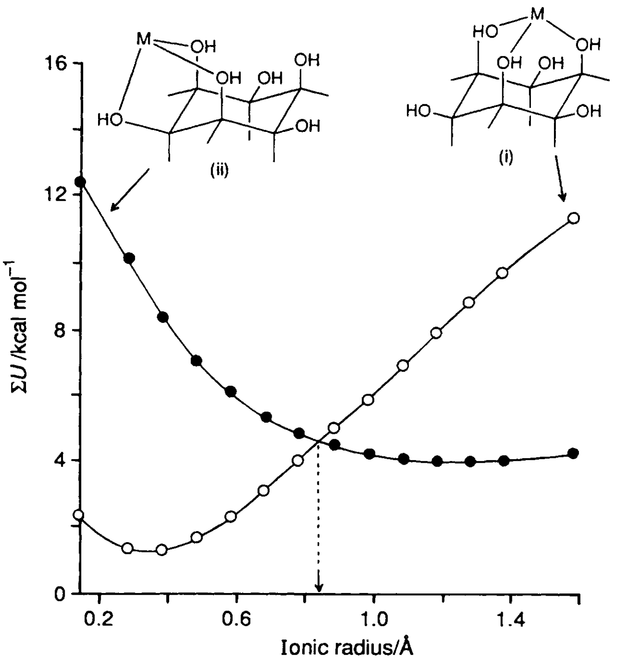

**Fig. 2** The strain energy of the type (i) and (ii) modes of co-ordination of metal ions to *cis*-inositol, calculated as a function of metal-ion radius,[4] as described in the text. The broken arrow indicates the ionic radius at which the transition occurs from the type (i) form being more stable to the type (ii) being more stable as ionic radius increases

Angyal[6] found that borate complexes exclusively in the type (i) form when it forms an ester with triply deprotonated *cis*-inositol. Since tetrahedral B$^{III}$ has[4] an 'ionic radius' of 0.11 Å, this makes excellent sense in terms of Fig. 2. Using SYBYL to calculate, with a sp$^3$-hybridized carbon atom as a reasonable representation of boron and alcoholic oxygens as the model for the oxygens bonded to boron, the energy of the boron–*cis*-inositol ester gives in its type (i) form an energy of 1.20 kcal mol$^{-1}$ and for type (ii) an energy of 20.3 kcal mol$^{-1}$, clearly illustrating the origin of the preference for the type (i) form.

The above borate ester has no protons on the three oxygens bonded to boron. If protons are added to these oxygens there is for the type (i) borate ester a significant rise in strain energy from 1.20 to 3.26 kcal mol$^{-1}$, which raises a second important point. Angyal[6] observed that metal ions of an ionic radius less than 0.6 Å such as Al$^{III}$ do not form complexes with *cis*-inositol that are not deprotonated. The reason for this is not evident from Fig. 2. It seems possible that, because the calculations used to draw up Fig. 2 included no co-ordinated water molecules, that this may be important. If three water molecules are included co-ordinated to the metal ion, to make it octahedral,

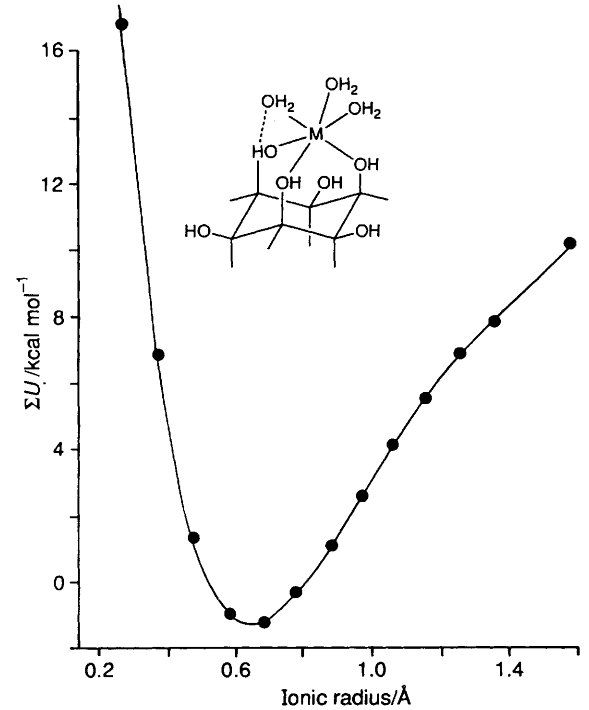

**Fig. 3** The strain energy of the type (i) metal *cis*-inositol complex as a function of metal-ion radius.[4] In contrast to Fig. 2, where the metal ions are bare apart from the co-ordinated *cis*-inositol, three water molecules have been added to the metal ion to make it octahedral. The presence of these molecules increases steric crowding at small ionic radii, resulting in a rapid increase in steric strain as the ionic radius decreases below 0.6 Å

