Transition metal–saccharide chemistry and biology: An emerging field of multidisciplinary interest

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The interactions of transition metal ions with saccharides have been a subject of current interest. This review presents, in brief, the understanding of these interactions through our recent work in this promising field. Methodologies have been developed to synthesize and isolate a large number of complexes of transition metal ions with saccharides, using readily available and/or easy to prepare starting materials. The characterized complexes have been classified into various structurally diverse categories. Biological relevances of some of the transition metal–saccharide complexes have been discussed.

SACCHARIDES are the most abundant class of compounds by weight in the biosphere[1]. Their multihydroxy functionality and well-defined stereochemistry project them as potential candidate ligands for the binding of metal ions[2–7] . The ability to form complexes depends largely on the conformation of the saccharides and the orientation of the OH groups. The interactions between saccharides and metal ions have been known since the turn of the nineteenth century when the first adduct of D-glucose with NaCl was reported[8]. The first comprehensive report of Rendleman Jr.[9], in 1966, deals with the formation of saccharide complexes by the interaction of saccharides with alkali and alkaline–earth metal salts, and metal bases. Notable among the alkali and alkaline earth ion interactions, are the structural analysis of Ca(II)–carbohydrate complexes by Bugg and coworkers[10–14], metal–saccharide adducts reported by Tajmir-Riahi[15–29], and extensive solution studies by Angyal[30–35]. These studies have provided a renaissance of interest in the metal–saccharide interactions. Angyal's studies were primarily directed toward predicting the metal complexing capacities of neutral saccharides, based on their conformations, and the charge and size of the metal ions. The study of transition metal–saccharide interactions has been limited in the literature and largely deals with solution studies of saccharide derivatives of carboxylate, sulphate, amine and other functional groups[36–58].

The interactions between the metal ions and simple saccharides can be considered analogous to the metal–alkoxide interactions. However, it is surprising that the field of transition metal–saccharide chemistry has lagged far behind the corresponding metal–alkoxide chemistry[59,60]. Moreover, as compared to other major polymer classes in biology, viz. proteins and nucleic acids, the saccharide interactions with transition metal ions have received only scant attention[61]. It is highly true that the synthesis and isolation of the complexes in solid state are hampered due to the formation of weak complexes from neutral saccharides because of the high pKa values of the hydroxy groups[62] ($pka_1 > 12$), and, hence, show pH-dependent formation of complexes, particularly under alkaline conditions.

In order to understand the biological roles of essential and toxic metal ions, it is necessary to identify the compounds involved and their possible reactivities, and to elucidate the underlying mechanism through enriching various areas involving bioinorganic, bioorganic and environmental inorganic chemistry aspects[63–66]. The metal-sequestering ability of the saccharides is of interest in the development of novel classes of metal-based affinity chromatography materials, chiral homogeneous catalysts, metal chelators of clinical use, and as models of biologically important chelates[67–71]. The high water solubility of the saccharides, weak immunogenicity and low toxicity makes them useful candidates in developing pharmaceutical agents, e.g. polysaccharide complexes of Mn(II) and Gd(III) as magnetic resonance imaging carriers[72].

Thus the characteristics of transition metal–saccharide interactions were largely unexplored in their solid state complexes and the work has been recently reviewed[6,7,73,74]. Crystallographically-characterized complexes include; a Mo(VI)–D-lyxose complex[75], vanadate–adenosine complex[76], Cu(II) complexes of sugar alcohols[77] and Co(III) and Ni(II) complexes of amino–glycosides[78]. In view of the current interest in transition metal–saccharide chemistry, we have adopted a systematic approach to develop methodologies to synthesize a large number of complexes of the first row transition metal ions with mostly monosaccharides and few disaccharides (Figure 1). The isolated complexes have been characterized in solid and solution states, using several analytical and spectroscopic techniques. The natural occurrence of transition metal–saccharide interactions in biological systems[79–83] has

prompted us to study the putative biological relevance of some of these complexes. This review comprises our recent work in transition metal–saccharide chemistry and biology, and is aimed to bring about a better understanding of the transition metal–saccharide interactions.

Coordinating abilities of saccharides towards metal ions

The coordination of polyhydroxy saccharides to the metal ions directly depends upon the spatial arrangement of the hydroxy groups. The metal complexing capacities of saccharides can be predicted simply by knowing some of their characteristics, such as, D or L, α or β, gluco or manno[84]. Thus the most favourable arrangements for polyols are the axial, equatorial, axial (a, e, a), and 1,3,5-triaxial conformations (Figure 2 *a*, *b*). In general, for the six-membered pyranose rings, both *cis* and *trans* diol arrangements are favourable, whereas in the five-membered furanose forms only *cis* diol provides a favourable orientation for complex formation. The saccharides, with open chain systems, possessing a *threo* conformation, exhibit better complexing ability than an *erythro* conformation (Figure 2 *c*, *d*), and the preference for these systems is, *threo* > *erythro* (t > e) for diols and tt > te > ee for triols. However, in saccharides with additional functional groups, like carboxylates, amines and amides, these functional groups are primarily involved in the complex formation.

Synthetic methodology

The rather weak acidic nature of the hydroxyl protons has been a limiting factor for their coordination. Earlier synthetic studies of saccharide interactions with the alkali and alkaline earth metal ions have revealed these interactions to be purely electrostatic, leading to the formation of metal–saccharide adducts[15–29]. We have synthesized transition metal–saccharide complexes, primarily using the sodium salts of saccharides. This method enhanced their reactivity towards metal ion coordination and resulted in the formation of complexes involving hydroxyl groups. Metal halides of divalent, $[NEt_4]_2[MCl_2Br_2]$ and $MCl_2 \cdot xH_2O$ (where M = Mn, Co, Ni, Cu and Zn), trivalent ($FeCl_3$), and tetravalent ($VOCl_2$) metal ions have been used as precursors for the synthesis by the saccharide–sodium salt method in nonaqueous solvents. The complexes of Cr(III) and VO(IV) were synthesized also from the reduction of chromate[85–90] and vanadate[91] respectively, using the saccharides as both reducing and complexing agents in aqueous and nonaqueous media. All the isolated complexes were purified using mixtures of aqueous and nonaqueous solvents to result in low molecular weight and water-soluble complexes. It was found that in some cases, e.g. Cu(II)–saccharide complexes[92], there was an initial formation of the polymeric complexes early in the reaction which later disintegrates to give lower molecular weight complexes. All the attempts to crystallize these complexes were unsuccessful.

