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Carbohydrates as ligands: coordination equilibria and structure of the metal complexes

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The authors wish to dedicate this work to Professor Kálmán Burger on his 70th birthday.

Contents

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Abstract

Simple sugars and their derivatives — with oxygen, nitrogen, sulphur or phosphorous anchoring donor groups — form metal ion complexes of various composition and stability. The emergence of new experimental methods allowed the assignment of the metal binding sites in the different isomeric complexes of these multidentate ligands, and also the determination of the most effective chelating isomers of the ligands — being present as a mixture of different conformational and/or configurational isomers in solution. We review the literature on the metal ion complexes of carbohydrate type ligands with the emphasis on the past 20 years, discussing the equilibria and structure in aqueous solution together with the structures determined for the solid state complexes. Stability and structural data are collected for comparison.

Keywords: Carbohydrate type ligands; Coordination structure; Equilibrium constants; Metal complexes

Nomenclature

AGGHA	2-amino-2-deoxy-D-glycero-D-gulo-heptonic acid
$AGlcNH_2$	2-amino-1,6-anhydro-2-deoxy-β-D-glucopyranose
$AMeManNH_2$	2-amino-1,6-anhydro-2-deoxy-4-*O*-methyl-β-D-mannopyranose
AmetGAL	1-(2-aminoethylamino)-1-deoxy-D-galactitol
ATP	adenosine-triphosphate
BnAGGHA	2-benzylamino-2-deoxy-D-glycero-D-gulo-heptonic acid
CD	circular dichroism
CPL	circular polarized luminescence
Daracys	D-arabinose-L-cysteine adduct
dRib	2-deoxy-D-ribose
DTPA	diethylene-triamine-pentaacetate
EPR	electron spin resonance
EXAFS	extended X-ray absorption fine structure
En	ethylenediamine (1,2-diamino-ethane)
Fru	D-fructose
Fru–gly	D-fructose-glycine
Fru-β-ala	D-fructose-β-alanine

Gal	D-galactose
$GalNH_2$	2-amino-2-deoxy-D-galactopyranose
GalpA	D-galactopyranosiduronic acid
Galcys	D-galactose-L-cysteine adduct
Galurcys	D-galacturonic acid-L-cysteine adduct
Glc	D-glucose
GlcA	D-gluconic acid
$GlcNH_2$	2-amino-2-deoxy-D-glucopyranose
$GlcANH_2$	2-amino-2-deoxy-D-gluconic acid
Glugly	*N*-D-gluconylglycine
GlupA	D-glucopyranosiduronic acid
HyA	hyaluronic acid
Ino(1,3,5)tp	*myo*-inositol 1,4,5 triphosphate
Ino(1,3,5)tp	*myo*-inositol 1,3,5 triphosphate
Ino(2,4,6)tp	*myo*-inositol 2,4,6 triphosphate
IR	infrared spectroscopy
ISE	ion selective electrode
LacbA	D-lactobionic acid (4-*O*-β-D-galactopyranosyl-D-gluconic acid)
Laracys	L-arabinose-L-cysteine adduct
Mal	maltitol (4-*O*-α-D-glucopyranosyl-D-glucitol)
Man	D-mannose
$ManNH_2$	2-amino-2-deoxy-D-mannopyranose
$MeGalNH_2$	1-*O*-methyl-2-amino-2-deoxy-β-D-galactopyranoside
$MeGlcNH_2$	1-*O*-methyl-2-amino-2-deoxy-β-D-glucopyranoside
$MeManNH_2$	1-*O*-methyl-2-amino-2-deoxy-β-D-mannopyranoside
NMR	nuclear magnetic resonance
PHTAc	2-(polyhydroxyalkyl)thiazolidine-4-carboxylic acid
Rham	L-rhamnose
Rib	D-ribose
RibA	D-ribonic acid
RS-abto	1-amino-(2*R*,3*S*)-4-butanetriol
RSR-aptto	1-amino-(2*R*,3*S*,4*R*)-5-pentanetetrol
RRS-dapto	1,5-diamino-(2*R*,3*R*,4*S*)-pentanetriol
Rutin	3-[6-*O*-(6-deoxy-α-L-mannopyranosyl)-(β-D-glucopyranosyl)oxy]-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-1-benzopyran-4-one
Sacc	saccharose
Sor	L-sorbose
Taci	1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol
Tdci	1,3,5-trideoxy-1,3,5-tris(dimethylamino)*cis*-inositol
Tmca	all-*cis*-2,4,6-trimethoxycyclohexane-1,3,5-triamine
Tmen	tetramethyl-ethylenediamine
Tren	tris(2-aminoethyl)-amine)
XANES	X-ray absorption near edge structure

1. Introduction

Although the interaction between the carbohydrates and their derivatives and metal ions has already been observed at the beginning of the last century, the field of sugar type complexes continued to remain largely unexplored. One of the reasons for this is that the quantitative characterization of metal ion coordination equilibria of polyalcohols and other sugar-type ligands, containing only alcoholic and aldehyde (or ketone) oxygen donor atoms, is difficult due to the low stability of the complexes in neutral or acidic aqueous solutions. The low electron densities on these donor oxygens cause, in spite of their relatively large number in one ligand molecule, that they do not readily substitute the water molecules bonded in the first coordination sphere of the metal ions. With increasing pH, however, the hydrolysis of some metal ions prevents the coordination of the organic ligands, thus complex formation can only be expected in strongly alkaline solutions, after deprotonation of alcoholic hydroxy groups. The fact that in solutions of carbohydrates, the species are in anomeric and conformational equilibrium, and the isomers interact in different ways with metal ions makes the studies even more complicated. Any shift in the above equilibrium due to the metal ion coordination, thereby resulting in the changes in the fraction of the isomers having suitably positioned sequences of alcoholic hydroxy groups in the total concentration of the ligand, will also influence the complex stability. Thus, the complex stability constants determined by the conventional techniques used in equilibrium measurements (pH-metric or ISE potentiometric titrations, spectrophotometric, calorimetric, polarographic studies, etc.) must be regarded as overall values concerning the association of all forms of the ligand.

The emergence of modern structural chemical methods such as NMR (especially multinuclear NMR), CD, FTIR and Raman spectroscopies, made it possible to assign the binding hydroxy or other groups, and also to characterize the metal ion coordination of carbohydrates monitoring the ligand conformation or/and configuration changes forced by the complexation processes.

Another possible investigation strategy is to determine some physical characteristics for the metal ions. For example, the complexes containing a Mössbauer active nucleus (iron, tin, europium, etc.) can be studied by Mössbauer spectroscopy to get inside information about the possible geometry and structure of the complexes, and the electronic state of the central ions. Beside the application of paramagnetic ions as NMR shift reagents, very useful information is contained in their EPR or ENDOR spectra. The EXAFS method seems to be suitable for the determination of the local structure of metal complexes of carbohydrates both in solution and in the solid state. It provides structural information related to the radial distribution of atom pairs in a system: the number of neighbouring atoms around a central atom (coordination number) in the first, second, and sometimes in the third 'coordination shells', and the interatomic distances between them. Additionally the XANES spectra should also be analyzed, to get information about coordination geometry, possible binding sites and

the oxidation number of metal ions in questions. It should be noted, however, that for analyzing EXAFS spectra further independently obtained information for the metal ion binding sites and suitable structural models are also needed.

X-ray crystal structure analysis provides the most adequate information on the structure of crystalline compounds. The regular packing in the solid state, held together by coordination, electrostatic and hydrogen bonds, may be broken upon the dissolution in polar solvents, therefore the results are not always applicable for the complexes existing in aqueous solution, although many examples proved that the main binding sites are the same in the crystal and in solution.

As a consequence of the developments in measuring methods the carbohydrate type compounds as ligands have received considerable interest. Another reason for this is the importance of such interactions in biological processes and also the application of carbohydrate complexes in many fields of science, which will be highlighted in Section 3.

Much of the work on the metal carbohydrate interaction published before 1904 was reviewed by Von Lippmann [1]. Several surveys have been published in the 1960's and 1970's. In 1964 Sawyer [2] summarized the results obtained on the metal complexes of GlcA, Rendlemann on the carbohydrate complexes of alkaline and alkaline earth metals [3] and on the complexes of polyhydroxy carboxylates [4] and Weigel [5] on the anionic complexes formed between a variety of oxyacids and polyhydroxy compounds. Volume 117 of the Advanced Chemistry Series in 1973 was devoted to the studies on carbohydrates in solution. Cook and Bugg [6] dealt with the crystal structure of calcium–carbohydrate complexes.

However, as the rapidly increasing number of the publications shows, the coordination chemistry of the carbohydrates came to surface only in the last two decades. Critical reviews were published by Angyal [7,8] on sugar-cation complexes formed in neutral solution, and by Yano [9] on the coordination compounds of transition metal ions — mainly Ni(II) and Co(III) — with amino-glycosides and related compounds. In the same year, two independently published reviews demonstrated the utility of organotin(IV) derivatives of alcohols in regioselective manipulations involving indirect acylation, alkylation and oxidation [10,11]. The metal binding characteristics of the naturally occurring cyclodextrins such as the (1,4)-linked hexamers and heptamers of Glc have been reviewed in Ref. [12]. The applicability of the ^{13}C-NMR relaxation method in studies of the interaction of paramagnetic metal ions with carbohydrates was pointed out by Dill and Carter [13]. Strong complexation between sugars and metal ions have been discussed by Burger and Nagy [14], Geraldes and Castro [15], Sarkar et al. [16] and Kozlowski et al. [17,18]. Three recent reviews by Yano and Otsuka [19], by Bandwar and Rao [20] and by Verchére et al. [21] collected the results obtained with carbohydrates containing only alcoholic hydroxy and aldehyde or ketone groups while Alekseev et al. [22] reviewed the papers published mainly before 1990 on metal complexes of natural carbohydrates. Piarulli and Floriani [23] overlooked the literature data on the complexes formed with protected sugars. But a comprehensive review on the

complexes of carbohydrates and carbohydrate derivatives is not available. The aim of this work is to summarize the results, with emphasize on the last 20 years, obtained by different equilibrium (pH-metric, ISE potentiometric and other electrochemical, spectrophotometric, and calorimetric methods) and structural (NMR, FTIR, EPR, EXAFS spectroscopic and X-ray diffraction) methods on the metal ion complexes of carbohydrates and their derivatives.

2. General properties

In aqueous solution, as already mentioned, carbohydrate complexes are formed by the displacement of water molecules from the first coordination sphere of cations by the alcoholic hydroxy groups. Since the water molecules solvate cations much better than monohydric alcohols or diols, the latter can not form stable complexes with cations in neutral aqueous solutions. They can only form (mainly polymeric) complexes in the solid state [24–27]. In general it seems to be true that at least three hydroxy groups in a favourable steric arrangement are required for complex formation. The general leading rule is that the cyclitols or sugars in pyranose form — in a chair conformation — containing an axial–equatorial–axial (*ax–eq–ax*) sequence of three adjacent hydroxy groups, or the 1,3,5 triaxial (*ax–ax–ax*) hydroxy groups, or in the furanose form with three adjacent hydroxy groups in *cis–cis* arrangement are the best coordinating ligands. The possible coordination sites are depicted in Fig. 1. The open chain alditols and carbohydrates with *threo–threo* arrangements of the hydroxy groups form more stable complexes than do those with *erythro* arrangements. All the above ligands form 1:1 complexes with metal cations in hydrophylic solvents [7,28,29] and give direct proof of the coordination of oxygen atoms of non-deprotonated alcoholic hydroxy groups. The relatively low stability of the complexes reflects (among others) the low donor ability of such oxygens.

Molecular modelling calculations have proved that in the gaseous phase Angyal's predictions are not respected [30]. The lowest energy is represented by a flexible β-pyranose form and some complexes are tetra- or pentacoordinated.

The size of the cation also appeared to be one of the leading factors in the complex formation. While the above mentioned *ax–eq–ax* and *ax–ax–ax* sites display similar geometries with three oxygen atoms at about 295 pm, they differ in the relative directions of the orbitals containing free electron pairs and in the ability to bring the oxygen atoms closer together. Furthermore, the *ax–eq–ax* site offers two five- and one six-membered chelate rings, while the *ax–ax–ax* site offers three six-membered chelate rings. These differences must lead to different complexations of metal ions with different ionic radii. The *ax–eq–ax* site only coordinates cations having ionic radii > 80 pm [31,32]. The triaxial site, found on *cis*-inositol, prefers cations that have ionic radii $\cong$ 60 pm, but < 100 pm [31,33]. Further important observation and discussion on the role of cation size, can be found in Ref. [34] on the basis of molecular mechanic calculations.

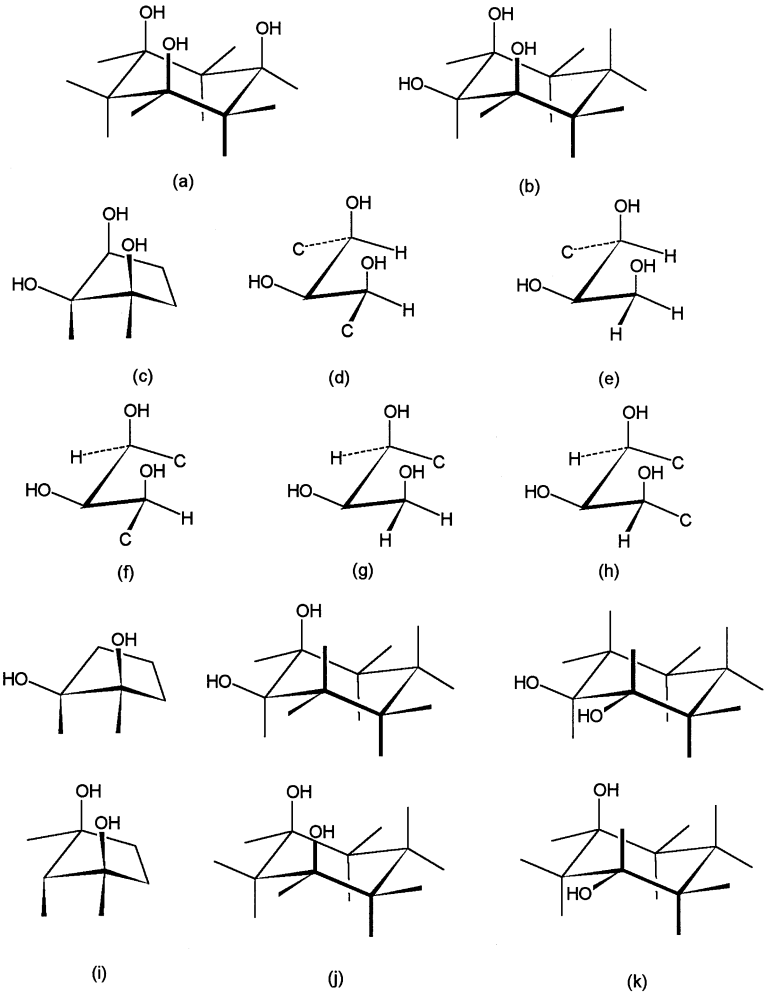


Fig. 1. The possible steric arrangements of the alcoholic hydroxy groups for metal complex formation in the order of the decreasing metal ion binding ability: 1,3,5-*ax–ax–ax* triol (a) and 1,2,3-*ax–eq–ax* triol (b) on six membered rings; *cis–cis*-triol on a five membered ring (c); acyclic *threo–threo*-triol (d); acyclic *threo*-diol adjacent to a primary hydroxy group (e); acyclic *erythro–threo*-triol (f); acyclic *erythro*-diol adjacent to a primary hydroxy group (g); acyclic *erythro–erythro*-triol (h); *cis*-diol on a five membered ring (i) and *cis*- (j) and *trans*- (k) diols on six membered rings.

On introduction of an anchoring group into a sugar molecule, which as a primary coordinating site may promote the coordination and deprotonation of the alcoholic hydroxy groups of the carbohydrate moiety, the complex-forming ability is enhanced by several orders of magnitude, even in acidic or neutral solution, this will be discussed later in detail. These donor groups might be the carboxyl, amino,

thiol, phosphate or other groups. In the equilibria of such systems complexes of different protonation states are often detectable. After deprotonation of one or more alcoholic hydroxy groups, the transition metal complexes having anionic character, are usually very stable. A general ionization scheme for the metal ion promoted deprotonation of the alcoholic hydroxy groups for e.g. polyhydroxycarboxylic acids was given by van Bekkum et al. [35]. In some cases, the formation of various amounts of alkoxo or hydroxo bridged dimeric (or oligomeric) species can be detected. The ligands with anchoring donor groups usually effectively compete with the hydrolysis processes of the transition metal ions, and keep them in solution in a wide pH range, but hydroxo mixed ligand complexes are also common among the species formed. All these facts allow the monitoring of the equilibria by means of simple pH-metric titrations. The combination of the species distribution curves obtained in this way, with spectroscopic measurements is required for getting structural information for the individual complexes. Spectroscopic measurements may also help in the evaluation of micro- and conformational-equilibria. Nice examples are e.g. the determination of the protonation constants of the individual anomers of amino sugars by ^{1}H-NMR [36], and the study on the interaction between borate and carbohydrates by ^{11}B- and ^{13}C-NMR spectroscopy [37]. The availability of more than one anchoring group may, however, prevent the coordination of alcoholic hydroxy groups fulfilling the coordination sphere of the metal ion. The metal ion promoted epimerization of the sugar type ligands may also occur [9,21,28,38].

The hard and soft character of the metal ions becomes an important factor in determining the composition and structure of the carbohydrate type complexes when the ligands contain donor atoms other than oxygen. A nice series of investigations in this direction have been performed with amino substituted *cis*-inositols and different metal ions by Hegetschweiler et al. [39–50].

3. Biological and chemical relevance of carbohydrate type complexes

Carbohydrates and carbohydrate derivatives, as the most abundant class of biomolecules, are known to have a large variety of biological functions. Through the interaction between these polyfunctional molecules and metal ions in living organisms, the modification of the biological function of both counterparts may be expected. Although the biological importance of the metal ion complexes of carbohydrates is not yet well documented, there are several directions of investigation on going in this field.