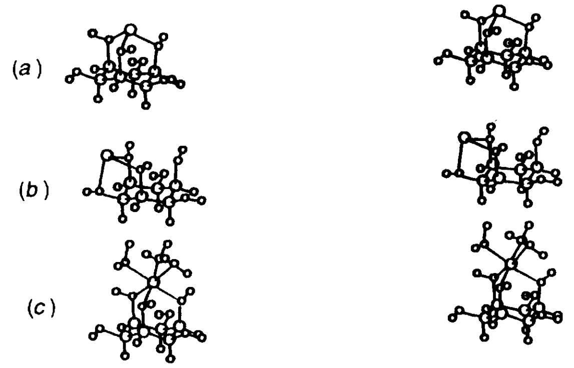

**Fig. 4** Stereoviews of (*a*) the type (i) and (*b*) type (ii) complexes of *cis*-inositol, plus (*c*) the type (i) complex with three water molecules co-ordinated to the metal ion, as generated by molecular mechanics calculation in this study

then the scan of strain energy *versus* metal-ion radius for a type (i) *cis*-inositol complex yields Fig. 3. In Fig. 3 the minimum in strain energy occurs at 0.63 Å, and for metal ions of ionic radius smaller than this there is a steep rise in strain energy. This result therefore suggests that Angyal's non-observation of complexes between neutral inositol and metal ions of ionic radius less than 0.6 Å is due to steric problems associated with water molecules co-ordinated to the metal ion in its *cis*-inositol complex. In Fig. 4 are shown stereoviews of the generalized type (i) and (ii) complexes of inositol with metal ions, as well as the type (i) complex with three water molecules also co-ordinated to the metal ion. The problem of steric crowding in the type (i) complex with three co-ordinated water molecules present relates to the general observation[9] that, for octahedral metal ions of ionic radius less than 0.6 Å, mutual van der Waals repulsions between the co-ordinated donor atoms and, more importantly, hydrogens or other atoms or groups directly attached to them leads to steric strain and a lengthening of the M–L bonds. This steric crowding will be a strong driving force for deprotonation of the co-ordinated *cis*-inositol so as to lessen steric crowding. Thus, metal ions such as $Al^{3+}$ should readily form complexes with *cis*-inositol in its deprotonated form, but steric-crowding problems rule out the observation of complexes with the oxygen donors protonated, in keeping with the results of Angyal.[6]

A final point is the observation[6] that *epi*-inositol forms complexes with a formation constant about half as large as that for *cis*-inositol with metal ions. *epi*-Inositol, as seen in Fig. 1, exists in a type **A** conformer with two axial or a type **B** conformer with three axial hydroxyls. Conformer **A** provides one ax-eq-ax coordination site only, while **B** provides one ax-ax-ax and two ax-eq-ax sites. The molecular mechanics calculations shows that conformers **A** and **B** have strain energies of 1.48 and 1.95 kcal mol$^{-1}$ respectively. Thus **A** will be the predominant conformer (about 75% of total inositol). This accounts for the much weaker co-ordinating properties than those of *cis*-inositol, which has only a single low-energy conformer which provides one ax-ax-ax and three ax-eq-ax binding sites for metal ions. Also present in solutions of *epi*-inositol to about 25% of total inositol will be the conformer **B**. One would thus expect *epi*-inositol to provide only $0.75 \times 1 + 0.25 \times 2 = 1.25$ ax-eq-ax and 0.25 ax-ax-ax co-ordination sites, compared to the three ax-eq-ax and one ax-ax-ax co-ordination site provided by *cis*-inositol, accounting for the fact that metal ions co-ordinate more strongly to *cis*- than to *epi*-inositol.

## Conclusion

In this paper it has been shown that molecular mechanics calculations account very satisfactorily for the metal-ion co-ordinating properties of inositol-type compounds, and by extension, of structurally related sugars. Specifically, the calculations show that, as observed in practice, metal ions with radii above 0.8 Å will co-ordinate at the ax-eq-ax site on *cis*-inositol while those with ionic radii less than 0.8 Å will co-ordinate at the ax-ax-ax site. This is as would be expected from ideas on the role of chelate-ring size in controlling metal-ion selectivity of ligands. A further result of the calculations is that metal ions with ionic radii less than 0.6 Å will suffer from considerable van der Waals repulsion between the hydrogen atoms, in particular those attached to the donor atoms of co-ordinated *cis*-inositol and adjacent co-ordinated water molecules. This accounts for the experimental finding that metal ions with ionic radii less than 0.6 Å do not form complexes with neutral *cis*-inositol. It is felt that molecular mechanics has again shown its value as a tool in co-ordination chemistry, and it is hoped to demonstrate further the value of this type of calculation for ligands of biological interest. Examples that spring to mind are the polyphosphoinositols so vital as messengers within the cell,[14] which involves complexation and release of $Ca^{2+}$.

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