Spectral, magnetic and electrochemical behaviour

The isolated complexes were characterized by several

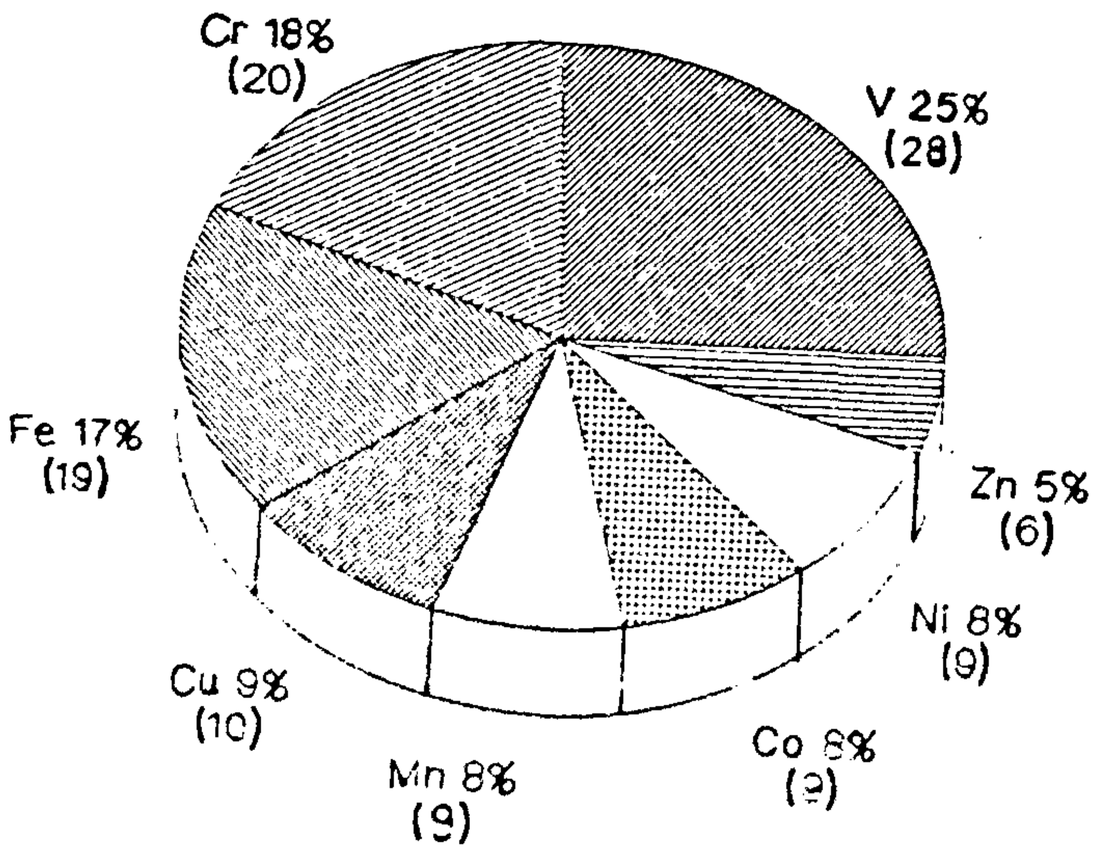

Figure 1. Pie chart showing the number of transition metal–saccharide complexes of each metal type synthesized (as given in brackets), along with percentages.