One of the known roles of the oligo- or polysaccharide complexes is the transport of metal ions through cell membranes. Concavalin A, a lactin from jack bean, containing Mn(II) and Ca(II) near the sugar binding site, associates with monosaccharides, and then with the cell surface. Its metal ion binding has been studied [51], but the mechanism is not yet understood in detail [52]. The studies on the structure and mechanism of calcium dependent C-type lectins provided information at the molecular level about protein–carbohydrate–Ca(II) interactions [53]. Many other

biological carbohydrate type compounds influence the distribution of Ca(II) ions in the organism [54,55].

Another, well documented interaction between carbohydrates and metal ions occurs in the metalloenzymes of the carbohydrate metabolism [56]. In these the metal ion coordination is related either directly to the function of the enzyme or to the suitable orientation of the carbohydrate moiety. The three dimensional structure of β-galactosidase was recently determined [57], for which a series of structure–reactivity relationship studies were performed and the role of Mg(II) ions in the catalysis was discussed [58–61]. The EPR study of the interactions between substrates and inhibitors and the binuclear active center of D-xylose isomerase, containing a Mn(II) in site A and Co(II), Cd(II) or Pb(II) in site B, demonstrated the direct coordination of xylitol to the Mn(II) ion [62]. The study of the effect of Zn(II) on the isomerization processes of sugars and sugar phosphates also showed the formation of sugar–metal complexes [63]. A very important enzymatic reaction presents the cleavage of the phosphate esters of sugars. For example, ribonuclease P also requires Mg(II) coordinated to the alcoholic hydroxy oxygens [64]. Recently, the study of the effect of sugar type complexes on the phosphate ester hydrolysis has also received considerable interest [65,66]. Zinc–saccharide complexes have been shown to influence the activity of some Zn(II) enzymes like the blood δ-aminolevulinic acid dehydratase, and were also investigated to ascertain the utility of these complexes as Zn(II) supplements and as preventive agents against lead intoxication in rats [67]. The crystal structure of the Zn(II) complex of erythromycin A — used as a topical anti-acne medication — revealed the direct coordination of the carbohydrate part of the ligand [68].

An important role of the carbohydrates is to increase the solubility of either the potential bioligands or the essential toxic metal ions. One of the most important clinical use of chelators is the treatment of iron overload [69,70], or iron deficiency. The Fe(III) ion is known to form strong complexes with oxygen-based ligands like the highly water-soluble and weakly immunogenic carbohydrates. One example is the already tested and introduced Fe(III)-D-sorbitol-GlcA mixed ligand complex, [71–83]. Another is the Fe(III)-lactobionic acid-acetate-cyclodextrin complex [84]. A polysaccharide–iron complex named 'Nifrex' obtained from Fe(III)-chloride and Glc is also being used for treatment of iron deficiency anaemia [85,86].

There are many experiments in progress to develop other sugar type ligands like the L-idopyranosiduronic acid — containing oligosaccharides (Sarkar et al. [16]), or modified inositols (Hegetschweiler et al., [39] and Spiess et al. [87,88]). The Zn(II)–HyA complex has been patented and used as a medicine for the treatment of crural ulcer, decubitus and primarily non-healing wounds [89]. It also seems possible to synthesize chelators for toxic metals such as Ni(II), Cu(II) and Pb(II), promoting their elimination into urine via the kidneys. A fraction of acidic oligosaccharides have been isolated and characterized from rat and human kidneys as a low-molecular-mass Ni(II) binding pool, derived from the degradation of internalized heparan sulphate [90]. Kohn found that Pb(II) coordinates strongly to GalpA oligomers [91]. Dithiocarbamates of an octose were used to remove Cd(II) from treated mice [92].

Water soluble polysaccharides were tested as carriers of paramagnetic contrast agents for magnetic resonance imaging. Particularly the Mn(II) and Gd(III) compounds were 60–240% more efficient proton relaxation agents than the corresponding low molecular weight metal chelates [93].

Organotin(IV) carbohydrate complexes are especially important for agricultural and clinical use. Several carbohydrate complexes have already been introduced to agriculture due to their fungotoxicity [94]. Organotin(IV) ions have also been used in the synthesis of sugar derivatives [95,96]. The chiral centres on the carbohydrate ligands may also promote asymmetric synthesis mediated by metal complexes like the structurally well characterized novel type homoleptic tris(diacetoneglucose)phosphite–Cu(I) complexes, with the [{CuCl[P(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside)$_3$]}$_4$] composition [97], or the chloro(cyclopentadienyl)-bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl)titanate(IV) complex being of special importance as a precursor for enantioselective allyl and ester enolate additions to aldehydes [98].

The extracellular polysaccharides exhibit extraordinary complexing ability to cations, consequently it is possible to use them for the extraction of metal ions. Furthermore, these polysaccharides have been used as gelling or thickening agents [99–102]. Alginates, the carrageenans from species of *Rhodophyceane* e.g. could gell with different monovalent cations [103]. Another example is the use of chitin derivatives for the selective removal of transition metal ions from brines, or removing radioactive ^{60}Co from nuclear effluents or Pb(II) and Cd(II) from drinking water [104–106].

Sugar complexes are also used in analytical chemistry. Differences in the electrophoretic mobility of carbohydrates in the presence of metal ions allows one to separate mixtures on a small scale and to assist in the identification of carbohydrates. Differences in the solubility or stability of the complexes permit the large-scale separation of polyhydroxy compounds.

4. Complexes of selected metal ions

In the rest of the review, complexes of selected metal ions will be discussed in the following order: (i) complexes of carbohydrates and polyols containing only weakly coordinating oxygen donor atoms; (ii) coordination compounds of sugar acids; (iii) complexes of carbohydrates with nitrogen or other donor atom containing anchoring group(s); and (iv) complexes of oligomeric and macromolecular carbohydrates. Where the comparison of the data requires, the equilibrium data and the results obtained by spectroscopic methods will be discussed separately also in the above order. The only deviation will be found in the case of platinum because of the historical evolution of its carbohydrate coordination chemistry. At the end of this section, tables containing data for selected metal ion complexes of carbohydrate type ligands are presented: the structural parameters determined by EXAFS spectroscopy (Table 1); the full equilibrium constant sets for metal ion-ligand systems (also including the protonation constants of the ligands) for the calculation

Table 1
Selected structural parameters for metal complexes formed with carbohydrates or their derivatives obtained by EXAFS[a]

Ligands	Interaction	N^c	r/pm	σ/pm	Ref.
Fru, solid	Fe–O	6	195	9.8	[239]
	Fe···C	4	277	6.9	
	Fe···Fe	1	310	6.0	
Sor, solid	$Fe–O_1$	2	194	6.0	[244]
	$Fe–O_2$	4	202	11.0	
	$Fe···Fe_1$	1	285	8.0	
	$Fe···Fe_2$	1	312	8.0	
Rib, solution	$Cu–O_{eq}$	4	191	7.5	[143,169]
	$Cu–O_{ax}$	2	230	13.0	
	Cu···C	2	271	10.0	
$GlcNH_2$, solution	$Cu–O_{eq}$	3	193	7.7	[143,169]
	$Cu–N_{eq}$	1	193	7.7	
	$Cu–O_{ax}$	2	234	13.0	
	Cu···C	2	274	10.0	
Adenosine, solution pH 6	$Cu–O_{eq}$	4	191	5.4	[170]
	$Cu–O_{ax}$	2	232	6.8	
	Cu···C	2	275	8.4	
Uridine, solution pH 6	$Cu–O_{eq}$	4	192	7.9	
	$Cu–O_{ax}$	2	234	7.9	
	Cu···C	2	279	9.6	
ATP, solution	$Cu–O_{eq}$	4	195	–	[171]
	$Cu–O_{ax}$	2	220	–	
GlupA, solid	Cu–O	4	196	–	[127]
Fru, Glc, solid	Cu–O	2	195	7.0	[174]
	Cu–Cl	2	208	8.0	
HyA, solid	$Cu–O_{eq}$	4	200	8.8	[192]
	$Cu–O_{ax}$	2	248	5.5	
	Cu···C	4	315	9.9	
	Zn–O	4	202	8.1	
	Zn···C	2	299	13.2	
N-glycoside, solid	Cu–O,N	3	195	–	[173]
	Cu–Cl	1	222	–	
	Cu–Br	1	233	–	
Glugly, solid	$Cu–O_{eq}$	2	190	5.6	[172]
	$Cu–N_{eq}$	2	190	5.6	
	$Cu–O_{ax}$	2	215	2.5	
	Cu···C	4	270	2.8	
	Cu···Cu	1	297	11.4	
Glugly, solid	Ni–O,N	6	204	6.6	
	Ni···C	6	285	5.4	
Glugly, solid	Co–O,N	6	200	11.9	
	Co···C	6	290	11.7	
	Co···Co	1	303	7.6	
(**I**)[b], solution	$Cu–O_{eq}$	2	193	4.6	[144]
	$Cu–N_{eq}$	2	193	4.6	

Table 1 (*Continued*)

Ligands	Interaction	N[e]	r/pm	σ/pm	Ref.
	$Cu–O_{ax}$	2	220	2.0	
	Cu···C	4	275	7.7	
	Cu···Cu	1	299	7.3	
PHTAc[f], solid	Zn–O,N	4	205	8.0	[324]
	Zn···C	6	290	10.0	
	Zn···O,C,S	6	386	14.0	
PHTAc, solid	Mn–O,N	6	216	9.5	[288]
	Mn···C	6	305	11	
	Mn···O,C,S	8	375	18.0	
PHTAc, solid	Ag–N	1	203	5.0	[288]
	Ag–S	1	230	4.6	
	Ag···C	4	294	19.0	
Fru, solid	Ni–O	4	202	–	[314]
	Ni···C	–	287	–	
	Ni···C	–	390	–	
	Ni···Ni	2	304	–	
Rham-Tmen	Ni–O,N	6	212	8.4	[545]
(**II**)[c], solid	Ni–O,N	5	214	7.7	
	Ni···Ni	1	359	4.5	
(**III**)[d], solid	Ni–O,N	6	221	12.2	
	Ni···Ni	2	328	9.6	
PHTAc, solid	Ni–O,N	6	203	8.0	[324]
	Ni···C	6	284	9.5	
	Ni···O,C,S	8	390	15.0	
Et_2SnLacbA, solid	$Sn–O_{intra}$	3	206	5.1	[510]
	$Sn–O_{inter}$	1	246	5.1	
	Sn···C	6	323	3.3	
	Sn···Sn	1	324	9.5	
Et_2SnGal, solid	$Sn–O_{intra}$	3	208	4.1	
	$Sn–O_{inter}$	1	255	4.1	
	Sn···C	6	307	5.1	
	Sn···Sn	1	362	6.3	
LacbA, solid	Mn(IV)–O	6	208	2.3	[289]
Mal, solid	Mn(IV)–O	6	208	3.5	
GlcA, solid	Mn(IV)–O	6	209	1.9	
Sacc, solid	Mn(III)–O	6	209	3.6	
Mal, solid	Mn(III)–O	6	206	1.0	
GlcA, solid	Mn(III)–O	6	208	3.3	

[a] The r, N and σ represented the bond distances, coordination number and the Debye–Waller factor, respectively.

[b] (**I**) = 2-amino-1,6-anhydro-2-deoxy-β-D-glucopyranose

[c] (**II**) = {([Ni_2(MeOH)(N-D-Man-N,N'-Me_2en)(N,N'-D-Man_2-N,N'-Me_2en)]$^{2+}$}

[d] (**III**) = [Ni-N,N,N'-trimethylethylenediamine-mannose]

[e] Fixed values

[f] The values given for PHTAc complexes are average values for several carbohydrate derivatives, discussed in detail in the appropriate references.

of the species distribution (Table 2); and the general binding modes and proposed coordination geometries (Table 3). The composition of the complexes is consequently given as $[M_pL_qH_r]$ where M is the metal ion, and L is the non-protonated carbohydrate type ligand molecule, with the exception of the complexes with more precisely determined structures from X-ray crystallography, where the proton loss can be assigned to a special carbohydrate ligand.

4.1. Copper complexes

The interaction of carbohydrates and their derivatives with Cu(II) is one of the most extensively studied topics in this field. However, carbohydrates without anchoring donor groups form very weak complexes with Cu(II) in aqueous solution. The careful study of Cu(II) alditol systems showed that there is almost no interaction with the Cu^{2+} ion itself, while the $[Cu_2(OH)_2]^{2+}$ hydroxo species may form more stable complexes at pH 5.6, where the ligands are coordinated tetradentately to the dimeric unit [107]. Site specific interaction of Cu(II) with aldopentopyranoses having arabinose type configuration at C(3) and C(4) was observed in dimethylsulfoxide [108]. The precipitation of hydrolyzed Cu(II) species can only be avoided by the introduction of an anchoring group into the carbohydrate molecules. Cu(II) has also been shown to oxidize D-galactose to D-galactonic acid in acidic medium [109].

Carboxylates may serve as a primary coordination site in sugar acids. According to the first studies on the Cu(II)–GlcA systems [110] dimeric species formed with Cu:GlcA ratios of 2:4, 2:2 and 2:1 in basic solutions. pH-metric measurements in the pH range of 3.5–6.5, have shown the formation of mononuclear complexes and a less convincing evidence for the existence of a dinuclear deprotonated complex $[Cu_2LH_{-3}]$ [111]. The formation of mononuclear complexes was later also proven, and the extension of the pH range of the potentiometric titrations revealed a major dimeric species with the composition $[Cu_2L_2H_{-3}]^-$ over the pH 5–9 range, while the formation of monomeric complexes was proposed at alkaline pH [112]. Dimeric Cu(II) chelates of polyhydroxy carboxylates were also found by EPR method [113]. The pH-metric results published in Refs. [114] and [115] are inconsistent with these results, as they did not reflect the existence of dimeric complexes in solution. Due to these conflicting results the calculated equilibrium constants of analogous complexes were also different and are not comparable. Recently, we published a combined potentiometric and spectroscopic study on the Cu(II) aldonic acid systems [116]. Mainly alkoxo bridged dimeric complexes were found above pH 5 with the composition of $[Cu_2L_2H_{-3}]^-$ and $[Cu_2L_2H_{-4}]^{2-}$, while a monomeric $[Cu(LH_{-1})_2]^{2-}$ species (Fig. 2), showing *cis-trans* isomerism, formed at high ligand excess. The metal-to-carbon distances, extracted from ^{13}C-NMR relaxation parameters, reflected chelated coordination through the carboxylate and the deprotonated α-hydroxy groups, while the C(4)–OH group came to an appropriate distance for hydrogen bonding to an axially bonded water molecule in the latter complex. Friedman et al. [117] have studied the Cu(II)–GlcA–amino acid mixed ligand complexes.

Table 2
Stability constants for the proton[a] and metal ion complexes of selected carbohydrate ligands[b]

Fru		*pqr*	*11-2*	*11-3*	*11-4*									
	$Me_2Sn(IV)$	logβ	−7.18	−15.46	−26.43									[478]
Glu		*pqr*	*11-3*	*11-4*										
	$Me_2Sn(IV)$	logβ	−16.88	−28.08										[478]
Rib		*pqr*	*11-3*	*12-4*										
	$Me_2Sn(IV)$	logβ	−15.72	−24.90										[483]
dRib		*pqr*	*11-3*	*12-4*										
	$Me_2Sn(IV)$	logβ	−17.22	−27.09										[483]
Mal		*pqr*	23-4	*23-6*										
	Mn(II)	logβ	27.2											[278][e]
	Mn(III)	logβ		52.5										[278][c]
GlcA		*pqr*	*110*	*120*	*12-1*	*12-2*	*11-1*	*11-2*	*11-3*	*13-1*	*13-2*	*22-3*	*22-4*	*011*	
	Cu(II)	logβ	2.51	4.59	−0.60	−8.28	–	–	−20.96	–	–	−7.25	−15.46	3.50	[116]
	Cu(II)	logβ	3.02	6.08	0.53	–	–	−11.96	–	–	–	−6.58	–	3.40	[112][c]
	Fe(III)	logβ	3.55	–	–	–	2.43	−0.80	−5.18	–	–	–	–	3.66	[209][c]
	Co(II)	logβ	–	–	–	–	−4.96	−13.29	–	−1.27	−9.21	−17.89	–	3.40	[321][c]
	Ni(II)	logβ	–	–	–	−11.55	–	–	–	–	−9.62	−16.80	–	+	[321][c]
	Cd(II)	logβ	2.3	–	–	–	–	−15.7	–	–	–	–	–	3.40	[546][c]
	Hg(II)	logβ	–	–	–	–	−0.09	−4.03	–	–	–	–	–	+	[546][c]
	Al(III)	logβ	–	–	–	–	−0.84	–	−10.70	–	–	–	–	3.40	[459][c]
	Al(III)	logβ	1.98	–	–	–	−0.89	–	−10.18	–	–	–	–	3.44	[458]
	Ga(III)	logβ	–	–	–	–	–	−2.83	−8.94	–	–	–	–	+	[459][c]
	In(III)	logβ	–	–	–	–	–	–	−9.21	–	–	–	–	+	[459][c]
	Pb(II)	logβ	2.49	–	–	–	–	−11.78	–	–	–	−10.66	–	+	[546][c]
RibA		*pqr*	*110*	*120*	*12-1*	*12-2*	*11-1*	*11-2*	*11-3*	*22-3*	*22-4*	*011*			
	Cu(II)	logβ	2.60	5.00	−1.03	−8.78	–	–	−20.74	−7.96	−16.17	3.78			[116]
	Cu(II)	logβ	3.52	6.10	0.01	–	–	−11.85	–	−7.26	–	4.02			[112][c]
	Fe(III)	logβ	3.43	–	–	–	–	2.86	−0.50	−4.89	–	3.88			[209][c]
	Co(II)	logβ	3.07	–	–	–	−1.72	–	–	–	–	4.02			[321][c]
	Ni(II)	logβ	2.28	4.86	–	–	–	−14.38	–	–	–	+			[321][c]
GlupA		*pqr*	*110*	*11-1*	*11-2*	*12-1*	*011*								
	Cu(II)	logβ	–	–	–	−3.03	3.06								[119]
	Fe(III)	logβ	3.98	0.90	−4.19	–	3.41								[209][c]

Table 2 (*Continued*)

GalpA		*pqr*	*110*	*120*	*130*	*11-1*	*11-2*	*12-1*	*12-2*	*12-3*	*12-4*	*13-2*	*13-3*	*011*	
	Cu(II)	logβ	–	3.0	–	–	–	−3.02	−10.06	–	−29.69	–	–	3.15	[119][f]
	Cu(II)	logβ	3.39	5.99	–	−2.60	–	–	–	–	–	–	–	3.15	[213][f]
	Fe(II)	logβ	3.09	5.58	–	–	–	–	–	–	–	–	–	3.15	[212][f]
	Fe(III)	logβ	3.89	–	–	1.07	−3.41	–	–	–	–	–	–	3.43	[209][c]
	Fe(III)	logβ	–	–	8.51	–	–	–	–	–	–	1.54	−2.03	3.15	[210][f]
	Ni(II)	logβ	1.04	–	–	–	–	–	–	–	–	–	–	3.15	[214][f]
	V(IV)O	logβ	–	–	–	–	–	0.47	−4.01	−12.98	−22.91	–	–	3.28	[119]
	Cd(II)	logβ	1.52	–	–	–	–	–	–	–	–	–	–	+	[214][f]
	Pb(II)	logβ	2.50	–	6.30	–	–	–	–	–	–	–	–	+	[214][f]
	$U(VI)O_2$	logβ	–	6.19	6.30	–	–	–	−2.03	–	–	–	−4.72	+	[214][f]
diGalpA		*pqr*	*110*	*111*	*011*	*012*									
	Cu(II)	logβ	2.49	5.71	3.61	6.49									[168]
triGalpA		*pqr*	*110*	*111*	*22-1*	*011*	*012*	*013*							
	Cu(II)	logβ	3.38	6.32	4.01	3.88	7.08	9.72							[168]
LacbA		*pqr*	*110*	*120*	*12-1*	*12-2*	*12-3*	*12-4*	*11-1*	*11-2*	*11-3*	*011*			
	Cu(II)	logβ	2.28	5.40	−0.44	−6.29	–	−27.14	–	−8.64	–	3.53			[130][c]
	Cu(II)	logβ	–	5.33	−0.61	−7.28	–	−27.51	–	–	–	3.53			[128]
	Cu(II)	logβ	–	5.46	−0.43	−7.05	–	−27.06	–	–	–	3.53			[129]
	Fe(III)	logβ	–	–	–	–	–	–	2.03	−1.86	−11.79	3.53			[220][c]
	Co(II)	logβ	–	–	–	–	–	–	–	−15.64	–	+			[130][c]
	Ni(II)	logβ	2.13	–	–	–	–	–	–	−13.77	–	+			[130][c]
	V(IV)O	logβ	–	6.07	2.32	−1.92	−10.31	−18.56	–	–	–	+			[129]
	Cd(II)	logβ	–	–	–	–	–	–	–	−15.54	–	+			[130][c]
	Hg(II)	logβ	–	–	–	–	–	–	−0.29	−6.64	–	+			[130][c]
$GlcNH_2$		*pqr*	*110*	*120*	*12-1*	*12-2*	*12-3*	*011*							
	Cu(II)	logβ	6.12	8.85	–	–	–	7.70							[136][be]
	Cu(II)	logβ	3.06	8.76	0.83	−5.82	−15.08	7.70							[135][e]
	Co(II)	logβ	2.30	4.95	–	–	–	7.70							[138][d,e]
	Co(II)	logβ	–	4.09	−3.89	−13.08	–	+							[136][d,e]
	Ni(II)	logβ	2.95	5.62	–	–	–	+							[138][d,e]
	Ni(II)	logβ	–	6.43	−3.03	−12.13	–	+							[136][d,e]
$AglcNH_2$		*pqr*	*240*	*12-1*	*12-2*	*011*									
	Cu(II)	logβ	18.6	0.71	−8.05	7.07									[141][e]

Table 2 (*Continued*)

$MeGlcNH_2$		*pqr*	*110*	*120*	*12-1*	*12-2*	*011*							
	Cu(II)	logβ	4.13	7.52	1.38	−6.85	7.67							[145][e]
	Co(II)	logβ	2.93	–	−1.95	−10.77	+							[145][e]
	Ni(II)	logβ	3.10	–	−2.59	−12.13	+							[145][e]
$GalNH_2$		*pqr*	*110*	*120*	*12-1*	*12-2*	*12-3*	*011*						
	Cu(II)	logβ	4.20	9.13	2.37	−5.21	−15.44	7.84						[137][e]
	Cu(II)	logβ	5.23	9.02	–	–	–	7.84						[138][d,e]
	Co(II)	logβ	–	6.50	–	−12.01	–	+						[137][e]
	Ni(II)	logβ	3.16	5.96	−3.08	−12.45		+						[137][e]
	Ni(II)	logβ	2.70	5.05	–	–	–	+						[138][d,e]
$MeGalNH_2$		*pqr*	*110*	*120*	*12-1*	*12-2*	*011*							
	Cu(II)	logβ	4.40	8.40	2.27	−5.18	7.75							[140][e]
$diGalNH_2$		*pqr*	*110*	*11-1*	*12-1*	*12-2*	*011*	*012*						
	Cu(II)	logβ	5.75	−1.04	2.30	−6.0	8.15	15.27						[168][e]
$ManNH_2$		*pqr*	*110*	*120*	*12-1*	*12-2*	*12-3*	*011*						
	Cu(II)	logβ	–	9.68	2.72	−3.66	−13.0	7.59						[140][e]
	Cu(II)	logβ	7.00	10.4	–	–	–	7.59						[139][d,e]
	Co(II)	logβ	–	–	–	−11.66	–	+						[140][e]
	Co(II)	logβ	2.50	5.70	–	–	–	+						[139][d,e]
	Ni(II)	logβ	–	6.11	−2.49	−11.08	–	+						[140][e]
	Ni(II)	logβ	3.20	5.85	–	–	–	+						[139][d,e]
$MeManNH_2$		*pqr*	*110*	*12-1*	*12-2*	*12-3*	*12-4*	*011*						
	Cu(II)	logβ	4.81	2.91	−4.29	−13.4	−23.7	7.47						[140][e]
$AmeManNH_2$		*pqr*	*110*	*120*	*12-1*	*12-2*	*011*							
	Cu(II)	logβ	3.88	8.01	1.88	−5.72	7.49							[142][e]
RS-abto		*pqr*	*22-2*	*22-3*	*22-4*	*011*								
	Cu(II)	logβ	0.54	−7.84	−16.68	9.34								[146]
RSR-aptto		*pqr*	*22-2*	*22-3*	*22-4*	*011*								
	Cu(II)	logβ	1.32	−5.53	−13.79	9.33								[146]
RRS-dapto		*pqr*	*22-1*	*22-2*	*22-3*	*22-4*	*011*	*012*						
	Cu(II)	logβ	16.3	10.9	2.64	−6.98	8.67	18.30						[147]
Taci		*pqr*	*110*	*120*	*121*	*22-2*	*12-1*	*12-2*	*12-3*	*12-4*	*12-5*	*011*	*012*	*013*	
	Cu(II)	logβ	12.1	18.79	24.60	12.0	–	–	–	–	–	8.90	16.30	22.25	[42]
	Fe(II)	logβ	6.40	11.18	–	–	–	–	–	–	–	8.90	16.30	22.25	[50]

Table 2 (*Continued*)

	Mn(II)	logβ	4.0	–	–	–	–	–	–	–	–	+	+	+	[50]
	Co(II)	logβ	9.10	15.64	–	–	–	–	–	–	–	+	+	+	[42]
	Ni(II)	logβ	12.37	20.94	–	–	–	–	–	–	–	+	+	+	[42]
	Zn(II)	logβ	8.40	13.56	–	–	–	–	–	–	–	+	+	+	[42]
	Cd(II)	logβ	6.48	10.95	–	–	–	–	–	–	–	+	+	+	[44]
	Al(III)	logβ	11.8	18.8	25.3	–	10.7	1.63	−7.45	−17.16	–	8.90	16.30	22.25	[45]
	Ga(III)	logβ	16.5	25.7	19.4	–	18.33	9.62	0.15	−9.38	−21.02	+	+	+	[45]
Tdci		*pqr*	*110*	*120*	*111*	*121*	*122*	*123*	*11-1*	*011*	*012*	*013*			
	Cu(II)	logβ	–	–	15.2	–	30.2	35.9	2.26	9.95	18.02	24.47			[225]
	Fe(III)	logβ	18.8	32.6	–	37.1	–	–	–	+	+	+			[225]
	Al(III)	logβ	14.31	26.4	–	30.6	–	–	8.9	+	+	+			[225]
Ino(1,4,5)tp		*pqr*	*110*	*120*	*111*	*112*	*011*	*012*	*013*	*014*					
	Ca(II)	logβ	4.59	7.22	12.20	18.44	8.74	15.76	21.56	24.17					[87]
Ino(1,3,5)tp		*pqr*	*110*	*111*	*11-1*	*210*	*211*	*011*	*012*	*013*	*014*				
	Cu(II)	logβ	6.25	13.26	−2.07	–	17.21	8.05	15.04	21.05	23.68				[88]
	Fe(III)	logβ	12.86	19.35	–	23.21	–	+	+	+	+				[88]
	Fe(II)	logβ	5.02	–	−3.21	9.77	16.22	+	+	+	+				[88]
	Zn(II)	logβ	5.45	12.30	−3.58	–	15.84	+	+	+	+				[88]
Ino(2,4,6)tp		*pqr*	*110*	*111*	*11-1*	*210*	*211*	*320*	*011*	*012*	*013*	*014*			
	Cu(II)	logβ	7.21	–	−1.32	12.77	17.49	–	8.20	15.04	20.85	23.49			[88]
	Fe(III)	logβ	13.52	–	–	25.05	–	42.86	+	+	+	+			[88]
	Fe(II)	logβ	5.85	–	−2.33	10.60	16.85	–	+	+	+	+			[88]
	Zn(II)	logβ	6.40	12.86	−1.89	–	16.77	–	+	+	+	+			[88]
AmetGAL		*pqr*	*110*	*120*	*130*	*111*	*121*	*11-2*	*22-2*	*22-3*	*12-1*	*12-2*	*011*	*012*	
	Cu(II)	logβ	10.1	17.2	–	13.63	22.2	−6.28	10.67	0.77	7.45	–	9.50	15.93	[167]
	Ni(II)	logβ	6.81	12.57	14.77	11.79	–	−12.31	−1.37	−11.03	2.97	−8.40	+	+	[167]
	Ni(II)	logβ	6.01	10.70	–	–	–	–	–	–	–	–	9.48	15.87	[436][c]
	Zn(II)	logβ	5.13	9.91	12.14	11.01	–	−12.06	−2.72	−11.91	0.86	−10.25	+	+	[167]
	Cd(II)	logβ	4.54	8.41	–	–	–	–	–	–	–	–	+	+	[436][c]
Glugly		*pqr*	*110*	*120*	*11-1*	*11-2*	*11-3*	*22-3*	*22-4*	*011*					
	Cu(II)	logβ	1.94	3.51	−3.82	−9.63	−20.01	−10.20	−16.63	3.39					[157]
	Et_2Sn(IV)	logβ	2.36	–	−0.96	−5.42	−15.78	–	–	+					[480]
	Me_2Sn(IV)	logβ	2.34	–	−0.96	−6.16	−16.35	–	–	3.39					[547]

Table 2 (*Continued*)

Fru–gly		*pqr*	*110*	*120*	*111*	*11-1*	*12-1*	*12-2*	*011*	*012*					
	Cu(II)	logβ	7.38	13.26	9.89	1.90	–	–	8.10	10.16					[163]
	Ni(II)	logβ	4.97	8.97	–	–	1.37	−8.25	+	+					[163]
Fru-β-ala		*pqr*	*110*	*120*	*111*	*11-1*	*12-1*	*12-2*	*011*	*012*					
	Cu(II)	logβ	6.31	–	10.5	2.06	–	–	8.74	12.06					[163]
	Ni(II)	logβ	4.13	7.92	–	–	−0.33	−10.02	+	+					[163]
$GlcANH_2$		*pqr*	*110*	*120*	*111*	*122*	*12-1*	*12-2*	*12-3*	*22-3*	*22-4*	*210*	*011*	*012*	
	Cu(II)	logβ	8.12	14.67	11.1	22.28	5.23	−4.94	–	−3.22	−13.03	–	9.02	11.26	[116]
	Cu(II)	logβ	7.72	14.39	–	–	4.88	−5.12	–	–	–	–	9.19	11.76	[150][f]
	Cu(II)	logβ	8.07	14.76	–	–	–	–	–	–	–	–	9.08	11.28	[149][g]
	Co(II)	logβ	4.35	8.04	–	–	–	–	–	–	–	–	+	+	[149][g]
	Ni(II)	logβ	6.54	12.33	–	–	4.99	−2.65	−11.86	–	–	–	+	+	[150][f]
	Ni(II)	logβ	5.39	9.85	–	–	–	–	–	–	–	–	+	+	[149][g]
	Zn(II)	logβ	4.63	8.64	–	–	–	–	–	–	–	–	+	+	[149][g]
	Cd(II)	logβ	4.69	9.39	–	–	0.97	–	–	–	–	7.48	+	+	[150][f]
	Pb(II)	logβ	5.08	9.53	–	–	1.28	−6.84	−16.34	–	–	–	+	+	[150][f]
	UO(VI)	logβ	7.01	13.36	–	–	–	–	–	–	–	–	+	+	[150][f]
AGGHA		*pqr*	*110*	*120*	*111*	*122*	*11-1*	*011*							
	Cu(II)	logβ	7.75	14.28	–	22.29	–	8.85							[152]
	Co(II)	logβ	4.20	7.85	–	21.70	–	+							[152]
	Ni(II)	logβ	4.93	9.50	–	21.73	–	+							[152]
	Zn(II)	logβ	4.62	8.10	–	22.46	−4.52	+							[152]
	Cd(II)	logβ	4.25	7.08	11.97	–	–	+							[152]
BnAGGHA		*pqr*	*110*	*120*	*121*	*122*	*11-1*	*011*							
	Cu(II)	logβ	7.11	13.13	–	21.4	–	8.20							[153]
	Co(II)	logβ	3.73	6.70	–	20.8	−4.57	+							[153]
	Ni(II)	logβ	4.02	7.97	–	–	–	+							[153]
	Zn(II)	logβ	3.88	6.33	–	20.8	−5.4	+							[153]
	Cd(II)	logβ	3.23	5.83	–	21.13	–	+							[153]
	Hg(II)	logβ	5.41	9.78	16.51	21.6	−1.80	+							[153]
Laracys		*pqr*	*110*	*120*	*12-1*	*12-2*	*22-1*	*22-2*	*22-4*	*011*	*012*				
	Mn(II)	logβ	2.43	–	–	–	−0.32	−9.41	−29.66	5.50	6.93				[280]
	Ni(II)	logβ	5.94	9.79	0.09	–	–	–	–	+	+				[280]
	Zn(II)	logβ	4.19	7.13	−0.18	−9.28	–	–	–	5.50	6.93				[323]
Daracys		*pqr*	*110*	*120*	*12-1*	*12-2*	*22-1*	*22-2*	*22-4*	*011*	*012*				
	Mn(II)	logβ	1.92	–	–	–	−0.59	−10.17	−30.77	5.37	6.84				[280]

Table 2 (*Continued*)

	Ni(II)	logβ	3.19	5.74	−2.65	−12.19	–	–	–	+	+			[280]
	Zn(II)	logβ	2.9	5.02	−1.46	−9.27	–	–	–	5.37	6.84			[323]
Galcys		*pqr*	*110*	*120*	*111*	*11-1*	*12-1*	*12-2*	*22-1*	*22-2*	*22-4*	*011*	*012*	
	Mn(II)	logβ	2.31	–	–	–	–	–	−0.66	−10.30	−30.40	5.53	6.96	[280]
	Zn(II)	logβ	4.01	6.93	–	–	−0.94	−9.20	–	–	–	5.53	6.96	[323]
	Et_2Sn(IV)	logβ	5.33	–	8.24	1.01	–	–	–	–	–	5.53	6.96	[481]
Galurcys		*pqr*	*110*	*120*	*111*	*11-1*	*11-2*	*12-1*	*12-2*	*22-1*	*22-2*	*011*	*012*	*013*
	Co(II)	logβ	4.10	6.65	7.12	–	–	–	–	–	–	5.67	9.06	10.56	[279]
	Ni(II)	logβ	5.41	9.09	8.70	–	–	–	–	–	–	+	+	+	[279]
	Zn(II)	logβ	4.08	5.83	7.32	−3.75	−12.51	−1.56	−10.75	–	–	+	+	+	[279]
	Ca(II)	logβ	1.61	–	–	–	–	–	–	–	–	+	+	+	[279]
		pqr	*110*	*120*	*111*	*11-1*	*12-1*	*12-2*	*12-3*	*22-1*	*22-2*	*22-3*	*22-4*	*22-5*	
	Mn(II)	logβ	2.27	–	–	–	–	–	–	0.77	−10.43	−19.31	−30.19	–	[279]
	V(IV)O	logβ	5.73	9.88	8.33	2.14	4.34	−2.40	−11.89	–	–	1.46	−4.96	−13.68	[279]
Rutin		*pqr*	*110*	*111*	*112*	*120*	*112*	*121*	*122*	*123*	*124*	*012*	*013*	*014*	
	Cu(II)	logβ	–	–	–	23.51	28.51	33.13	41.23	48.61	55.72	10.04	18.34	25.29	[548][c]
	Co(II)	logβ	8.23	17.37	25.03	–	–	–	–	–	–	+	+	+	[548][c]

[a] The protonation constants for the ligands are only given at the first occasion when a reference occurs in the table. The + signs stem for the protonation constants already given.

[b] Most of the data were determined by pH-metric titration ($I = 0.1$, $T = 25$°C). In each case the overall stability constant, β_{pqr} corresponds to the following equilibrium process:

$$\beta_{M_pL_qH_{-r}} = \beta_{M_pL_q(OH)_r} \cdot K_W^r = \frac{[M_pL_qH_{-r}][H]^r}{[M]^p[L]^q} = \frac{[M_pL_q(OH)_r]K_W^r}{[M]^p[L]^q[OH]^r}$$

(Charges are omitted for simplicity; M denotes the metal ion and L the non-protonated ligand molecule.)