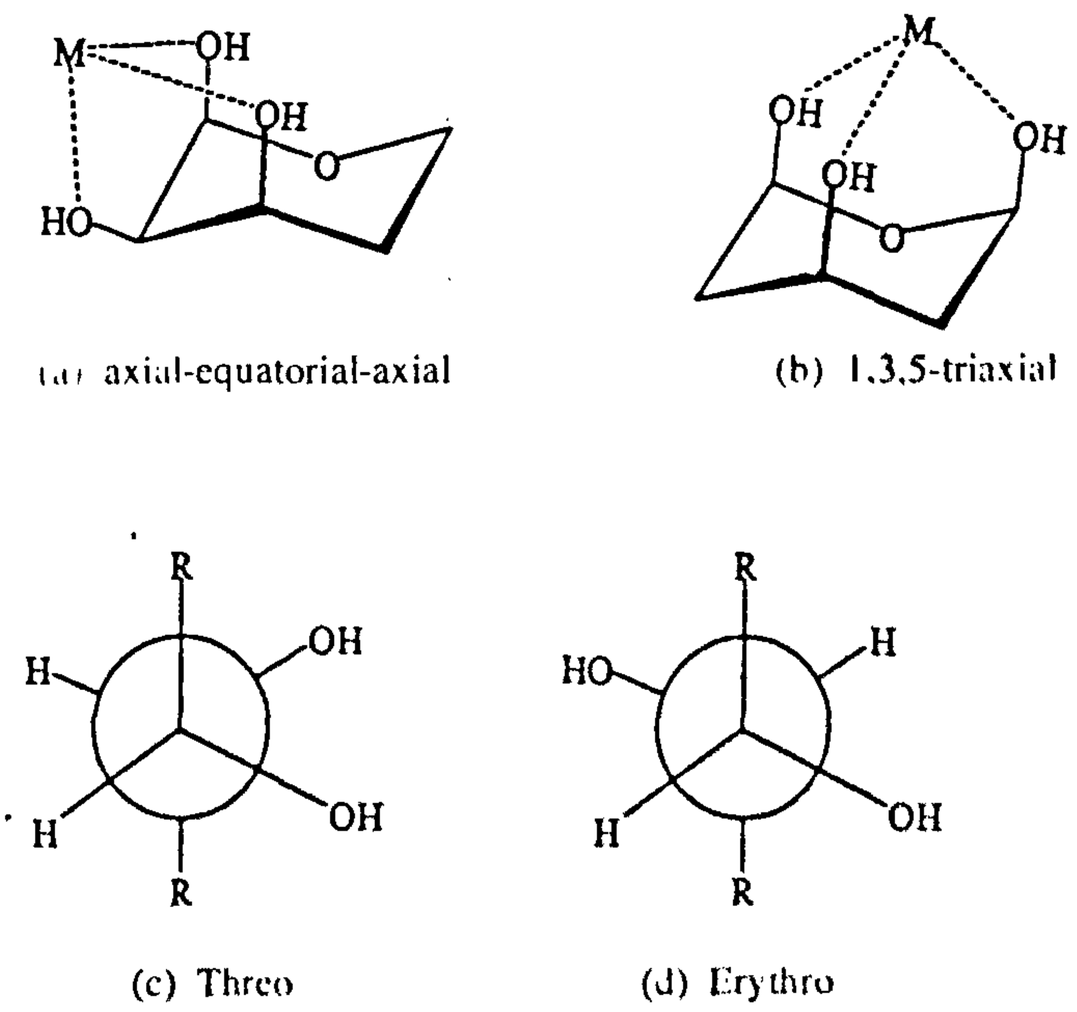

Figure 2. Favourable arrangements of hydroxy groups of cyclic and open polyols.

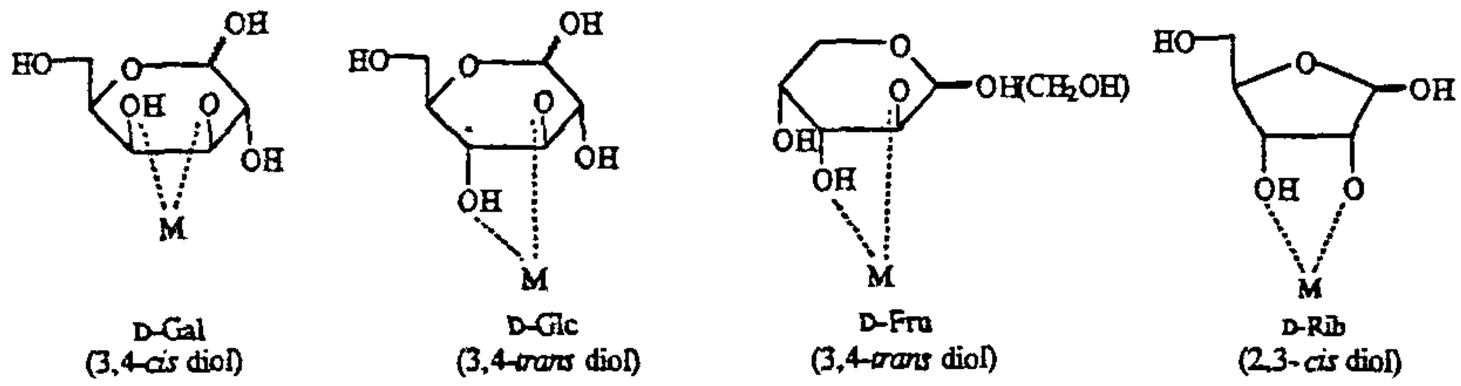

Figure 3. Favourable coordination modes of various saccharides.

spectroscopic and analytical techniques. The similarities found between the diffuse reflectance spectra and aqueous absorption spectra indicated the structural integrity of these complexes in the solid and solution states. Circular dichroism spectra exhibited strong cotton effects in the visible region for VO^{2+} (ref. 93), Co(II) (ref. 94) and Cu(II)–saccharide[92] complexes and a weak cotton effect for Ni(II)–saccharide complexes[95]. An inversion of absolute configuration was observed for D-galactose complexes compared to those of D-glucose and D-fructose. This is attributed to the differences in the orientation of the hydroxy groups on the corresponding saccharides. On the basis of the coordinating abilities of the various saccharides studied, a 3,4-*cis* diol arrangement is proposed for D-galactose complexes and that of 3,4-*trans* diol arrangement for D-glucose and D-fructose complexes. For five-membered rings, *cis*-diol group is the only preferred orientation; D-ribose has been proposed to coordinate via 2,3-*cis* diol groups. The coordination modes of these saccharides are shown in Figure 3. The Cu(II)–saccharide complexes exhibited opposite signs of curves compared to the corresponding VO^{2+}, Co(II) and Ni(II)–saccharide complexes. This is attributed to the ability of Cu(II) to catalyse mutarotation, resulting in the conversion of the saccharide moiety from the stable $^{14}C_1$ chair conformation to the high energy $^1C_4$ conformation[96] as shown in Figure 4.

The Fourier transform infrared (FTIR) studies of the complexes exhibited extensive rearrangement of hydrogen bonding network of the saccharides upon ionization and subsequent complexation. In most cases the presence of α-anomer of saccharides was detected from the FTIR studies[94,95,97]. The information in the far IR region indicated the presence of M–Cl binding in some of the complexes[97]. The ^1H and ^{13}C NMR studies of the complexes in aqueous solution revealed the presence of the open form of oxidized saccharides in Cr(III)–saccharide complexes synthesized by chromate reduction[85–90]. EXAFS studies have shown the primary interaction of the saccharide units through oxygen coordination in the complexes of Cr(III), Fe(III), Ni(II), Cu(II) and Zn(II)–saccharide complexes. The solid state XANES and EXAFS spectra of the Ni(II)–saccharide complexes indicated an octahedral geometry with an ordered interaction between the metal and the saccharide[95]. The

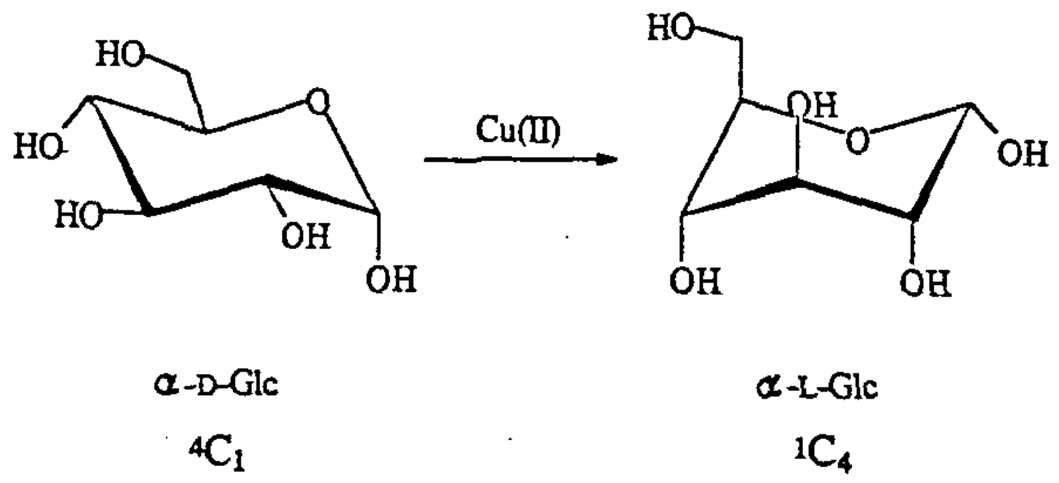

Figure 4. Conversion of $^4C_1$ to $^1C_4$ conformation in the presence of Cu(II) ions.