[c] $T = 20$°C.

[d] Polarography.

[e] $I = 0.15$.

[f] $I = 1.0$.

[g] $I = 0.05$.

Table 3
Generalized binding mode and proposed coordination geometry for metal ion carbohydrate complexes[a]

Metal ion	Coord. Number	Coordination geometry	Binding mode
Alkaline	6, 9	Octahedral	Mono and polyol
Mg	6	Octahedral	Mono and *cis*-diol
Ca	7, 8	Variable	Mono and polyol
Ln	8, 9	Variable	Mono and polyol
Mn	6	Dist. octahedral	*Cis*-diol, triol
Ni	6	Octahedral	*Cis*-diol, triol
Cu	6	Dist. octahedral	*Cis*-diol, triol
Fe	6	Dist. octahedral	*Cis*-diol, triol
Zn	4, 6	Planar, octahedral	*Cis*-diol
Cd	6	Octahedral	*Cis*-diol
Ag	2	Linear	Monodentate
Hg	4	Tetrahedral	*Cis*-diol
Al	6	Octahedral	Polyol
B	4	Tetrahedral	*Cis*-diol
$R_x(Sn)$	4, 5, 6	Tetrahedral	*Cis*-diol
		Trigonal bpy.	*Cis*-diol, triol
		Octahedral	*Cis*-diol, triol
Sn^{2+}	3	Pyramidal	Monodentate
Sn^{4+}	6	Octahedral	*Cis*-diol
VO^{2+}	5	Pyramidal	*Cis*-diol
VO_4^{3-}	4, 5	Tetrahedral	
		Bipyramidal	Mono and *cis*-diol, *cis*-triol
UO_2^{2+}	6	Bipyramidal	*Cis*-diol, triol
MoO_2^{2+}	6	Octahedral	*Cis*-diol, triol
WO_2^{2+}	6	Octahedral	*Cis*-diol, triol

[a] The data were partly adapted from [15].

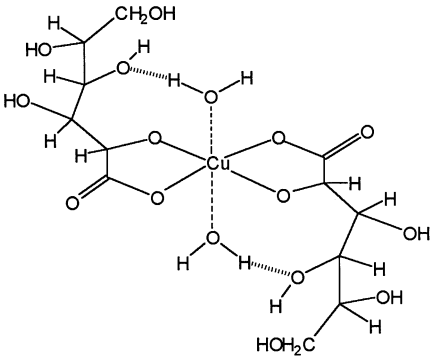


Fig. 2. The proposed structure of the *trans* $[Cu(LH_{-1})_2]^{2-}$ species formed in the Cu(II)–GlcA system containing high ligand excess [116].

The interaction of Cu(II) with uronic acids like GlupA and GalpA (Fig. 3) has been studied by potentiometry [112,118–120], CD [121], spectrophotometry [122], calorimetry [123], polarography [119,124,125], NMR [126] and EPR [119,120] methods. An average Cu–O bond distance has also been measured to be 196 pm by EXAFS spectroscopy [127]. Generally it was stated that while aldonic acids keep Cu(II) in solution in wide pH range, the precipitation of the hydrolysed metal occurs in the presence of uronic acids around pH 7–8. The proposed models for the calculation of stability constants are contradictory [112,119] and also the binding sites could not be established, although the assignment of the carboxylate as coordinating group is conclusive. From the differences in the stabilities of GlupA and GalpA complexes the supporting coordination of C(4)–OH was proposed [112]. In Refs. [118], [121] and [122] the monodentate carboxylate coordination to Cu(II) was assumed, but in Refs. [121] and [122] it was mentioned that a multiple equilibrium is present at pH 5. On the basis of comparative thermodynamic data, Aruga [123] postulated that at pH 4.3 the ligand coordinated in a bidentate manner: directly via the carboxylate group and by the endocyclic oxygen of the sugar ring through an outer sphere electrostatic bond. Two models were proposed for bis-complexes in Ref. [127]: in the first model the ligands are coordinated through the ring oxygen and the glycosidic hydroxy groups, in the second one through the C(3) and C(4) hydroxy groups, while the carboxylate group did not participate in the coordination in both models. According to the differential line broadening analysis of ^{13}C-NMR spectra the primary coordination of Cu(II) to the carboxylate, and above pH 4 also to the endocyclic oxygen was proposed. Cu(II) in this complex catalysed the mutarotation of the ligand. This process led to the observation of a 'time averaged complex' with the ligand coordinated by C(3)–OH, C(5)–OH and the carboxylate groups [126].

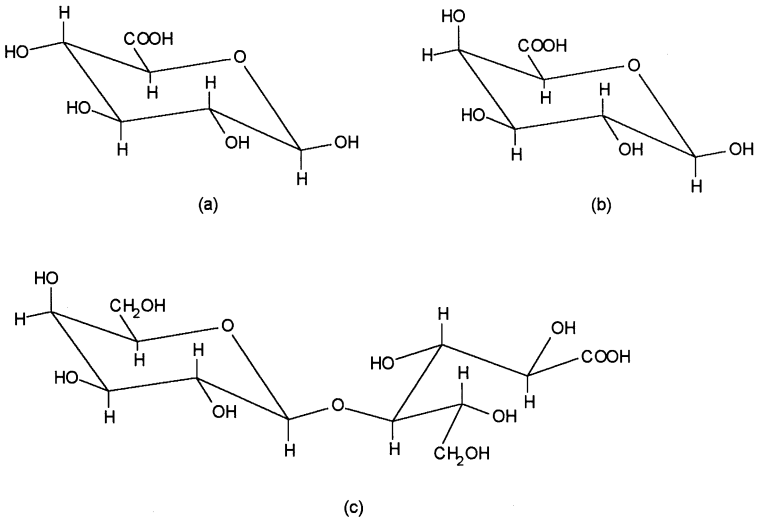
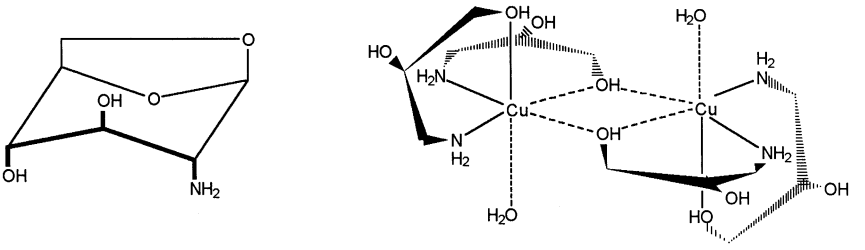


Fig. 3. The schematic structure of (a) GlupA, (b) GalpA and (c) LacbA.

LacbA (Fig. 3) has an unusually high ability to coordinate Cu(II) ion. Since the carboxyl group is not a very effective donor, the metal interaction with the set of the non deprotonated hydroxy groups increases the complex stability. Mainly bis complexes were shown to form in different protonation states the deprotonation processes starting from pH 6 [128–130]. In contrast Co(II), Ni(II), Cd(II) and Hg(II) formed only complexes with M:L = 1:1 composition [130]. The Cu(II)–$GlcNH_2$–LacbA ternary system has also been studied [131].

Large number of papers have been published on the Cu(II) complexes formed with amino sugars [132–144]. It was shown that all the monomeric amino sugars act as bidentate ligands with the amino group as the main donor towards Cu(II). The second donor centre derives from one of the aminosugar hydroxy groups. In case of $GlcNH_2$ and $GalNH_2$ it appears to be the C(1)–OH which binds to the metal ion. The results obtained for $MeGlcNH_2$ with this hydroxy group blocked indicated, however, that other hydroxy groups may also be involved in the metal ion coordination [145]. Potentiometric and spectroscopic studies on the coordination ability of $ManNH_2$ [140] have shown that this ligand is more effective in sequesting the Cu(II) ions than $GluNH_2$ or $GalNH_2$ [137,138]. Aminosugar complexes in minor concentration, not seen by the potentiometric titration, were detected by polarography [138,139].

The 4-aminobutanetriols and 5-aminopentanetetrols coordinated to Cu(II) via amino nitrogen and the adjacent deprotonated hydroxy group, the latter acting as a bridge between two metal ions giving stable, EPR-silent dialkoxo-bridged dimeric species [146]. The dimers formed with 1,5-diaminopentanetriols and 1,6-diaminohexanetetrols are also EPR silent, however, here the two Cu(II) ions are bridged by the two ligand molecules, being at a much larger distance than in the case of a dialkoxo-bridge [147]. The 1,6-anhydro derivatives of amino sugars formed very specific EPR inactive dimeric complexes of the type $[Cu_2L_4]^{4+}$ (Fig. 4) even in slightly acidic or neutral solutions [141]. The local structure of dimeric species was determined by EXAFS [144] to be similar to the dimeric species with tetradentate coordination mode in Cu(II) xylitol system above pH 5 [107].



(a) (b)

Fig. 4. The schematic structure of (a) $AGlcNH_2$ and the local structure of (b) its $[Cu_2L_4]^{4+}$ dimeric species [144].

$GlcANH_2$ formed amino acid type $[ML_2]$ complexes at physiological pH [116,148–150] with a series of transition metal ions. The complexes are more stable than those of e.g. alanine suggesting the supplementary coordination of non-deprotonated alcoholic hydroxy groups. Similarly to the amino sugars this ligand also coordinates to Cu(II) by the amino and the adjacent deprotonated hydroxy groups in bis-complexes at pH 10.7. The additional coordination of the carboxylate oxygen was suggested presumably in the axial position [151]. In equimolar solutions dimeric species were also observed [116]. Amino derivatives of aldoheptonic acids formed amino acid type complexes with Cu(II), Ni(II), Co(II), Zn(II) and Cd(II) ions [152–155].

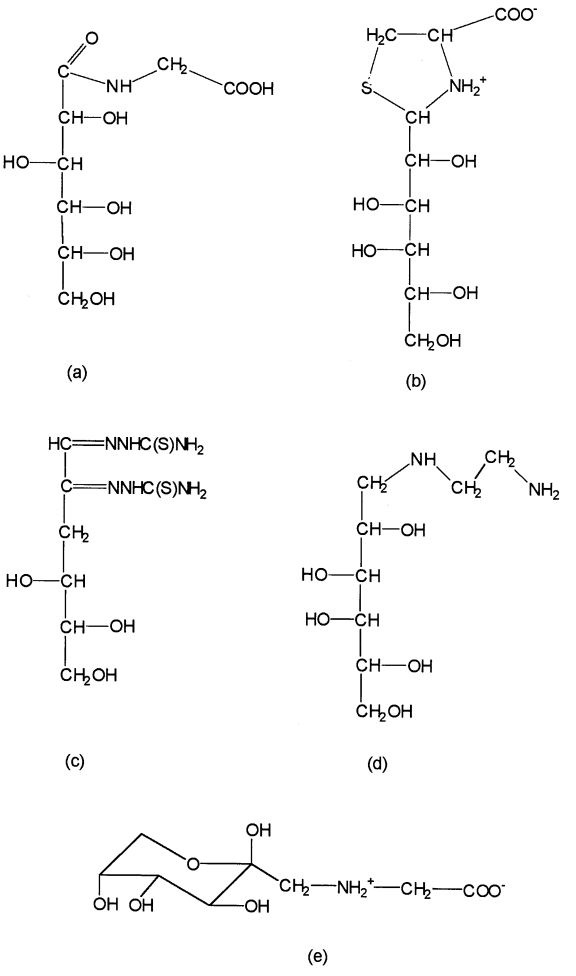


Fig. 5. The schematic structure of some carbohydrate derivatives: (a) Glugly, (b) Galcys, (c) Glc bis(thiosemicarbazone), (d) AmetGAL and (e) Fru–gly

A number of *N*-D-gluconylamino acids (Fig. 5a)-pseudopeptide derivatives of D-glucono-1,5-lactone and amino acids-were prepared to obtain suitable chelating agents for Cu(II) [156]. The X-ray diffraction measurements of the Glu-β-ala showed that there is no lactonization in the ligand molecule. The Cu(II) ion and Glugly formed carboxylate and non deprotonated alcoholic hydroxy coordinated parent ($[CuL]^+$, $[CuL_2]$) complexes with low stabilities in acidic medium. Between pH 5 and 9 beside the carboxylate the deprotonated amide and the hydroxy group, in α-position to the amide, also coordinated to the metal ion in either monomeric $[CuLH_{-2}]^-$ or EPR silent dimeric $[Cu_2L_2H_{-4}]^{2-}$ species [157].

Amino acids readily react with Glc to give "fructose-amino acids" as a results of Amadori rearrangement. Such compounds form in the digestive tract and during the cooking of food, therefore having a great biological significance. They also affect the bioavailability of bulky and trace metals [158] including Ca(II) [159] and Zn(II) [160]. Terasawa et al. [161] studied the Cu(II) chelation by the fractions of the reaction products with glycine, while Rendleman et al. [162] have shown that the Cu(II) ion has a great influence on the reaction rate of glycine and Glc in vitro. Later it was demonstrated [163] that beside the amino acid type coordination the non deprotonated alcoholic hydroxy groups also participated in the complex formation. The deprotonation of the alcoholic hydroxy groups was detected in $[CuLH_{-1}]$ species already at pH 5. The presence of ligand excess, however, prevented this process by the formation of $[CuL_2]$ complexes as the species distribution shows (Fig. 6). Similarly, bis amino acid type coordination was proposed to Cu(II) in solid state for both the fructose-amino acid and PHTAc (the adducts of monosaccharides with L-cysteine) derivatives (Fig. 5b) on the basis of IR and NMR results [164,165]. The carbohydrate part of Gal and Glc bis(thiosemicarbazone) derivatives (Fig. 5c) also remained uncoordinated in Cu(II) and Ni(II) complexes [166].

In the Cu(II) AmetGAL (Fig. 5d) system ethylenediamine type coordination was found in very stable $[CuL_2]^{2+}$ species. However, the increase of the pH above 8 resulted in the displacement of one of the ligands from the coordination sphere in parallel with the deprotonation of the carbohydrate hydroxy groups. The formation of dialkoxo-bridged dimeric species was detected in equimolar solutions [167].

It was shown that the di-sugars (e.g. digalactosamine, or digalacturonic acid) bound less efficiently the metal ions than the monomeric units, while the trimeric ligands can probably simultaneously use terminal subunits to coordinate a metal ion [168].

The Cu *K*-edge EXAFS and XANES methods have been applied to determine the structure of the Cu(II) complexes of Rib and $GlcNH_2$ in alkaline solution [143,169], of adenosine and uridine at different hydrogen ion concentration in mixed water–DMSO solvent [170], of ATP in solution [171], of Glugly [172], of GlupA [127] in solution or in solid state, of $AGlcNH_2$ in solution [144], of *N*-glycoside ligands (derived from aldoses and En) [173] and of Glc, Fru, Gal and Xyl in solid state [174]. The structural parameters obtained, together with data measured for other carbohydrate complexes, are collected in Table 1. All data indicated that the oxygen/nitrogen coordination geometry around the Cu(II) ion

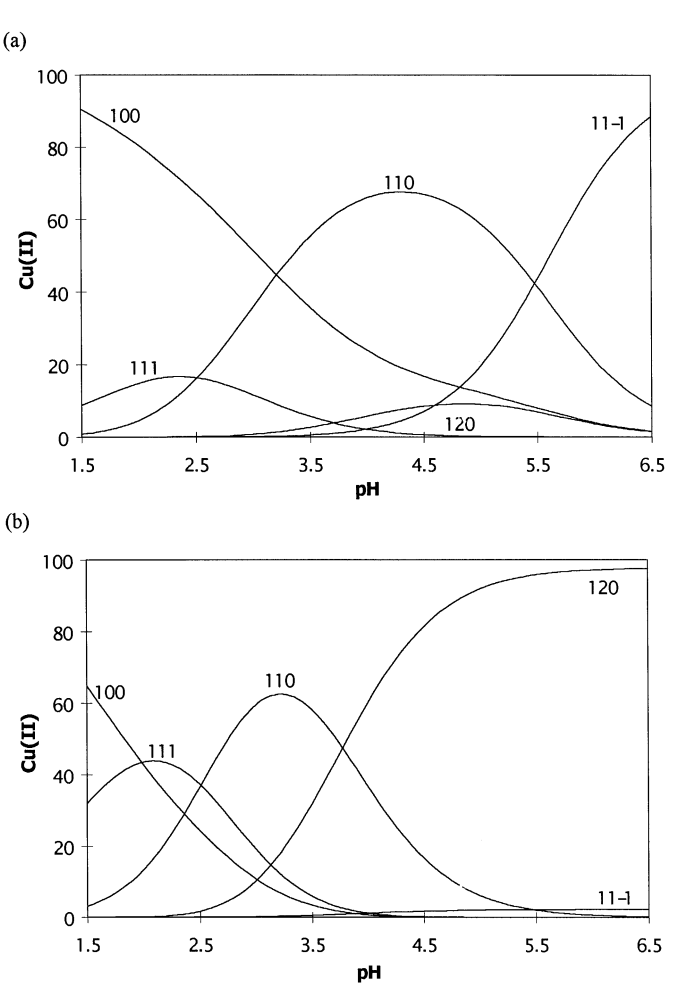


Fig. 6. The species distribution diagrams for the Cu(II):Fru–gly 1:1 (a) and 1:5 (b) systems ($c_{Cu(II)} = 0.008$ M. The complexes are denoted as *pqr* according to the formula $[Cu_p(Fru–gly)_qH_r]$) [163].

(distorted elongated octahedral or rhombic structure), and the Cu–O/N bond lengths within the complexes are not very different from those for the hexaaqua Cu(II) ion ($d(Cu–O_{eq}) = 192$ pm, $d(Cu–O_{ax}) = 230$ pm). EXAFS Fourier transform curves clearly showed a peak ascribed to non-bonding Cu···C distances (270–275 pm), indicating the formation of chelate rings around the Cu(II) ion, and in cases of dimeric (or oligomeric) complexes, additionally the Cu···Cu distances. (Sometimes the overlapping peaks prevent the determination of the non-bonding Cu···Cu and Cu···C distances simultaneously [143]). The dimerization usually occurred through μ-hydroxo bridges ($d(Cu···Cu) = 295$ pm), although the dimer formation with involvement of the non deprotonated hydroxy groups has been postulated for complexes formed with simple polyol ligands [107,144,175]. The formation of

dimeric species via hydroxide ions or deprotonated alcoholic hydroxy groups resulted in strong antiferromagnetic interaction between central ions, in EPR 'silent' solutions [143,170]. Other examples for association complexes have been reported for Cu(II)-β-cyclodextrin complexes by Matsui et al. [176]. If-instead of sodium hydroxide-lithium hydroxide was used for alkalization of solution, blue crystals were obtained with varying water content by adding ethanol. The complex proved to be tetranuclear, where the Cu(II) ions bound to oxygen atoms of β-cyclodextrin in distorted square-planar coordination geometry forming a double torus structure [177]. The complexation of α-cyclodextrin to copper(II) also depends on the counterion used to neutralize the complex anion, namely $M_6[Cu_3(LH_{-6})_2]$ complexes were formed with $M = Na^+$ or Li^+ ions, while $M_4[Cu_2(LH_{-4})_2]$ with $M = K^+$ [178]. It was stated that the formation of a specific oligosaccharide-metal assembly strongly depends also on the competitive intramolecular hydrogen bonding in the ligand. In the polymeric complexes with erythritol and dulcitol [179] the metal ions were bridged by the organic ligands. A number of single crytals of monomeric Cu(II)- carbohydrate complexes were obtained by Klüfers et al. like the anionic complexes with methyl-α-D-mannopyranoside [180], with anhydro-erythritol and glycerol [181]. These monomeric units are able to associate through the counterions and/or hydrogen bonds. Twice deprotonated ligands coordinated to the metal ion in the Cu(II)-methyl-α-L-rhamnopyranoside [182] and Cu(II)-1,6-anhydro-β-D-glucose [183] bis complexes via the C(2)–O^- and C(3)–O^- in the former and C(2)–O^- and C(4)–O^- in the latter one. The O···O distances of the chelating donor groups in the above complexes have been reduced by 18 pm in the methyl-α-L-rhamnopyranoside complex, and by 38 pm in the 1,6-anhydro-β-D-glucose complex compared to the same distance in the free ligands, indicating the suprisingly enhanced flexibility of the bicyclic ligand. The interactions in the ammonia, Cu(II) and anhydro-erythritol or methyl-4-*O*-methyl-β-D-glucopyranoside [184] and En, Cu(II) and methyl-α-D-mannopyranoside [185] and *R,R-trans*-1,2-diaminocyclohexane, Cu(II) and methyl-β-D-xylopyranoside [186] ternary systems led to the formation of a $[Cu(NH_3)_2(LH_{-2})]$, $[Cu(En)(LH_{-2})]$ and [Cu(*R,R*-Chxn)(LH_{-2})] mixed ligand complexes, respectively, as major species at pH 12 (L denotes the sugar moiety). The sugar derivatives were coordinated as chelates through their deprotonated C(2)–O^- and C(3)–O^- hydroxy groups. The $d(Cu–O_{eq})$ and $d(Cu–O_{ax})$ bond lengths from the X-ray diffraction measurements were similar (ca. 195 and ca. 225 pm, respectively) to those mentioned above and obtained by the EXAFS method, the $d(Cu–N_{eq})$ being around 202 pm. In the bis complexes formed in more alkaline solutions the carbohydrate ligands coordinate exclusively [184].

Association complexes between transition metal ions and macromolecules in solution have been the subject of a number of studies either to elucidate the structural features of the polymers, by using the metal ions as probes, or to investigate model systems of naturally occurring compounds. The interaction of Cu(II) with ionic polysaccharides of natural origin is strongly influenced by many independent variables, e.g. by the chemical nature, composition, and charge density of the polysaccharides, the Cu(II):polymer ratio, the polymer concentration and the

ionic strength [187]. Polarographic investigations reflected the following sequence of Cu(II)-binding affinity for a series of polysaccharides: polyacrylate pectate > bacterial alginate ca. algal alginate > glucuronate-rich oligomers > alternating mannuronate-glucuronate oligomers > mannuronate-rich oligomers [188].

Previously a summary of the results obtained in metal ion containing glycosaminoglycan systems was given [14]. The binding of Cu(II) to the carboxylate groups of HyA has been demonstrated by spectrophotometry [121] and polarography [189] in 2:1 = HyA:Cu complex. The analysis of the ^{13}C and ^{1}H relaxation data for the Cu(II)–HyA complex indicated binding sites involving the carboxyl group and C(1)–O^- of the GlupA moiety [190], while the amide group of HyA was ruled out from the Cu(II) complexation [191]. The XANES spectra of the complex supported the latter observation [192]. Although tetragonal geometry of Cu(II)–HyA complex was proposed in Ref. [193], the recent EXAFS measurements unambiguously have shown the distorted octahedral structure (Fig. 7) [192]. The relatively large Debye–Waller factor obtained for the non-bonding Cu···C distances reflected the macrochelate coordination mode of HyA. By the investigation of Hya fragments obtained by enzymatic digestion, it was found that the interaction between the metal ion and HyA was less dependent on the degree of depolymerization than that between proton and HyA, indicating an almost negligible role of long range electrostatic forces in the Cu(II)–HyA interaction [194].

The attachment of different substituents to chitosan at the amine function led to the formation of attractive ligands for Cu(II). EPR measurements on the water soluble compounds have shown that all association complexes basically have tetragonal symmetry [195].

4.2. Iron complexes

Fe(III) ions may coordinate to the oxygen donor atoms of carbohydrates and their derivatives without the loss of the protons from the hydroxy groups of the ligand. The characterization of these equilibria by potentiometric measurement is not feasible because no Fe(III) ion selective electrode, suitable for this purpose, has been developed so far. The simultaneous deprotonation of alcoholic hydroxy groups of polyalcohols or sugars already in slightly acidic solutions due to the metal ion coordination, the formation of mixed hydroxo and polynuclear complexes

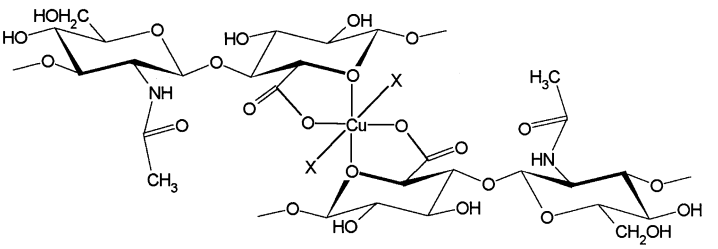


Fig. 7. The central part of the Cu(II)–HyA complex (X = water or methanol molecule) [192].

and/or the precipitation of hydrolyzed metal ion are pH-dependent processes and can be examined by potentiometric equilibrium measurements using a glass electrode, but also make the evaluation more complicated.

The chelating power of several polyhydroxy compounds for Cu(II), Co(II), Ni(II) and Fe(III) have firstly been compared by Weigel et al. [196]. It was shown that Fe(III) chelates to hexitols to a greater extent than the other three metal ions. Later Sarkar et al. demonstrated that Fe(III) forms a Fe:L = 1:1 complex with Fru even at pH 2.5 [197]. The stability constant of this complex was determined as $K_{app} > 1$, and the catalytic action of Fe(III) in the photochemically induced oxidation of the ligand with atmospheric oxygen was also observed in alkaline medium [198]. Both Fe(II) [199] and Fe(III) [200] were shown to form weak complexes with 2-deoxyribose at pH 7. It seems to be generally accepted that D-aldoses have low tendency to bind Fe(III) [201]. According to the spectrophotometric measurements, the composition of Fe(III) tartaric acid Sacc mixed ligand complex is 1:2:1 in strongly alkaline solution [202]. It was also found that the removal of various mono-, di-, and polysaccharides from aqueous solutions by adsorptive binding to precipitated Fe(III) hydroxide is very selective with respect to their stereochemistry and chain length [203].

Iron complexes with sugar acid ligands are potential pharmaceuticals, since their stability is high enough to prevent the hydrolysis of the metal ion in biological systems. The concentration distribution of Fe(II) complexes of different organic acids (among them GalpA and GlcA) showed that GalpA and malate were the most promising ligands in oral iron therapy [204]. The sequence of the relative stability of 1:1 Fe(III) complexes with polyhydroxy acids was found to be GlcA > GalA > GalpA > GlupA [205–208]. The equilibrium studies on Fe(III) complexes revealed that D-aldonic acids form mainly $[MLH_{-3}]^{-}$ species at physiological pH, while precipitation of Fe(III) hydroxide occurred above pH 4 in the presence of D-alduronic acids in 1:1 systems [209]. The determination of stability was further complicated by the extremely low free Fe(III) concentration in the solutions, thus a ligand competition method had to be used. Due to this and the different conditions, the published stability constants are not comparable.

The nature of the complexes formed in Fe(III)/Fe(II)–GalpA [210] and polygalacturonic acid [211] systems and the stoichiometry of the Fe(III) to Fe(II) reduction [212] were determined by Gessa et al. The addition of a second metal ion to the binary system (Cu(II) [213], $U(VI)O_2$, Ni(II), Pb(II) and Cd(II) [214]), as well as of an additional ligand, ($GlcANH_2$ [150]), accelerated the slow reduction of Fe(III) to Fe(II) by GalpA when the second metal ion formed particularly stable chelate complexes with GalpA.

Mössbauer spectra reflected the presence of different hexacoordinated monomeric Fe(II) species in the fully hydrated, air-dried, and anhydrous polygalacturonic acid complexes. On the other hand, Fe(III) gives rise to polynuclear structures, which are stable over a wide pH range [215]. The same can be said about Fe(III) complexes of pectic acid derivatives, which contain polygalacturonic acid and some neutral carbohydrates, e.g., Rham [216].

The stability of the GlcA, LacbA, and Lactose complexes were shown to decrease in the above sequence [217]. The same stability sequence was observed by means of polarography in 0.1 M acetate buffer solution at pH 4.2, as well [218]. In the system containing Fe(III) and LacbA in 1:1 concentration ratio three protons (including the carboxylate proton) were released from the ligand between pH 1 and 5 and one from the coordinated water molecule above pH 6 followed by the dimerization of the complex in the presence of chloride ions. In the $[Fe^{III}(LH_{-2})(OH)]^{-}$ complex the ligand was coordinated via the 1,2,3,6 site [219]. Both GlcA and LacbA were suggested to bind two Fe(III) ions [217]. The formation of dinuclear species, however, was not confirmed later [220]. The contradictory results have shown that further combined equilibrium and spectroscopic studies are warranted for Fe(III)-LacbA system.

The composition and stability constants of D-(+)-saccharic acid complexes with Fe(III), Mn(II), Co(II), Ni(II), Cu(II), and Cd(II) ions have been determined [221–223]. The results showed that both carboxylate groups are coordinated in 1:3 iron complex and also in the 1:2 copper complexes (the latter formed a polymer chain).

The high affinity of Tdci for Fe(III) has already been recognized in 1984 [224]. Above pH 7 this ligand could displace EDTA from the coordination sphere of Fe(III) and can, therefore be used as analytical reagent [225]. The crystal structure determination of the bis complexes of Fe(III) and Taci revealed, that one of the ligand bound via three axial alkoxo, and the other via the three axial amino groups [48]. By introducing bulky substituents on either the oxygen or nitrogen donors of Taci, pure amino or alkoxo coordination was achieved (Fig. 8) [49].

A water-soluble Fe(III)–Fru complex was first isolated by Saltman et al. [226]. The complex formed at pH 9.0 contained two Fe(III) ions per two Fru ligands. The pH-dependence of the EPR signal intensity, the NMR line width, and the magnetic susceptibility showed a minimum at pH 7 in the presence of excess Fru. The results are consistent with the formation of a dimeric species, which breaks up at higher pH [227]. A very convenient preparation procedure for the Fe(III)-Glc and -Fru complexes was recently described by Rao et al. [228,229]. The complexes were

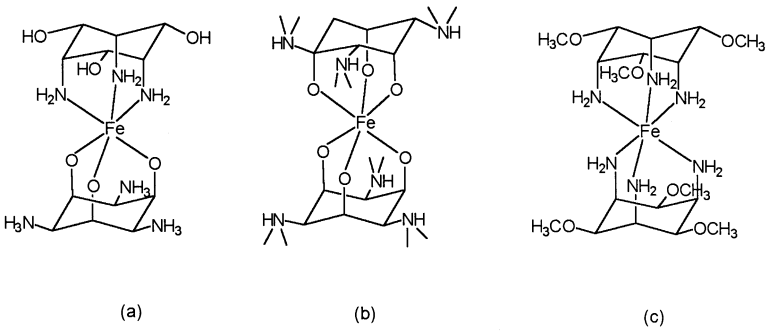


Fig. 8. The schematic structure of the bis complexes of Fe(III) Taci (a) and its substituted derivatives: Tdci (b) and Tmca (c) [49].

synthetized in methanol using stoichiometric quantities of Fe(III) and the sodium salts of the corresponding sugars prepared by the reaction of metallic sodium with the sugars. This pathway made possible to prepare monomeric complexes, as well. The Mössbauer spectroscopic measurements reflected polynuclear structures both in solution and in solid state for Fe(III) complexes of Fru, Sor [230], LacbA [84], D-sorbitol, GlupA, $GlcNH_2$ [231], and some other pentoses, hexoses and sugar acids [232]. The Mössbauer parameters (IS = 0.47–0.72 mm/s, QS = 0.72–0.92 mm/s) revealed the presence of high-spin Fe(III) central atoms within the complexes [229,231–234]. For complexes of reducing sugars (Glc, Gal, Man, lactose), or in solutions containing reducing compounds formed as a response to heat treatment (for example in case of the Fe(III)–LacbA–dextrane–acetate mixed ligand complex [84]) the Mössbauer spectra indicated the presence of a certain amount of Fe(II) in the systems [232,235,236]. The opposite phenomena is also true. In the ferrous GlcA with composition of $[FeL_2]\cdot 2H_2O$, the Mössbauer spectra indicated the presence of some amount (ca. 10%) of Fe(III) [237]. The Mössbauer parameters of Fe(III) (IS = 0.63, QS = 0.74 mm s^{-1}) [232] and Fe(II) ethylene glycol complexes (IS = 1.39, QS = 3.25 mm $^{-1}$) [25] have also been determined for comparison.

To collect information on the factors influencing the composition and structures and the magnetic interactions a large number of Fe(III)–carbohydrate complexes with aldoses, ketoses, polyalcohols, sugar acids, di- and trisaccharides were prepared [233,234,238,239]. The composition of the complexes were determined by standard analytical methods. In contrast with the results obtained in Ref. [235], it was found that deprotonated alcoholic hydroxy groups participate in the complex formation, and anionic species were formed.

The concentration ratio of the interacting (g_{ia} ca. 2) and isolated (g_{is} ca. 4.3) Fe(III) centres were determined by EPR spectroscopy for a number of carbohydrate complexes as discussed in the earlier review in detail [14]. Recent results confirmed that:

1. The nature of the organic ligand influenced the above ratio. The presence of carboxylate prevented the association of metal centres in e.g. the Fe(III)–LacbA system in aqueous solution, where no dimeric species were detected [220].
2. As concerns the mode of preparation of the compounds, an increase of the ligand-to-Fe(III) ratio in the initial solution and an increase of the pH favoured the formation of isolated Fe(III) centres [233,234,238]. Yokoi et al. [240,241], Hegetschweiler et al. [242] and Rao et al. [228,229] got the same conclusions for aqueous Fe(III) solutions of 1,2-ethanediol, 1,3-propanediol, glycerol, D-glucitol, Fru, two oligo-sugars [240,241], of selected diols, glycerol and sorbitol [242] and of several mono-, and disaccharides [228,229], respectively, by magnetic susceptibility, laser light scattering and different spectroscopic measurements.
3. The anion of the Fe(III) salt also influenced the composition of the complex, although it did not participate in the inner coordination sphere. This behaviour may be explained by the change in water activity in the rather concentrated solutions response to the anion change [234].

Recently Tonkovic et al. have shown by ^{13}C-NMR method that Fe(III) is preferably coordinated to the β-pyranose ring form of Fru, which is present in the

greatest amount in an equilibrium solution [243], while we have found that the Sacc and Glc coordinated the Fe(III) ions by non-specific way [234]. In the latter systems the ^{13}C-NMR spectra indicated the presence of a mixture of coordination isomers of Fe(III) complexes containing the sugar ligand in differently bonded forms.

All the Fe(III)–carbohydrate complexes precipitated from alkaline solutions were brownish coloured amorphous solids. Their local structure have been determined by EXAFS method in solution and in the solid state [239,244] (Table 1). In all of the complexes studied, the Fe(III) ion had a coordination number of six. The average Fe–O distance was 195 pm, consistent with the literature values for octahedral oxygen coordination of Fe(III), irrespective of the nature (polyalcohols, ketoses, sugar-acid) of the ligands. This seems to indicate that the Fe–O (hydroxide ion), Fe–O (sugar ligand), and Fe–O (water molecule) bond lengths are not distinguishable by EXAFS [239]. In spite of this in the hexanuclear Fe(III) Sor [244] complexes two different Fe–O distances (194 and 202 pm) were measured, similarly to the two Fe–O distances for the hexanuclear Fe(III) *cis*-inositolato complex (192 and 206 pm) determined by X-ray crystallography (Fig. 9) [245]. In these complexes five hexa- and one pentacoordinated Fe(III) centres were found. The Fe···Fe distance of 310 pm obtained for Fe(III)–Fru complex [239] is characteristic for complexes containing di-μ-hydroxo bridge units [246]. Similar Fe···Fe distance was found in μ_6-oxo-centered hexanuclear Fe(III) alkoxide complexes (316-323 pm) [247,248]. At the same time two different Fe···Fe distances were found for the inositolato (290 and 316 pm) and Sor (285 and 312 pm) complexes, the shorter

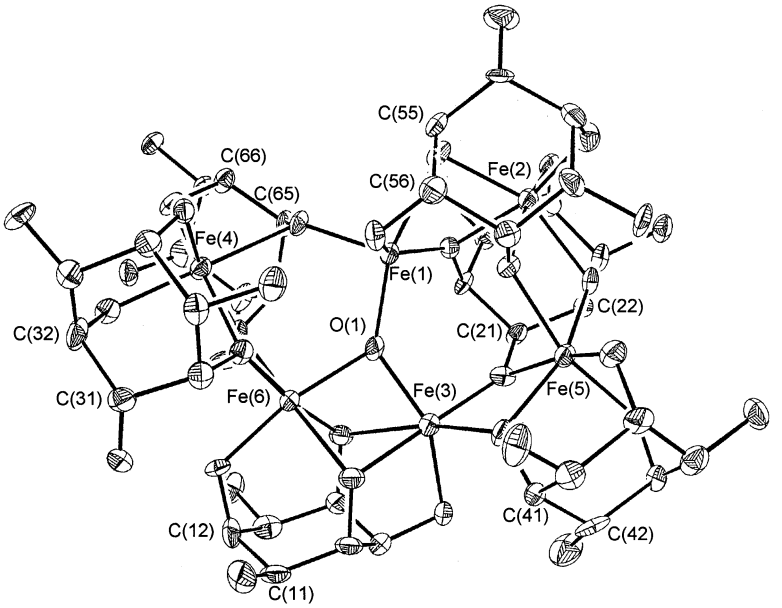


Fig. 9. The crystal structure of the hexanuclear Fe(III) *cis*-inositolato complex. ORTEP representation of the complex anion $[OFe_6\{(Ino)_6\text{-}21H\}]^{5-}$ with numbering scheme [245].

distances indicating multiple μ-alkanolato bridging mode between the Fe(III) centres [244,245].