Ni . . . Ni interaction observed in these complexes was found to be shortest in the dimeric Ni(II)–saccharide complexes reported so far[78]. Similar studies with Cu(II)–saccharide complexes supported the presence of divalent copper and indicated the tetrahedral nature of these complexes by binding through two oxo-groups and two chlorides[92]. Satisfactory EPR spectra were obtained in case of Cr(III), VO^{2+}, Mn(II), Fe(III), Co(II) and Cu(II)–saccharide complexes characteristic of their corresponding oxidation states. The studies also indicated a rhombic symmetry in Co(II)– and Cu(II)–saccharide complexes and the presence of spin forbidden $\Delta m_s = \pm 2$ transition, typical for dimers, was observed in Co(II)–D-glucose complex at ~ 10 K with a high spin to low spin cross over[94].

All the complexes, except for Zn(II)–saccharides, were found to be paramagnetic at room temperature. The variable temperature magnetic susceptibility studies of the complexes showed a weak antiferromagnetic coupling characteristic of hydroxo bridging of the metal centres for Cr(III)[87] and some Fe(III)–saccharide complexes[98,99]. The Mn(II)–D-glucose complex also exhibited a weak antiferromagnetic behaviour in the range 5–300 K for a dimeric nature with a presence of about 5% monomer impurity[100].

The electrochemical behaviour of the complexes was studied by cyclic voltammetric measurements. At the neutral pH, the E_p^c for VO^{2+}–saccharide complexes ranges from – 1.45 to – 1.65 V, whereas for Cr(III) and Fe(III)–saccharide complexes, the E_p^c ranges from – 1.12 to – 1.46 V and – 1.20 to – 1.35 V respectively. These E_p^c ranges may serve as guidelines for addressing

metal–saccharide interactions. In the case of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)–saccharide complexes, the metal–saccharide interactions were found to be strengthened under strongly alkaline conditions and almost no complexation was observed under acidic conditions. Intermediate chloro-bound metal–saccharide species were proposed under weakly acidic conditions whereas under highly acidic conditions the complexes completely dissociated to give final anionic metal-chloro species as represented in a scheme for Co(II)–saccharide complexes.

$$[CoCl_m]^{2-m} \underset{\text{(strongly acidic)}}{\rightleftarrows} [Co(Sacch)_nCl_p]^{2-p} \underset{\text{(weakly acidic)}}{\rightleftarrows}$$

$$[Co(Sacch)_q]^{x-} \underset{\text{(neutral)}}{\rightleftarrows} [Co(Sacch)_q]^{y-} \underset{(y > x)}{\text{(alkaline)}}$$

Structural diversity

Our efforts in the transition metal–saccharide chemistry have resulted in the synthesis of more than one hundred complexes of first row transition metal ions with mostly monosaccharides and a few disaccharides and the complexes are found to be structurally diverse in nature. The diversity ranges from mononuclear to tetranuclear complexes with few exceptions of polynuclear ones. A metal-wise distribution of all these complexes into various nuclearity categories is shown in a three-dimensional bar diagram in Figure 5. In the synthesis of metal–saccharide complexes from simple, unprotected saccharides, the nuclearity of the complexes turned out to be in 1 : 2 : 1 ratio for mono, di and higher nuclear ones with almost half of the complexes being dinuclear. Formation of dinuclear complexes in the majority is explained on the basis of the available free hydroxyl groups on the saccharides. While all the 28 VO^{2+}–saccharide complexes are exclusively mononuclear, constituting 31% of the total complexes synthesized, the Cr(III) and Zn(II)–saccharide complexes, and a majority of the remaining complexes were predominantly dinuclear, constituting 47% of the total complexes. About one-fifth of the complexes were found to be of higher nuclearity, with tri (14%), tetra (4%) and higher nuclear ones (4%). The geometry of all the first row transition metal–saccharide complexes in the solid state was found to be either octahedral (Cr, Fe, Co, Ni, Cu), or tetrahedral (Mn, Co, Cu, Zn), with the exception of square pyramidal VO^{2+}–saccharide complexes. However, the aqueous solution spectra of all the complexes, including those of VO^{2+}–saccharide complexes, synthesized from $VOCl_2$ have shown characteristics of six coordination.

The polyhydroxy nature of the saccharides leads to the formation of multinuclear complexes. In the absence of any single crystal X-ray studies of these complexes, a clear picture of the structure of these complexes is only speculative. The metal centres are expected to be bridged by hydroxyls in case of Cr(III) and Fe(III)–saccharide complexes, whereas those synthesized from the metal–halide precursors are expected to be mostly bridged by halides and/or hydroxyl groups. Proposed structures of some of the complexes are shown in Figure 6.