Fivefold deprotonated D-Mannose ligand containing homoleptic dinuclear complexes of Fe(III), V(III), Cr(III), Al(III) and Ga(III) were synthesized and characterized by X-ray diffractometry by Klüfers et al. with $Ba_2[M_2(LH_{-5})]$ composition. These complexes do not contain hydroxide or oxo ligands despite the preparation from aqueous solutions. The polyolate is derived from the β-furanose form of the free mannose, which is insignificant in solution, but is the only form with all the hydroxy groups on one side of the ring– as an example of the coordination forced conformational change of the ligand. The environments of the two metal ions are not equivalent: since one forms five- and six-membered chelate rings with the open-chain part of the ligand, and the other is surrounded by two oxolanetriolato fragments in a distorted envelope conformation. The M···O distances are within a rather narrow range (196–208 pm) with the exception of Al(III) where these distances are somewhat shorter (185–196 pm) [249]. Recently, three new crystalline ferrates(III) with diolato ligands, derived from anhydroerythritol by deprotonation, were synthetized and their structure was determined by X-ray diffraction method by Klüfers et al. [250]. The almost colourless, monoclinic crystal, obtained from ethanol ($Na_2[Fe(LH_{-2})_2(OH)]$) contains mononuclear bis diolato hydroxo ferrate(III) dianions. Trinuclear hexakis diolato μ_3-methoxo triferrate(III) tetraanions constitute the anionic part of $Na_4[Fe_3(LH_{-2})_6(OMe)]\cdot 2.5NaNO_3$ which is a yellow–green hexagonal crystal, obtained from wet methanol. The third one is a yellow–green triclinic crystal ($Ba_2[Fe_2(LH_{-4})_2(\mu\text{-}OH)_2]$), crystallized from aqueous solution. In all the crystals the Fe···O distances were around 196-200 pm, but around 210 pm for the bridging oxygens. The Fe···Fe distances in di- and trinuclear complexes were 325 and 329 pm, respectively. From the diacetoneglucose Fe(II) system a trinuclear complex with linear trimetallic skeleton has been crystallized, the average Fe···Fe distances being 288 pm [251].

The promising results in the development of highly receptor-specific glycopeptide derivatives for clinical use led Tonkovic et al. to examine the Fe(III) chelating properties of some simple model compounds in which *N*-acylated or free amino acids are linked by glycosidic ester bond to a protected or unprotected carbohydrate molecule. It was found that the molecular weight (the polymerization degree) of the complexes decreases with increasing level of ligand protection [252]. It was also emphasized, that the preparation mode has a great influence on the composition, and consequently on the structure of complexes. Namely, the complexes prepared by molecular sieve method are monomeric [253], while in the complexes prepared by precipitation method the ligands bound to a pentameric Fe(III)–hydroxide/oxide core [254]. The same group have found that the Amadori compound derived from L-tyrosine coordinated to the Fe(III) through the amino and carboxylate groups of the tyronise part of the ligand in octahedral geometry [255]. The Fru part of the compound did not participate in complex formation.

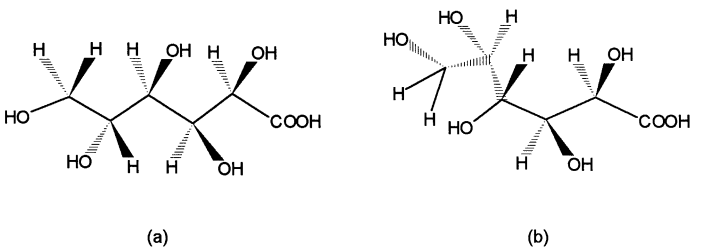
The iron absorption from an Fe(II)–oligosaccharide complex-produced by yeast in wine-was shown in the rat gastrointestinal tract, showing a special transport system other than the passive diffusion [256]. The complexes of iron with dextrans

and some polysaccharides have been found by EXAFS [257,258] and Mössbauer [258–261] studies to have high spin Fe(III) in a distorted octahedral environment of oxygens, similarly to the iron storage protein ferritin.

4.3. Manganese complexes

The redox behaviour of metal ions is determined by the complex formation in a great number of life processes. One of the most thorough investigations of this kind has been reported for manganese-carbohydrate complex systems. It is well known from pioneering works of Dolezal et al., [262–267] that polyhydroxy compounds can effectively stabilize the Mn(III) and Mn(IV) oxidation states in aqueous alkaline solutions. The stabilization of manganese in different oxidation states in alkaline GlcA solutions and the interaction of this system with hydrogen peroxide and with dioxygen have been discussed in detail by Sawyer et al. [268,269]. Stable complexes of Mn(II), Mn(III) and Mn(IV) were found with $[Mn^{II}(LH_{-1})_2]^{2-}$, $[Mn^{III}(LH_{-1})_2(OH)]^{2-}$, $[Mn^{IV}(LH_{-1})_2(OH)_3]^{3-}$ and $[Mn^{III}(LH_{-1})_3]^{3-}$ apparent formulae. In the crystal structure of Mn(II)-GlcA dihydrate complex the metal ion is octahedrally coordinated by one carboxylate and one hydroxy oxygen from both GlcA ligands and by two water molecules in *cis* positions. The Mn–O distances are between 209 and 227 pm [270]. Below pH 6, dioxygen did not oxidize the Mn(II)–GlcA complex; between pH 6 and 12 the stable oxidation products are Mn(III)–GlcA complexes, since the formation of Mn(IV)-GlcA starts above pH 12 and above pH 14 the oxidation of the Mn(II) complex by dioxygen to the corresponding Mn(IV) complex is stoichiometric. They also described, that after acidifying the system, dioxygen is evolved from the solution of the Mn(IV)–GlcA complex [268,271]. It was also shown that the Mn(II)–GlcA complex has both peroxidase and catalase activity in alkaline medium [272]. From NMR relaxation measurements it was concluded, that GlcA changes its conformation with the increasing temperature, existing mainly in straight chain form below, and in bent chain form above 308 K (Fig. 10) in the Mn(II) [273], Mg(II) [274] and Co(II) [275] complexes.

Mn(II) is known to form polynuclear complexes with carboxylate ligands [276]. Electrochemical and magnetic measurements indicated that the Mn(II)–GlcA complex dimerizes at high pH. Similar observation was made by means of EPR method



(a) (b)

Fig. 10. The straight chain (a) and bent chain (b) forms of GlcA [274].

on the Mn(II) complexes with Sacc [277], Mal [278], Taci [50], Galurcys [279], and some other PHTAc derivatives [280], but still there is no evidence for the formation of oligomeric Mn(II) complexes with D-sorbitol, D-mannitol [267]. Recently we have re-examined [281] the Mn(II)-LacbA systems studied earlier [282]. It was found by EPR measurements that dimerization occurred at pH 9 and above. ^{13}C-NMR relaxation studies have shown that the Mn(II)–GlupA complex also dimerized through the carboxylate group [283]. The Mn(II) and Rib or D-arabinose interaction have also been studied by ^{13}C-NMR, although the results have not been completely interpreted [284].

Several manganese-carbohydrate complexes in different oxidation states have been prepared as brown coloured solids. Magnetic susceptibility measurements confirmed that in each case dimerization occurred in smaller or larger extend [285]. It was also emphasized that the well defined solution structure of complexes did not correspond roughly to the structure existing in solid state. Oxidation of Mn(II)–Sacc complex by O_2, H_2O_2 or electrochemically led first to a dimeric mixed valence Mn(II,III) complex, which could be oxidized to the purely Mn(III) containing complex [277]. Several monosaccharides and the maltose complexes of Mn(II) proved to be dimeric or trimeric in the solid state. The complexes were found to be hydrolytically stable in solution [286]. The crystal structure of homoleptic complexes of Man pentaanions and Mn(III,III) an Mn(III,IV)-prepared from near neutral aqueous solutions-were also determined [287].

IR spectroscopy of amorphous manganese complexes of carbohydrates or PHTAc, precipitated from aqueous alkaline or methanolic solutions, showed that the ligands are coordinated to the central metal ion via $\{O,O\}$ and $\{N,O\}$ donor sets, respectively. Their local structure were measured by EXAFS. It was concluded, that the Mn(II)–PHTAc complexes exerted distorted octahedral structure. The Mn—O,N, Mn···C and Mn···O,C,S distances in the first, second and third shells are in the range of 213-220, 300–325 and 368–397 pm, respectively, depending on the conformation of polyhydroxy chains [288]. According to the EXAFS measurements in the Mn(III) and Mn(IV) GlcA, LacbA and Sacc complexes the average Mn-O distances are 208 pm, characteristic for manganese ion in distorted octahedral environments [289] (Table 1).

Crystalline air-stable solid manganese complex of Taci with $[Mn(L)_2](NO_3)_2{\cdot}2H_2O$ composition, containing discrete, mononuclear units (Fig. 11) was obtained [50]. The Mn(II) ion bound to six axial nitrogen donors. The complex cations are linked to each other by hydrogen bonds of the type N–H···O. The structure is further stabilized by additional hydrogen bonds between the complex cation, the counterions, and the water molecules of crystallization. The Co(II) [50] and the Cd(II) [44] complexes are isotypic with the Mn(II) complex.

Spectrophotometry has been used to characterize the binding mode of Zn(II) and Mn(II) to the polyelectrolite dextrane sulphate (DS), a highly sulphated polymeric product of Glc [290]. No significant difference was found in the binding of these cations, supporting the idea of a non-specific electrostatic interaction between the cations and the ligand. It was also found that among the bivalent transition metal ions only Mn(II) retains its inner hydration sphere during the interaction with

polygalacturonic acid. The other ions formed inner-sphere carboxylate complexes [291].

4.4. Cobalt, nickel and zinc complexes

4.4.1. Cobalt

Less attention has been paid to carbohydrate complexes of cobalt than to the other 3d transition metals. An early study showed that in acidic solution the stability of Co(II) complexes decreases in the following sequence of ligands: maleic acid > trihydroxy-glutaric acid > GlcA [292]. The interaction of D-mannitol with Co(II) and Co(III) in strongly alkaline medium has been observed later [293]. Only 1:1 complex was detected, where the ligand acts in tridentate manner. pH-metric equilibrium studies have also been performed, for the stability constants see Table 2. Recently Co(II) complexes of some aldoses have been prepared and characterized by CD and EPR spectroscopies [294]. Optically active mixed ligand complexes have been prepared with *cis*-$[Co(NH_3)_4(H_2O)_2]^{3+}$ and D-ribose, L-sorbose, D-glucosamine [295], with $[Co(En)_2]^{3+}$ and aldonic acids [296], aldoses [297,298], substituted aldoses and anhydroerythritol [299]. Exceptionally poor yields of the desired species have been reported, probably due to dismutation reactions during synthesis [297,298]. The complexes were characterized by electronic absorption, CD and NMR methods, the conformational analysis of the sugar units were performed by means of semiempirical AM1 calculations [300]. The results demonstrated that the Man and Rham units existed in the pyranose form, while the Rib units adopted furanose form in the complex. Similar studies on the ternary system containing

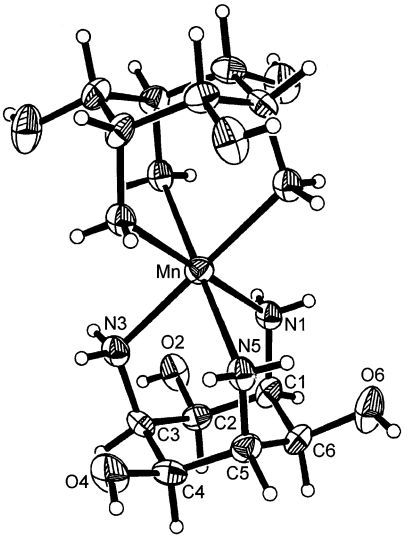


Fig. 11. The crystal structure of $[Mn(Taci)_2](NO_3)_2 \cdot 2H_2O$. ORTEP representation with the numbering scheme and vibrational ellipsoids at the 50% probability level [50].

Co(III), Fru and phenanthroline showed that the sugar ligand coordinated through the C(2)–O^- and C(3)–OH groups of its pyranose form in the $[Co(phen)_2(LH_{-1})]^{2+}$ complex [301]. On the basis of CD spectroscopic results on a series of aldonic acid ligands Katzin suggested that Co(II) coordinates to the carboxylate and α-hydroxy groups in acidic, and to the β-hydroxy group in neutral solutions [302] similarly to the Ni(II) complexes [303]. A very detailed and extensive work, published by Harrowfield et al. [38], has shown that the reaction between *cis*- and *trans*-$[Co(En)_2Cl_2]^+$ and $GlcNH_2$ in neutral aqueous solution results in a very complicated product mixture including several isomeric complex ions as major components in which the coordination sphere is formally made up from two En and one sugar unit. The presence of fructosamine moiety revealed that the complex formation reaction was accompanied by the Amadori rearrangement. The crystal structure determinations have definitely characterized eight out of all the reaction products [38], contrary to the earlier findings for the same system [304], or for $[CoL(En)_2]^+$ (where L denotes D-gluconate or L-mannonate) [296], where only Λ- and Δ-enantiomers were found. One reason for the differences observed may be the much more extensive chromatographic treatment used in Ref. [38], and the other one is that the experimental conditions (pH, temperature, the exact time of reaction) might have influenced the product distribution. The crystal structure of the $[Co(En)_2(AnErytH_{-2})]I$, $\Delta[Co(En)_2(Me\text{-}\alpha\text{-}D\text{-}Manp3,4H_{-2})]ClO_4\cdot 2H_2O\cdot NaClO_4$ and $\Delta[Co(En)_2(Me\text{-}\beta\text{-}D\text{-}Galp2,3H_{-2})]ClO_4\cdot H_2O$ complexes have also been determined [299]. The interaction between $[Co(NH_3)_5Cl]Cl_2$ or $[Co(NH_3)_4Cl_2]Cl$ and L-ascorbic acid led to the formation of the $[Co(NH_3)_5(LH_{-1})]Cl_2\cdot H_2O$ and $[Co(NH_3)_4(LH_{-2})]Cl\cdot H_2O$ complexes. The ascorbate anion is coordinated monodentately in the former (pentammine) complex via ionized C(3)–O^-, and bidentately in the latter one (tetrammine) through ionized C(1)–O^- and C(4)–O^-, in both cases leading to the formation of pseudooctahedral hexacoordinated Co(III) complexes [305]. Much of the work on stereoselective C(2) epimerization of aldoses in *N*-glycoside complexes-derived from aldoses and diamines-of metal ions, mainly Ni(II) and Co(III), has been reviewed [9,19]. Recently Yano et al. also reported on a chiral inversion around seven coordinated cobalt centres (Fig. 12) in *N*-glycoside

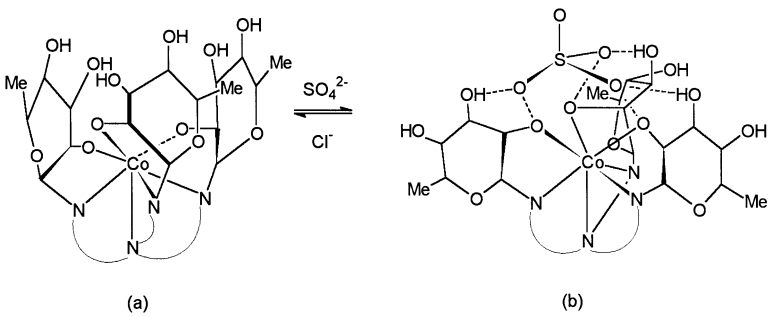


Fig. 12. The chiral inversion around seven coordinated cobalt centres in *N*-glycoside complexes: (a) Λ and (b) Δ forms of $[Co\{(Rham)_3Tren\}]^{2+}$ complex [306].

complexes [306–308]. Some of the *N*-glycoside complexes derived from amino sugars proved to have antitumour or antifungal activity [309–311]. *cis*-Inositol and triamino cyclohexane mixed ligand Co(III) complex showed a rearrangement of the coordination site from 1,3,5-triaxial to the *ax–eq-ax* adjacent hydroxy groups in aqueous solution [47]. In the bis Taci complexes, however, Co(III) coordinated to the *ax–ax–ax* amino groups of the ligands [41]. The direct coordination of $[Co(En)_2]^{2+}$ to cyclodextrins have been demonstrated in Ref. [312].

4.4.2. Nickel and zinc

Several monosaccharides (Fru, Rib, Gal, Glc, Xyl) and a disaccharide Mal complexes of Zn(II) were prepared in solid state. All of them were found to be anionic with M:L ratios of 1:1 and 2:1 for mono-, and disaccharide complexes, respectively. Dissolving these complexes in water under alkaline condition mixed hydroxo species were formed. The ligands were present both as α- and β-anomers. The complexes have biological effect in the liver on metallothionein synthesis [313]. Similarly, the Ni(II) complexes of some aldoses were prepared and characterized by CD, FTIR, EXAFS and XANES [314].