Solution stability

The synthesis of first-row transition metal–saccharide complexes from different precursors and methods has led to the formation of highly water soluble complexes. However, the most striking feature among these complexes is the remarkable hydrolytic stability of VO^{2+}, Cr(III) and Fe(III)–saccharide complexes compared to Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)–saccharide complexes. The saccharide complexes of VO^{2+} synthesized from $VO(acac)_2$ (refs 101, 102), and those of Cr(III)

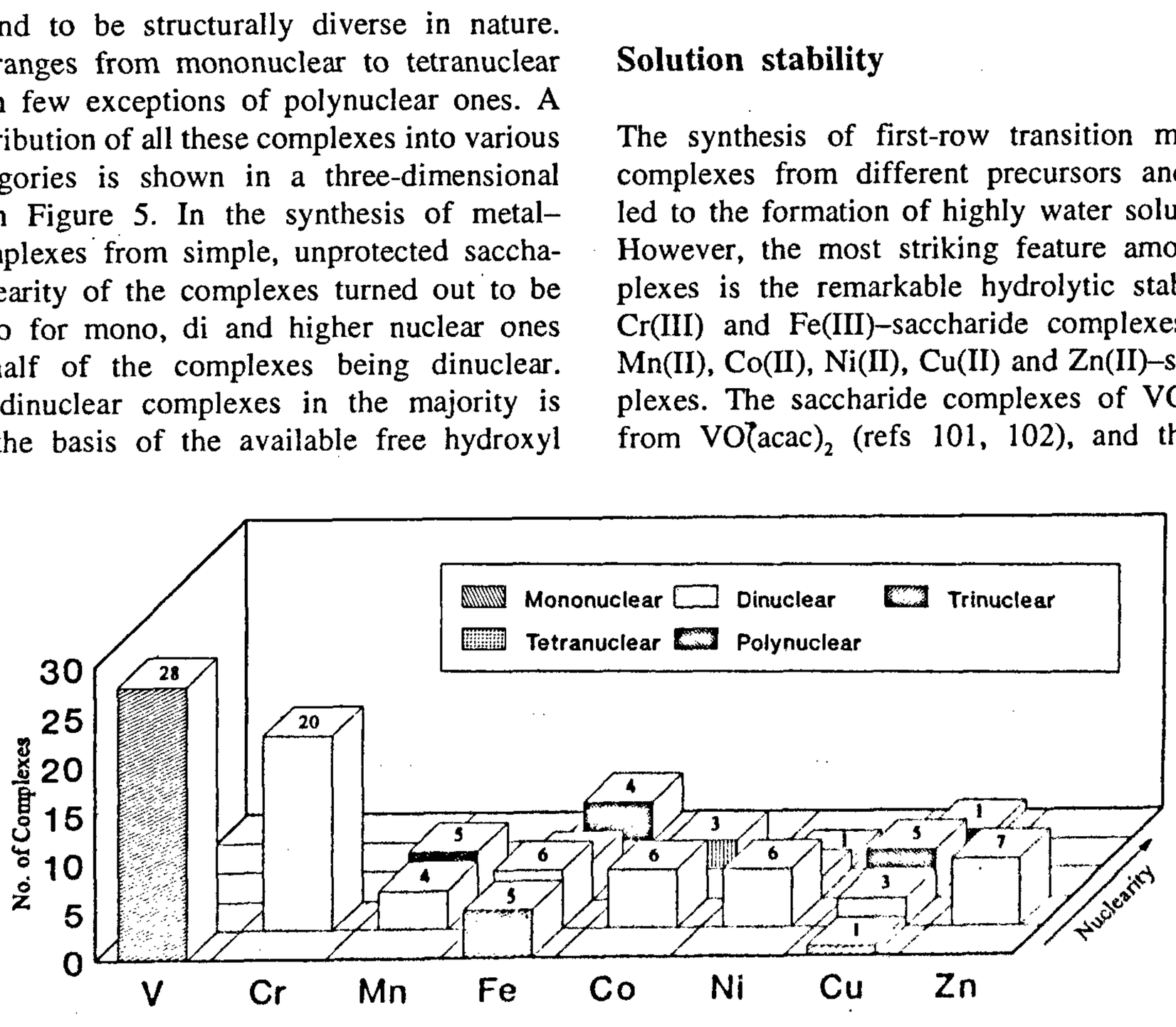

Figure 5. Metal-wise distribution of transition metal–saccharide complexes into different nuclearities.

(ref. 85–90) and Fe(III) (ref. 103) were found to be stable in the pH range 2–12 as studied by absorption spectroscopy and cyclic voltammetry. These complexes exhibited a linear behaviour between the cathodic peak potentials (E_p^c) and pH exhibiting different slopes for different compounds, indicating their relative hydrolytic robust natures. The variable stability of transition metal–saccharide complexes is not only dependent upon the metal ions but also on the nature of the saccharides as illustrated in Figure 7. This behaviour is similar to Irving–Williams series for the stability of divalent first-row transition metal ions[104]. The differences in the stability of saccharide complexes of various metal ions have been explained on the basis of the ionic size of these metals[30]. Generally, the most suited radius for complex formation is ~ 1.0 Å. Therefore, Mn(II) (0.80 Å) forms relatively more stable complexes than Zn(II) (0.74 Å), Co(II) (0.74 Å), Ni(II) (0.72 Å) and Cu(II) (0.69 Å). The higher stability of Fe(III) and Cr(III)–saccharide complexes, in spite of their smaller radii [Fe(III): 0,64 Å and Cr(III): 0.69 Å] is attributed to their higher charge and the involvement of carboxyl groups in the coordination at least in case of Cr(III) complexes. This also follows the complexing ability trend of metal ions in the order, $M^{3+} > M^{2+} > M^{+}$ for a given ligand. The general tendency of the oxo-cations such as those of V and Mo to complex strongly to saccharides[105], explains the unusual stability of VO^{2+}–saccharide complexes.

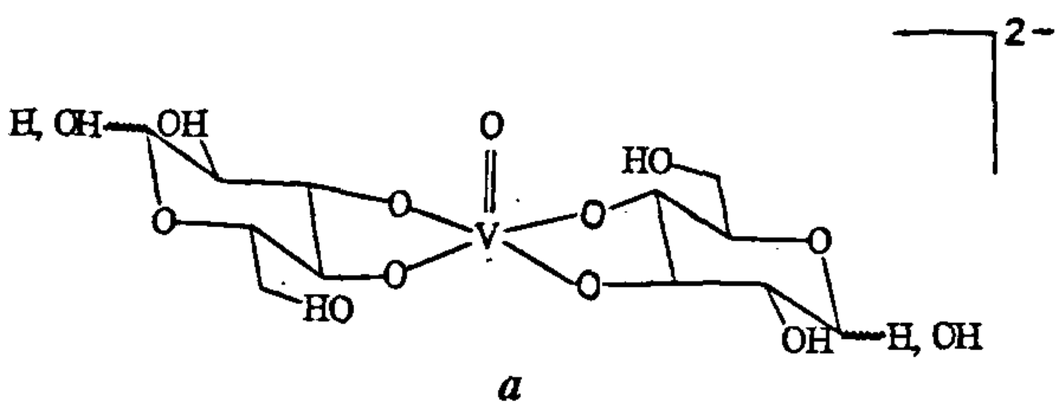

Figure 6. Proposed structures of some selected transition metal–saccharide complexes: *a*, VO–D-Glc complex; *b*, Zn(II)–D-Glc complex; *c*, Cu(II)–D-Fru complex.