A polarographic study of the Zn(II)–GlcA system reflected the formation of five different species [315]. In another study the formation of only the species with 1:1 metal:ligand ratio was observed in solution, while 1:2 species were isolated as solid compounds [316]. The formation constants of 1:1 Zn(II) complexes of iduronic acid and its derivatives (related to heparin) were determined by ^{1}H-NMR spectroscopy to be in the order of 10^3 M^{-1} [317,318]. Also in the Zn(II) LacbA system only one (1:1) complex was formed [319]. By spectrophotometric and electrochemical methods $[NiL]^+$ was found below pH 7 and $[Ni_2L(OH)_4]^-$ above pH 9 in Ni(II)–GlcA system. Between pH 7 and 9 the complex $[Ni_2L(OH)_3]$ precipitated [320]. Later, in contrast to this $[Ni(LH_{-1})_2]^{2-}$ complexes have been suggested to be present in alkaline medium [321]. Lactobionic acid formed mixed ligand complexes with Ni(II) 2,2′-bipyridine both in aqueous solution and in solid state [322].

Carbohydrates bonded to the amino group of amino acids (or to the *N*-terminal amino group of peptides) serve as models of biologically important molecules. The PHTAc ligands formed parent $[ML]^+$ and $[ML_2]$ and mixed hydroxo $[ML_2H_{-1}]^-$ and $[ML_2H_{-2}]^{2-}$ complexes with Ni(II) [280] and Zn(II) [323] in slightly alkaline conditions. The differences in protonation and complex stability constants were explained in terms of the conformation of the polyhydroxy moiety. FTIR data showed the coordination of carboxylate and amino groups of the ligands in solid state complexes. The structure of Ni(II), Zn(II), Mn(II) (M:L = 1:2), and Ag(I) (M:L = 1:1) complexes (Fig. 13) were measured by EXAFS (Table 1). Ni(II) and Mn(II) proved to be hexa-coordinated, Zn(II) tetra-coordinated, while the Ag(I) ion was two folded, alternatively bound to nitrogen and sulphur atoms, the Ag–N (203 pm) and Ag–S (232 pm) bond distances being separable [288,324].

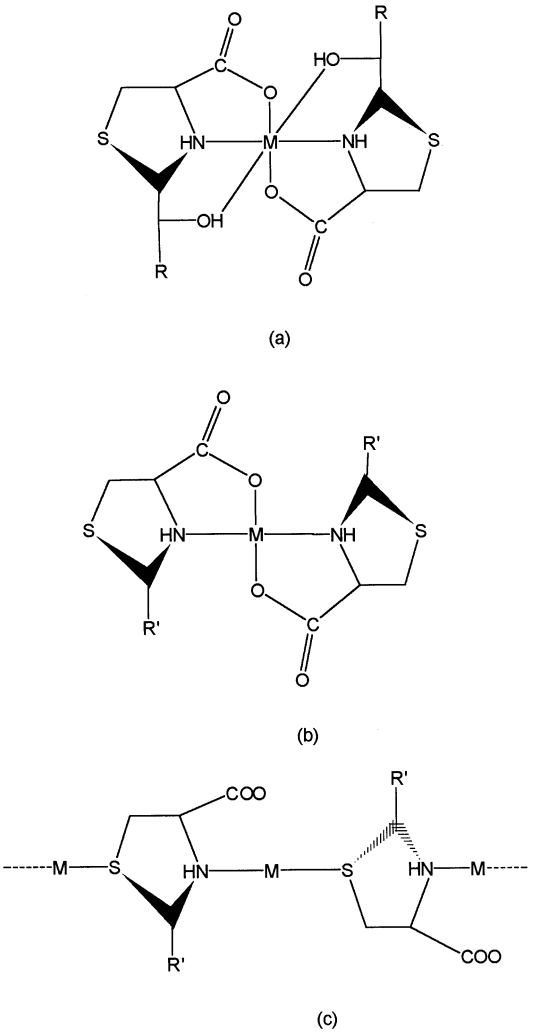


Fig. 13. The proposed structure of PHTAc complexes on the basis of EXAFS measurements: (a) M:L = 1:2, M = Ni(II), Mn(II); (b) M:L = 1:2, M = Zn(II); and (c) M:L = 1:1, M = Ag(I) [288,324].

4.5. Vanadium, chromium, molybdenum and tungsten complexes

The solution chemistry of titled metals is very complicated due to the formation of oxo anions and extensive polymerization. The complexation of these metals to carbohydrates depends very much on pH, metal-to-ligand ratio, total analytical concentration of reactants, ionic strength and temperature of initial test solutions. For these reasons the equilibrium studies should be accomplished with spectroscopic techniques (EPR, CD, multinuclear NMR, UV–vis) in order to be able to characterize the complexes formed in solution or in solid state. These investigations

may be of interest because of the possible biological role of these metal ions [325], like the insulin mimetic behaviour of vanadium complexes, the toxic property of Cr(V) or the suggestion that sugars are possible complexing sites for molybdenum in certain enzymes [326–328].

4.5.1. Vanadium

Due to its strong hydrolytic tendency, the V(IV)O ion needs the presence of anchoring donor groups (e.g. carboxylates) in the sugar molecule, but once bonded to the ligand, it can easily deprotonate the alcoholic hydroxy groups and strongly coordinate up to four of them [119,329,330]. The carboxylate group of GalpA initiated the coordination at pH 3, with one or two deprotonated sugar hydroxy groups of both ligands coordinated in the major bis-complexes with increasing pH. EPR and ENDOR spectra indicated the formation of a dimeric complex (Fig. 14) with metal-metal distance of about 500 pm in concentrated alkaline solutions, where the ligands existed in open-chain form [330]. GlupA formed polymeric species in pH range 5–9 with V(IV)O [119]. These ions formed five bis-complex species with LacbA during the stepwise deprotonation of the ligands from $[VOL_2]$ to $[VO(LH_{-2})_2]^{4-}$ [129]. EPR and ENDOR methods were also used to investigate the vanadium-polygalacturonic acid systems [329]. V(V) reduced to V(IV) which is rigidly bonded to the polysaccharide matrix through the carboxylate groups [291,331]. The parent complexes of V(IV)O–Galurcys were surprisingly stable. The ligand was assumed to coordinate in tridentate manner, one of the binding sites being the deprotonated C(1′)–OH. In solution with 1:1 metal-to-ligand ratio dimeric species were also detectable [279]. Spectrophotometric, CD and polarographic measurements in the pH range 5–14 revealed that the stoichiometry of the V(IV)O–GlcA complexes varies from a metal-to-ligand ratio of 1:1 (at pH 6.0) to 1:2 (above pH 12) [332]. While no deprotonation of the alcoholic hydroxy groups was suggested in this system, in all the above mentioned complexes the first deprotonation process has been observed at around pH 4 similarly to other V(IV)O α-hydroxy-carboxylic acid complexes [333].

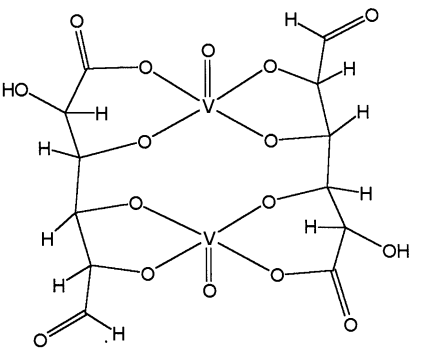


Fig. 14. The stabilization of the open chain structure of GalpA by V(IV)O in the dimeric complex formed in alkaline media [330].

The isolation and characterization of V(IV) carbohydrate complexes in solid state were published by Rao et al. The complexes were found to be monomeric, but in solution (pH 7–8) dimerization or oligomerization reaction takes place in parallel with the hydrolysis of the metal ion. Further deprotonation of the alcoholic hydroxy groups occurred at higher pH [334,335]. Anionic complexes of Glc, Fru and some disaccharides were obtained from alkaline aqueous solutions. All the ligands formed monomeric complexes with M:L = 1:2 composition, with the exception of Fru, which formed complexes with 1:3 stoichiometry [336]. The X-ray analysis of the cyclic vanadate(V) complexes of *O*-4,6-benzylidene-α-D-mannopyranoside showed the formation of dialkoxo bridged dimeric species, where each vanadium bound to the deprotonated *cis*-diol of one mannopyranoside. The geometry of the five-coordinated V(V) atoms was intermediate between a square pyramid and a trigonal bipyramid [337]. Three V(IV)O D-ribose-5-phosphate microcrystalline complexes have been synthetized: the light blue crystals of the $Na[VO(L)(OH)(H_2O)_2]\cdot 2H_2O$ and $[VO(L)(H_2O)_3]$ *mono* complexes showed coordination through the phosphate group, while in the green $Na_6[VO(LH_{-2})_2]\cdot 6H_2O$ bis complexes the ligands were coordinated by the pairs of two adjacent deprotonated hydroxy groups of the sugar moiety, similarly to the Rib complex itself in the $Na_3[VO(LH_{-2})_2(OH)]\cdot 4H_2O$ [338]. *Bis* complexes of guanosine-5′-monophosphate with the latter type coordination (Fig. 15) were also shown to exist in aqueous solution around pH 7.5 by EPR spectroscopy [339]. A survey on V(IV)O complexes of nucleotides has been published recently with the conclusions that the coordination of the deprotonated alcoholic hydroxy groups of Rib takes place at high pH values, but the participation of non deprotonated hydroxy groups in acidic medium can not also be excluded [340].

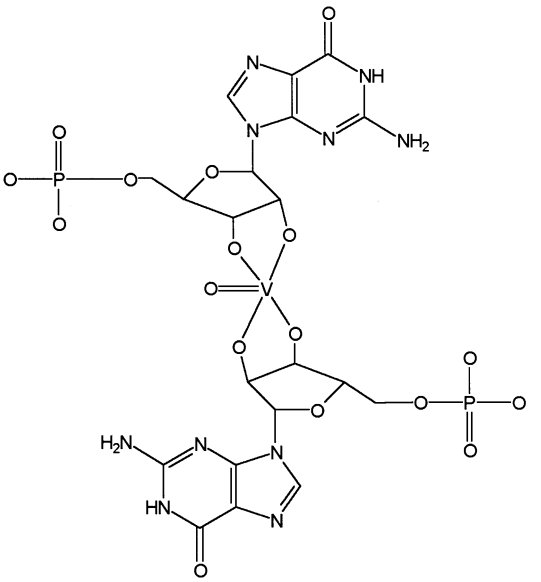


Fig. 15. The schematic structure of the bis complex of guanosine-5′-monophosphate with V(IV)O [339].

Investigation of simple sugars (Man, Rib, Glc) and vanadate [341–343], as well as V(IV)O [344] interactions led to the following conclusions: (1) the aldoses, containing three hydroxy groups, in *cis–cis* position to each other in their pyranose forms, formed tridentate complexes of trigonal bipyramidal geometry at pH 7; (2) other aldoses can form weaker bidentate cyclic diesters using two consecutive pyranose *cis* hydroxy groups. The interaction of vanadate with e.g. nucleosides [345,346] and nucleotides [347] occurs preferentially via the ribose *cis*-diol hydroxy groups, rather than the phosphate groups.

If metavanadate solutions are acidified with hydroxycarboxylic acids, or perchloric acid in the presence of polyalcohols (sorbitol, mannitol, dulcitol, arabitol, adonitol, or xylitol), coloured (from yellow to deep red) V(V)–hydroxy–carboxylate (or polyalcohol) complexes are formed beside the decavanadate ions. According to these measurements, the tetravanadato complexes, formed primarily, have been partly converted into monovanadate complexes by an excess of the ligand [348].

The deprotonation of alcoholic hydroxy groups was observed in the vanadate(V) dithiothreitol system with pK_a values around 6.5 the alcoholic oxygens being bridges between the metal ions [349].

V(III) was shown to be able to form a homoleptic dinuclear complex with fivefold deprotonated D-Mannose, similarly to Fe(III) as mentioned above [249]. It was also reported that the V(III) ion formed trigonal bipyramidal mixed ligand chiral complex with protected Glc and pyridine [350]. The structure of the complex was determined by X-ray diffraction method. In the reaction of the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose V(III) complex [VL_3] with the complex [LiL] a product of $Li_3[VL_6]$ composition has been formed the V(III) ion being coordinated to the six C(3)–O^- non-protected alcoholate groups of six different ligand units. Each lithium ion with two already coordinated alcoholate oxygens should be regarded as a bidentate chelating unit for V(III) ion, thus the surroundings of the latter metal ion may be regarded as an octahedral complex containing three bidentate ligands with a Λ configuration [351]. Such oxygen-rich cavities may function as binding sites for ions or for species bound via hydrogen bonding.

4.5.2. Chromium

Chromium readily undergoes oxidation reduction reactions with appropriate ligands. The tripeptide glutation readily reduces Cr(VI) to Cr(III) in stepwise processes, but in the presence of sugars, the Cr(V) oxidation state was stabilized by two vicinal hydroxy groups [352]. Due to its great oxidation capacity Cr(VI) is toxic and carcinogenic, however, it has been proposed that Cr(V) is actually the active species [353,354].

Carbohydrates have been shown to reduce chromate(VI) under both acidic and neutral conditions. The reaction kinetics of the oxidation of Rham and Man [355,356], GlcA [357], 2-acetamido-2-deoxy-D-glucose [358], 2-deoxy-D-glucose [359,360], D-galactono-1,4-lactone [361] by Cr(VI) in perchloric acid solution have been studied by Sala et al. In each case, the first reaction step involved the formation of a chromic ester right before the slow redox steps with C(1)–OH and

C(2)–OH, being the preferred coordination sites in the electron transfer precursor. It was also found that free radicals were formed during the reaction and these reacted with Cr(VI) to yield two or three intermediate Cr(V) complexes. The build-up and decay of Cr(V) species accompanied the decay of Cr(VI). It means that the rates of Cr(V) decay are similar or slower than those of Cr(VI), consequently the intermediate complexes can be observed by EPR (g_{iso} ca. 1.977) and by visible spectrophotometry (λ_{max} ca. 750 nm, ε ca. 38 M^{-1} cm^{-1}). Similar observation was made in the course of oxidation of GalpA by Cr(VI) in slightly acidic conditions (pH 5–7) [362]. In neutral solutions the reaction led to the formation of stable Cr(III)–carbohydrate products [363–367]. The Glc, Fru, Gal, Man and Sor ligands and some acid derivatives, such as GalpA and GlcA formed anionic binuclear complexes with Cr(III), containing hydroxo or dihydroxo bridges. The complexes have pseudo-octahedral geometry where the metal ion bound to both oxidized (via carboxylate group) and unoxidized carbohydrate units. [367,368]. These investigations led to the final conclusion, that probably the reducing sugar content of bovine milk is responsible for the reduction of Cr(VI) to Cr(V), and consequently for the toxicity [369].

Cr(IV) can also be stabilized in aqueous solutions by the excess of carboxylate ligands among them quinic acid, which is coordinated to the metal ion through the carboxylate and the α-hydroxy groups in the bis complex [370].

The formation of optically active mixed ligand Cr(III) complexes of neutral sugars has been reported in Ref. [371]. Two isomeric Cr(III) complexes were formed with Taci in one crystal. The unit cell contained two $Cr\{N_3O_3\}$ (d(Cr–O) = 194.3, d(Cr–N) = 208.9 pm) and one $Cr\{O_6\}$ (d(Cr–O) = 198.3 pm) complexes of Taci, four sulphate groups and 30 water molecules. The structure is predominantly stabilized by N–H···O and O-H···O hydrogen bonds [40].

4.5.3. Molybdenum and tungsten

A very recent and detailed review has dealt with the Mo(VI) and W(VI) complexation of alditols and simple carbohydrates and revealed, that these compounds may behave as tri-, tetra- or pentadentate ligands, offering different types of chelating sites depending on their configuration [21]. An overview of the most important conclusions will only be given here and few examples demonstrating the complexity of these systems. For further information the reader is referred to the above mentioned paper.

Both Mo(VI) and W(VI) ions react with alditols and simple sugars in acidic solution to form anionic binuclear complexes. The alditol complexes of W(VI) are more stable than their Mo(VI) analogues ($\log K_W - \log K_{Mo}$ ca. 3) the difference being almost independent on the nature of the sugar, which is a strong indication that the reason for that is the intrinsic property of these inorganic elements.