Relative reducing abilities of saccharides towards metal ions

As mentioned earlier, one of the methods of synthesizing transition metal–saccharide complexes is to reduce the metal precursors using saccharides followed by the complexation. The reducing abilities of the saccharides play a significant role on the availability and transport of toxic and non-toxic metal ions as part of soil biochemistry. These reactions occur at different rates and give rise to a variety of products. We have studied the relative reducing abilities of the various hydroxy containing compounds, including monosaccharides, towards V(V), Cr(VI) and Mo(VI) reductions in acidic medium[106–108]. Based on the quasi-kinetic approach, the relative reducing abilities of various compounds towards these three metal ions were found to follow an order, L-ascorbic acid > L-cysteine > monosaccharides > glycols > ethanolamines. Among the metal ions, the corresponding relative oxidizing abilities followed a trend, Cr(VI) ≫ V(V) > Mo(VI), as expected, based on their

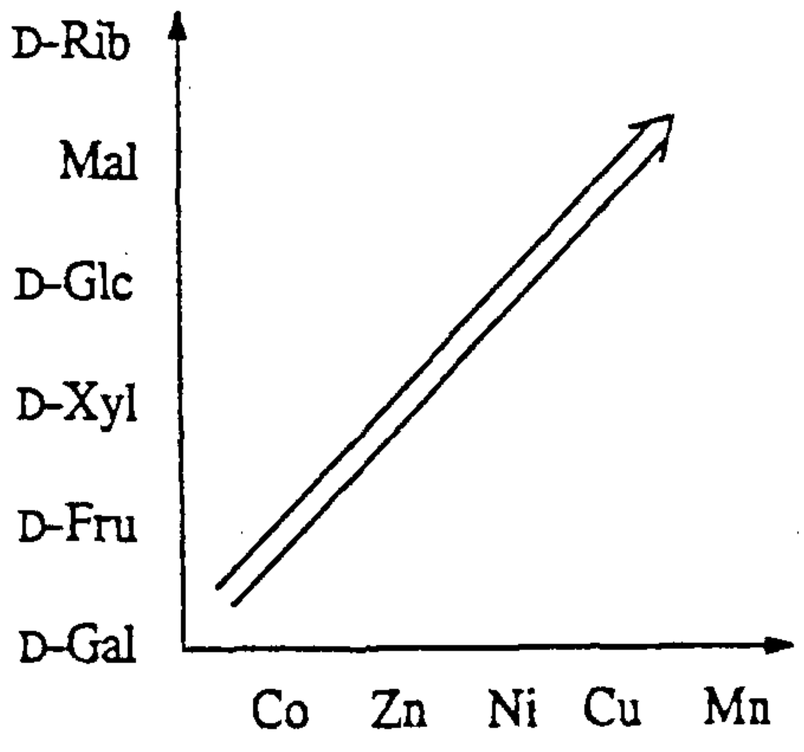

Figure 7. Plot showing the general trend in the solution stability of transition metal–saccharide complexes as dependent on the corresponding saccharides and the metal ions.

reduction potentials. A plot showing the oxidizing ability of these metal ions and the reducing abilities of various reductants is shown in Figure 8, which could be used in predicting the relative reducing or oxidizing abilities. A working model for chromium toxicity has also been proposed[109].

Putative biological relevance

Metal–saccharide interactions are of biochemical importance in relation to absorption, transport and detoxification of metal ions in biological systems. Some enzymatic reactions of saccharides, alkali, alkaline earth and some of the transition metal ions have been suggested to act in cooperation with saccharides. *Vanadobin*, a low-molecular weight compound containing a reducing sugar as the vanadium-binding substance, has been isolated from various tunicates[83]. Low molecular weight saccharide complexes of Ni(II) have been found in mammalian kidneys[81,82]. Thus there is a concrete evidence for the existence and various implications of metal–saccharide complexes in biological systems. Some of the transition metal–saccharide complexes prepared in our laboratory, such as those of VO^{2+}, Cr(III), Fe(III), Cu(II) and Zn(II), have been tested for their putative biological relevances.

The *in vitro* DNA interaction studies with VO^{2+} (refs 91, 102), and Cr(III) (refs 87, 110) and Fe(III)–saccharide complexes have shown them to be potent DNA cleaving agents in the presence of hydrogen peroxide, leading to the formation of open circular and linear forms from the native supercoiled form of DNA (pUC 18 or pSV2 neo plasmid) as demonstrated using gel electrophoresis. A histogram indicating the amounts of different forms of DNA formed due to incubation with vanadium saccharide complexes is shown in Figure 9. Studies carried out in the presence of sodium azide and mannitol have delineated the involvement of oxygen-based species in the DNA cleavage studies. However the ascorbate complexes of these metal ions have shown their DNA cleavage even in the absence of hydrogen peroxide and in their presence these have shown complete conversion of supercoiled form and exhibited more amounts of linear form.

Studies with VO^{2+}–saccharide complexes on the *in vitro* interactions with RNase and DNase exhibited inhibition of RNase but not DNase, suggesting that these complexes could act as transition state analogues (Figure 10) to this enzyme[102]. These complexes also caused lipid peroxidation, cytotoxicity in isolated rat hepatocytes, and were efficient inhibitors of protein biosynthesis in rabbit reticulocyte lysates. As the soluble vanadyl–saccharide complexes are found to be toxic to cells, even if these are found to be good in reducing the blood sugar levels,

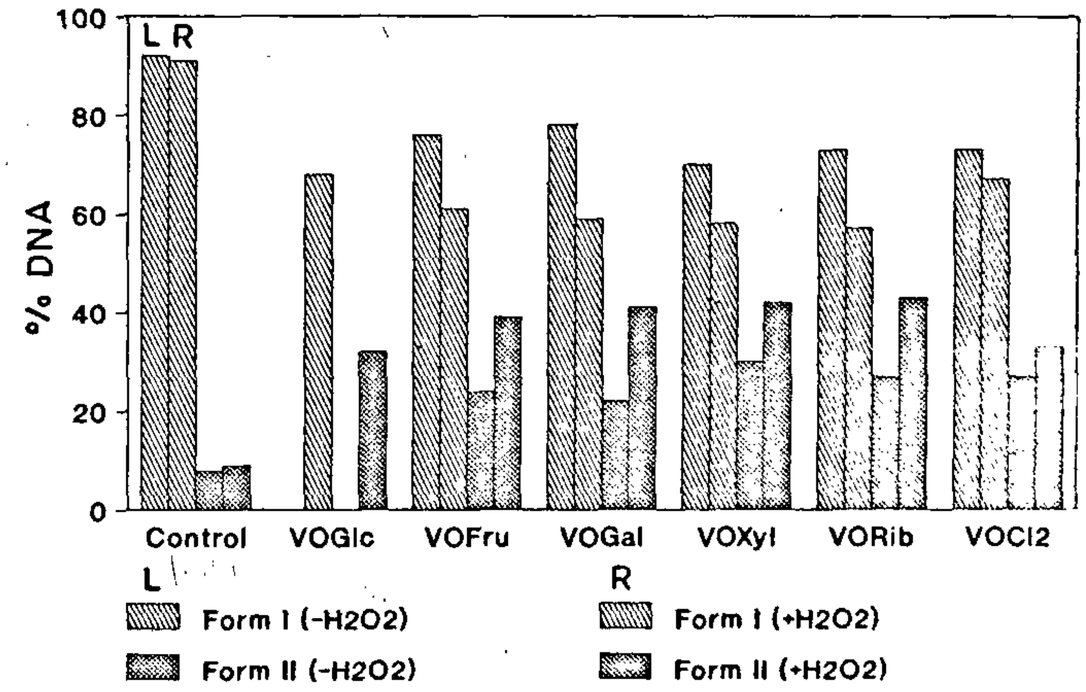

Figure 9. Effect of VO^{2+}–saccharide complexes of D-Glc, D-Fru, D-Gal, D-Xyl, D-Rib on pUC-18 DNA, compared to $VOCl_2$, showing percentages of Form I (supercoiled) and Form II (nicked) in the presence and absence of H_2O_2.

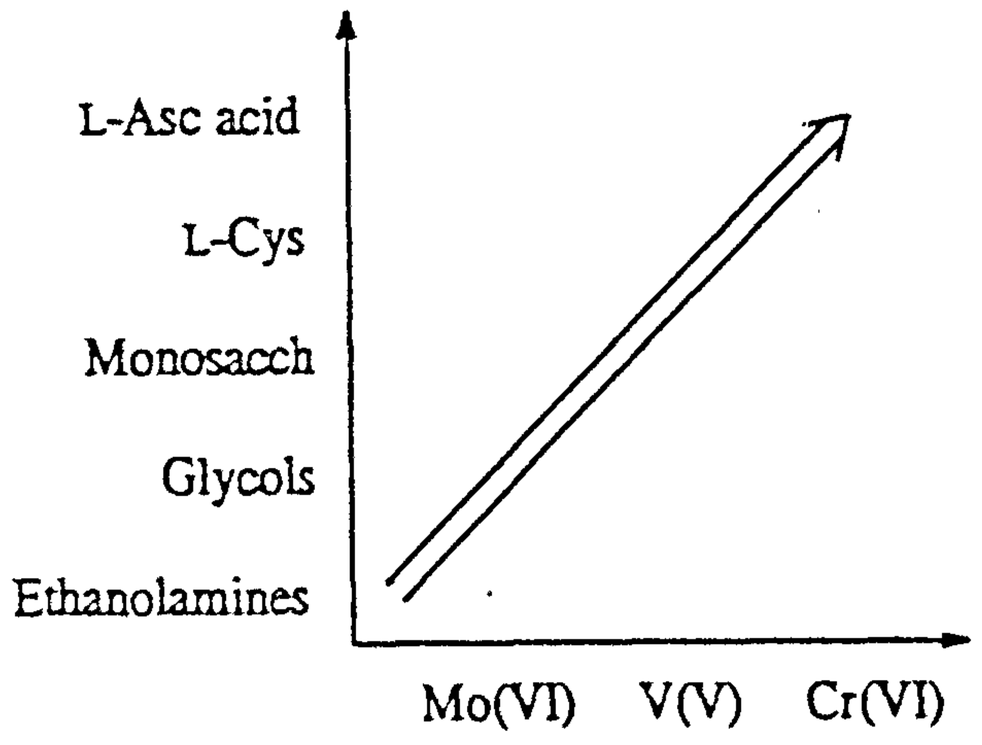

Figure 8. Plot showing the general trend in the oxidizing abilities of Mo(VI), V(V) and Cr(VI) towards various reducing agents.

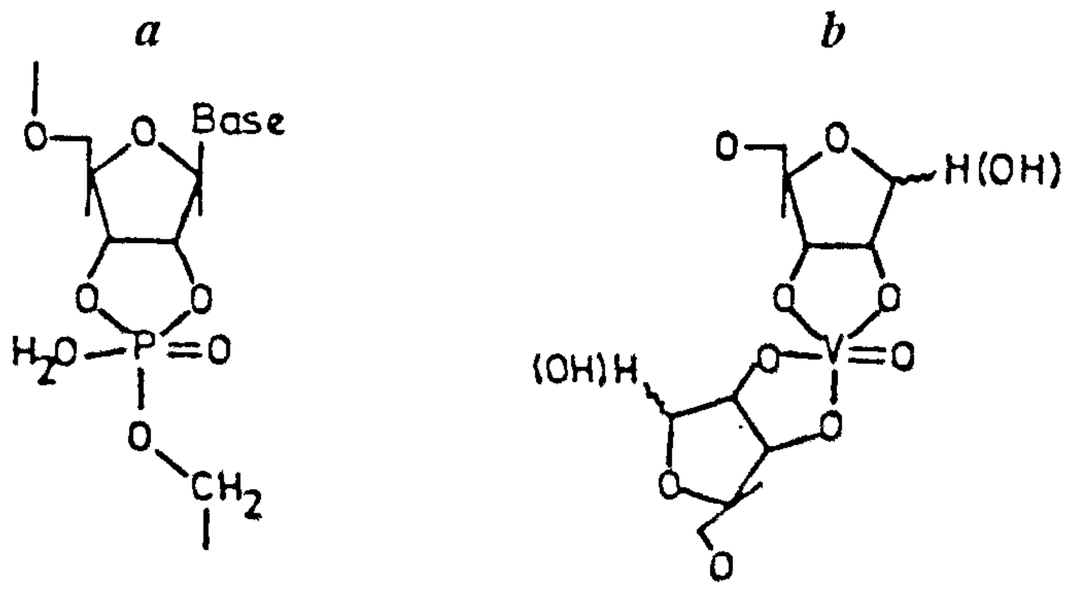

Figure 10. *a*, Transition state complex in the RNase-catalysed hydrolysis of RNA, and *b*, proposed schematic representation of complex $[VO(D\text{-}Rib)_2]^{4-}$.

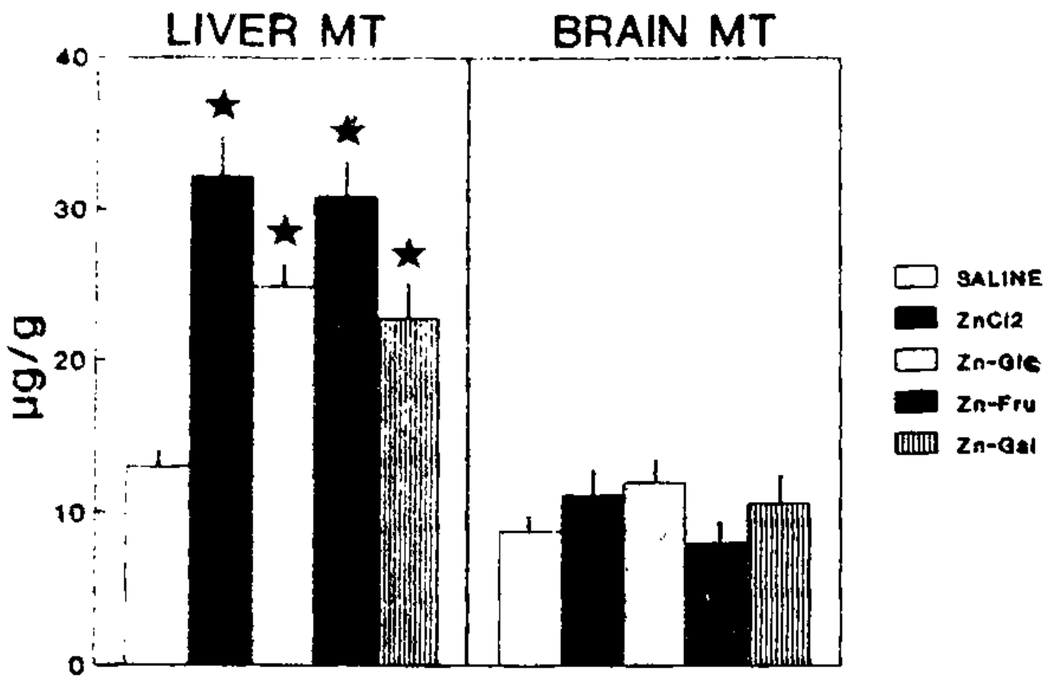

Figure 11. Effect of Zn(II)–saccharide complexes on rat liver and brain metallothionein (MT) levels compared to $ZnCl_2$ at a dose of 5 Mg/kg body weight in all the cases.

their use as oral insulin mimic is debatable. However, these complexes can perhaps be developed as specific agents of DNA cleavage.

The Fe(III)–D-glucose complex showed ATP-dependent intestinal absorption in rats, and was found to be relatively better absorbed than the free salt as studied using the everted sacs of rat intestines. The iron complexes have also been demonstrated for their controlled reductive release of iron in the presence of sodium dithionite as reducing agent using UV-Vis absorption and cyclic voltammetry experiments.

The Cu(II) (ref. 92) and Zn(II)–saccharide[97] complexes were found to significantly induce *in vivo* metallothionein synthesis in mice liver but not in brain. Corresponding data is shown in Figure 11 through histogram in case of Zn–saccharide complexes. The effect of these complexes was comparable to that of their corresponding salts even at very high concentration doses without showing any sign of toxicity. Further studies on the effect of Zn(II)–saccharide complexes on the δ-aminolevulinic acid dehydratase (ALAD) activity, urinary δ-aminolevulinic acid (u-ALA), blood zinc protoporphyrin (ZPP) and glutathione (GSH) levels suggested these to be potential oral Zn supplements[111]. These complexes were also capable of restoring the lead-induced biochemical disorders (ALAD activity, u-ALA, GSH levels) in lead poisoned male rats. All these biological studies reveal that the transition metal–saccharide complexes have some biological significance and promise to be of potential medicinal/clinical value.

Implications

The transition metal–saccharide interactions have wide occurrence in nature and regulate the bioavailability of metal ions through various primary and secondary interactions. Though a large volume of solution studies in the literature have demonstrated the complex formation, our group has been instrumental in developing the subject of transition metal–saccharide chemistry and biology. In the process, a plethora of low-molecular weight, water soluble, first-row transition metal–saccharide complexes are synthesized and characterized, but the real lack of crystal clear demonstration of metal–saccharide interactions through X-ray structures undermines the contributions made in this field. Some of the main reasons for non-crystallization of these complexes arise not only from the anomeric nature of the saccharides, but also due to the involvement of free-hydroxyl groups in various interactions, including those of ion (counter cation) . . . dipole type, leading to the formation of extensive aggregations. Such futile interactions can be prevented by selecting saccharides in their specific derivatized forms and to further enhance the crystallizable characteristics of the transition metal–saccharide complexes. The efforts in this direction are currently underway in our laboratory. The X-ray crystal structures and catalytic applications of some transition metal complexes with derivatized saccharides are reported in the literature[112–118]. The role of saccharides in the reduction and complexation of metal ions has been understood and the biological relevance of transition metal–saccharide complexes is of growing interest in the future. Given the importance of transition metal–saccharide interactions in agricultural, industrial, and pharmacological applications[6], the field of transition metal–saccharide chemistry and biology attracts attention of scientists with diverse interests.

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