A good example for the determination of the coordination sites of the ligand served the investigations on the Mo(VI) and W(VI) complexes of perseitol (D-glycero-D-galacto-heptitol). The first results suggested the formation of two tetradentate species that were believed to involve the *galacto* (OH-2,3,4,5) and the *manno* (OH-3,4,5,6) sites of the ligand [372,373]. On the contrary the results of ^{13}C-NMR

studies, performed later, demonstrated that no chelation occurred at the *manno* site of the ligand and that the complexes of perseitol were a pair of isomers involving the *galacto* site occupied in reversed orientations as shown in Fig. 16a. [374]. This is in agreement with the result that mannitol forms complexes of low stability [374–377]. Results of ^{183}W- and ^{13}C-NMR investigations showed, that a novel bis-binuclear type complex with a mixed binding mode of the (OH-4,5,6,7) and (OH-1,2,3) sites (Fig. 16b) was also formed [378]. Generally, it can be said, that the tetradentate Mo(VI) alditol complexes, which contain the ligand with a central *erythro*-diol group in a sickle arrangement (galactitol or arabinitol) are more stable than those of a ligand with central *threo*-diol group in a zigzag arrangement (treitol or xylitol). The former type of complexes may exist as a pair of isomers, if the lateral carbons of the coordination site have different substituents. The analogy

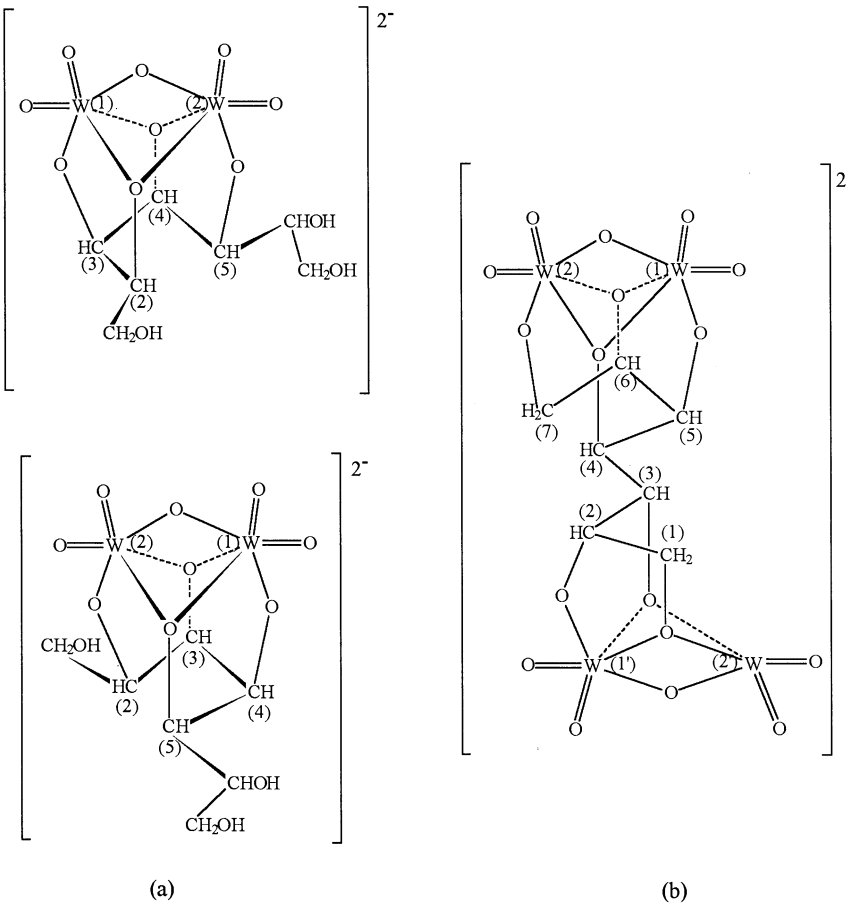


Fig. 16. Tungstate complexes of perseitol: (a) the pair of isomers involving the *galacto* site occupied in reversed orientations and (b) the bis-binuclear type complex with a mixed binding mode of the (OH-4,5,6,7) and (OH-1,2,3) sites [378].

between Mo(VI) and W(VI) complexes has been proved for the complexes of *erytrho* ligands, while W(VI) may form different types of complexes with *threo* ligands depending on the pH [379]. The stability of the Mo(VI) and W(VI) complexes of cyclitols is usually smaller than for those of the acyclic alditols.

CD spectroscopy also proved to be useful in determining the type of coordination since the complexation enhances the optical activity of alditols. The CD studies on the complexes of several alditols and free 1,3-diol containing sugar derivatives showed that the sector rule can be applied for the prediction of the signs of the Cotton effects [380,381]. Among other methods CD spectroscopy was used to caharacterize some *cis*-dioxomolybdenum(VI) monosaccharide complexes [382].

The stability of the Mo(VI) and W(VI) complexes of pentoses has been shown to decrease in the following sequence: D-lyxose > Rib > D-xylose > D-arabinose [383–385]. It appears that the *erythro* C(2), C(3) diol group (*lyxo* and *ribo* series) is a much favourable site for the complexation in such systems than the *threo*-diol group (*xylo* and *arabino* series). In the first case, in the binuclear Mo(VI) and W(VI) complexes, the ligands were suggested to coordinate in pyranose ring form [386], however, an X-ray diffraction measurement has shown that the complexation of Mo(VI) by D-lyxose occurs through C(1,2,3)–OH in the furanose form, with a triple-oxygen bridge linking the two molybdenum atoms [387]. In the case of *threo* series the ring opening of the sugar moiety may occur as a consequence of the coordination, which may led to the anomerization on C(1) [385].

The epimerization of simple sugars at C(2) is catalyzed by Mo(VI) but not by W(VI) ions [388,389]. During the glucose–mannose interconversion reaction the maximum rate was observed at pH 2.5 [390,391].

The stability constants of the adducts formed by Mo(VI) and mannitol, GlcA, citric, lactic and D-saccharic acids are of the order of 10^8 [392,393]. A spectroscopic study of the W(VI)–GlcA system at a ligand excess has shown the presence of two mononuclear and two binuclear species, with 1:2 and 2:2 compositions, respectively [394,395]. A series of multinuclear NMR studies on Mo(VI) and W(VI) complexes of aldonic acids showed the presence of at least eight different complexes in aqueous solutions depending on the pH and concentration ratios [396–398]. In the bis complexes the ligands were coordinated by the carboxylate and the adjacent deprotonated hydroxy groups, while in the M:L = 2:1 species the ligand was coordinated either through four hydroxy or the carboxylate and three hydroxy groups.

The study of the Mo(VI) complexes of uronic acids by ^{1}H- and ^{13}C- NMR method in aqueous solution in the pH region 3.5–5.8 revealed that the complexation occurred on C(6)–O carboxylate and C(4)–O hydroxy oxygens of a $^4C_1$ pyranose form [399]. In contrast to this, it has been shown that in the Mo(VI) and W(VI) complexes of GalpA, the ligand is coordinated by carboxylate and the adjacent hydroxy groups. As a consequence of this the conformation of the ligand is shifted from the pyranose to furanose form [400,401].

Multinuclear (^{1}H, ^{13}C, ^{17}O) NMR studies have shown that in the pH range 2–9, four major complexes are detectable as reaction products between Mo(VI) and D-galactaric, D-mannaric [402] or D-glucaric [403] acids, while a very recent work

[404] showed the formation of 1:1, 2:1 and 1:2 species by using electrospray mass spectrometry. In the reaction of D-galactaric and D-mannaric acids with W(VI) in a wide pH-range mainly 2:2 species were formed, in which the ligands bound to the metal by the two carboxylate groups and the adjacent OH groups. Above pH 6.5, an M:L = 2:1 species is also detectable, in which all the OH functions are coordinated to the metal ions, the two carboxylate groups remaining free [405].

Recently, it was reported that Mo(VI) and V(V) oxidized the hexoses and pentoses in strongly acidic solution yielding Mo(V) and V(IV) [406], while in neutral solutions Mo(VI) retains its oxidation state in the presence of uronic acids [407].

4.6. Complexes of other transition metal ions

4.6.1. Platinum

Many platinum complexes have been examined since the anti-tumour activity of cisplatin (*cis*-diamminedichloroplatin(II) or *cis*-DDP) was shown by Rosenberg et al. [408]. Since the soft Pt(II) ion shows low affinity toward oxygen donor atoms of the alcoholic hydroxy groups, the search for new *cis*-DDP analogues with better water solubility lead to the use of functionalized carbohydrate type ligands with anchoring groups, like the amino sugars [309,409,410] and chiral or raceme diaminoalcohols [411]. The preparation of neutral or ionic, extremely water soluble complexes formed with $GlcNH_2$ and its derivatives have been reported in Refs. [412] and [413]. Pt(II) complexes containing methyl-2,3-diamino-2,3-dideoxy-α-D-mannopyranoside and -α-D-glucopyranoside, or 2,3-diamino-2,3-dideoxy-D-glucose have also been prepared [309,414]. No intermolecular interactions were observed between platinum atoms but intramolecular hydrogen bonds were suggested between the solvate water molecules, chloride ions, hydroxy groups and amino groups within the coordination sphere. The Pt···Cl distances were ca. 230 pm and the Pt···N distances $\sim$202 pm. The *cis*-DDP analogues with 2,3-diamino-2,3-dideoxy-1,4-di-*O*-methyl-D- and L-threitol [415] and other diaminotetritol, -pentitol, and -hexitol ligands [416] (prepared by stereo controlled manipulation of the hydroxy groups) were synthetized. The X-ray structure and antitumour activity of monomeric square-planar *cis*-$[PtCl_2(L\cdots L)]$ chelate complexes have been determined in the latter work. The mean Pt-Cl and Pt-N distances (232 and 203 pm, respectively) are comparable with those found in the above mentioned Pt(II) chelates with $\{2Cl,2N\}$ donor sets [309,414]. Chiral non-racemic diaminoplatinum(II) analogs were prepared from methyl-2,3-diamino-2,3-dideoxy-L-xylopyranosides and from 2,3-diamino-2,3-dideoxy-1,5-anhydro-L-xylitol complexes by the reaction with dipotassium cyclobutane-1,1-dicarboxylate, with the enhanced antitumor activity and water solubility. The Pt···N distances were ca. 202 pm and the Pt···O distances $\sim$201 pm. The complex units associated through hydrogen bonds bringing the Pt(II) ions as close as 333 pm [417].

The binding of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isocyano-α-D-glucose and -β-D-glucose through the isocyano and carbon groups to several metal ions, among them Rh(III), Pd(II), Pt(II) Au(I) and Ir(III) have been shown by Beck et al. [418]. The

structure of the latter complex was determined by X-ray crystal structure analysis. The same team reported the formation of mixed ligand Pt(II) complex with *cis*-di(2,3,4,6-tetra-*O*-acetyl-1-mercapto-α-D-glucopyranosid)bis(triphenylphosphane)-platinum(II) composition [419], and furthermore the synthesis and spectroscopic data for complexes of several metal ions with nitrogen and sulphur containing monosaccharid derivatives [169]. According to the IR spectra, PHTAc ligands formed bis-complexes with Pd(II) via {*N*,*S*} and {*O*,*S*} atoms [165,420]. In the Pd(II) and Pt(II) complexes of Fru–gly and Fru-β-ala the ligands were coordinated to the metal ions through the amino and carboxylate groups in the square planar arrangement (Fig. 17) [164]. Likewise, the coordination of amino acid residue dominates in Pt(II) and Pd(II) *N*-6-deoxy-galactopyranosyl-α-amino acid complexes as shown by crystal structure analysis [421]. Accordingly, the sugar residue remained also free in Pt(II), Pd(II), Ru(II), Rh(III) and Ir(III) complexes of deoxyfructosazine [422].

Kidani et al. [423,424] announced that the antitumour activity of *mono*- and bis-complexes of GlupA with Pt(II)-1R,2R-cyclohexanediamine adduct was higher than that of *cis*-DDP. FTIR and ^{1}H-NMR spectroscopic, X-ray diffraction, and other evidence indicated that both GlupA and GlcA bound monodentately via their carboxylate groups in *trans*-$[PtL_2(NH_3)_2]\cdot H_2O$ and bidentately through the carboxylato and a sugar oxygen in *cis* analogue.

Only few platinum complexes of nonfunctionalized carbohydrates are known. Regioselective coordination of the ionized *cis*-diol groups of unprotected carbohydrates was observed in the bis(phosphine)Pt(II) alditolate complexes [425,426]. The fact that *threo*-diols formed stronger complexes than the *erythro*-diols was explained in terms of the inter- and intramolecular hydrogen bonding interactions. The strong intermolecular hydrogen-bonding network in carbohydrates has also been found to be altered by the interaction with platinum amine resulting in sugar-OH···$NH_3(H_2O)$···HO-sugar H-bonds [427]. The crystal structure of square-planar, mixed ligand Pd(II) complex with bipy and multiply charged polyolato ligands was also determined [428].

Recently, Pt(IV) complexes of 1,2-*O*-isopropylidene-α-D-glucofuranose and -allofuranose [429] and several glucopyranosides [430] were also prepared. The former ligands were coordinated by the three nonprotected alcoholic hydroxy groups, while glucopyranosides coordinated by two hydroxy and the acetal oxygen atoms (Fig.

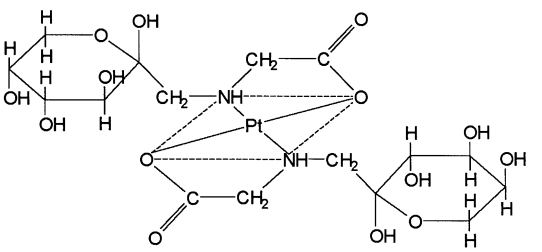


Fig. 17. The proposed structure for Pt(II) Fru–gly complex [164].

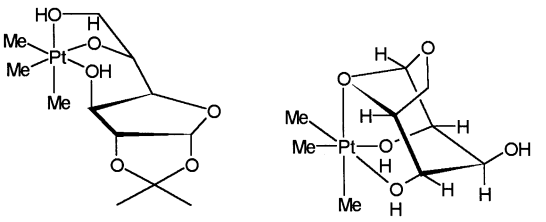


Fig. 18. The schematic structure of Pt(IV) complexes of (a) 1,2-*O*-isopropylidene-α-D-glucofuranose and (b) 1,6-anhydro-β-D-glucopyranose [430].

18). The Pt–O bond lengths for the hydroxy oxygens are around 224 pm, all the same within the tolerance limit in the above complexes, while for the acetal oxygen it is significantly longer: 229 pm. The study on the kinetics of the oxidation of aldoses by Pt(IV) in alkaline medium showed that the oxidation rates decreased with the increasing chain length of the aldoses [431].

Sugar moiety has been proved effective not only as carrier in Pt(II) complexes, but also as leaving groups. A series of LacbA and Glc, Gal and $GlcNH_2$ derivatives have been tested against murine leukemia L1210 cell line, and some of them showed excellent antitumour activity [432].

4.6.2. Silver(I) and Mercury(II)

Silver(I) and Mercury(II) complexes of LacbA were crystallized from their aqueous solutions as coordination polymers self-assembled by hydrogen bonds between the galactosyl units of the ligands. The $[AgL]\cdot H_2O$ unit displayed a distorted trigonal bipyramidal, while the $[HgL_2]\cdot 2H_2O$ complex had an octahedral local geometry. The ligand was coordinated through the C(3)–O and C(6′)–O alcoholic oxygens in the former and by the carboxylate and C(6′)–O oxygens in the latter complex [433]. The equlibria of the Hg(II) complexes of carbohydrate amino acids derived from Glc and Man were studied by pH-metric measurements [434]. $[ML_2]$ parent and $[MLH_{-1}]$ mixed hydroxo species were formed. In Ag(I) oxide assisted *O*-alkylation of 2,4-di-*O*-benzoyl-myo-inositol-1,3,5-orthoformate and its derivatives the complex formation between the ligands and metal ion has been suggested [435].

4.6.3. Cadmium

Complexation of Cd(II) by *N*-alkylamino sugars was investigated by potentiometry and multinuclear NMR methods. In the parent complexes, formed at physiological pH the ligands were coordinated by the amino groups, and the additional coordination of hydroxy groups was observed at pH 12 [436].

4.6.4. Rhodium

The crystal structure of the octahedrally coordinated Rh(V) complex with 1,3,5-trideoxy-1,3,5-tris(2-hydroxybenzyl)amino-*cis*-inositol have also been reported [43].

4.6.5. Titanium

The asymmetric C–C bond formation using titanium carbohydrate complexes have been described in several papers [437]. Such complexes are readily available, offer interesting reactivity, and so intrinsic toxicity could be related to this element. Recently, the behaviour of the organotitanium ions to induce stereoselective alkylative cleavage of benzyl pentopyranosides was reported [438].

4.7. Main group metals

4.7.1. Group II

Simple sugars form adducts of low stability with alkaline earth metal ions. Ca(II) is clearly the most extensively investigated metal ion in this group and it was found to bind to the *ax–eq-ax* site of the ligand [6]. Ca(II) induced conformational changes were also observed [439]. The vast majority of the studies was performed in solid phase, the complexes being characterized by FTIR spectroscopy. Ca(II) and Mg(II) were shown to bind only the α-anomers of Glc [440]. In the crystal structure of tetrahedral bis-anhydroerythritolate Be(II) complex the Be···O distances were found to be around 163 pm [441]. Ca(II), Sr(II) and Ba(II) formed octacoordinated, while Mg(II) formed hexacoordinated complexes with GlupA. The three ligands, completing the coordination sphere, were bonded in different mode: one coordinating by carboxylate and C(5)–OH, the second by carboxylate and C(4)–OH and the third by two adjacent hydroxy groups [442,443]. Single crystals have been prepared recently from GlcA and LacbA with Ca(II) [444] as well as from LacbA with sodium, potassium [444] and cesium [445]. X-ray diffractometry revealed that Ca(II) ions coordinate exclusively to the open chain part of LacbA via the carboxylate and the non-deprotonated alcoholic hydroxy groups, similarly to the GlcA complex, but the Ca···O distances are between 242–252 pm range in the former and ca. 241 pm in the latter case. An interesting feature of the alkaline cation containing LacbA complexes is that the metal ions coordinate to both the gluconato and the galactose residues of the ligand enhancing the possibility of an intramolecular hydrogen bond. Group(II) metals bound exclusively through the alcoholic hydroxy groups to Taci in the bis complexes, showing an almost regular octahedron for Mg(II), while the coordination number of 8 for Ca(II) and 9 for Sr(II) was achieved by additional coordination of two and three water molecules, respectively [44].

Much stronger interaction can be expected between these metal ions and polyfunctional molecules. Hya was shown to bind Ca(II) ions, and the comparison of the stability constants of different metal ions yielded the following preference sequence: $K^+ < Ag^+ < Ca^{2+} < Cu^{2+}$ [446]. Other Ca(II) binding biological molecules have already been mentioned in Section 3.

4.7.2. Group III

Borate esters formed with carbohydrates were studied by potentiometry and NMR by Verchére et al. [447,448]. van Bekkum et al. determined the local association constants of borate esters with a series of carbohydrates and derivatives by ^{11}B- and ^{13}C-NMR spectroscopy. The smallest K_1 values were obtained for alditols, 1–3 M^{-1}, while for the carboxylate containing sugars K_1 varied between 3 and 45 000 M^{-1} depending on the conformation of the sugars [37,449]. Borate esters were also formed with polyhydroxycarboxylates [450], polyhydroxyoximes [451] and polyhydroxyalkylamines [452] in aqueous solution. Borate was also observed to selectively catalyze the alkaline oxidative degradation of mono- and disaccharides by H_2O_2 [453,454]. Complexes of borate-and also Al(III)-with polyhydroxycarboxylates are known for their synergetic metal ion complexing properties, depending on the metal ion, pH and the stability of the borate ester [455–457].

Al(III) has a strong tendency to displace the protons of the hydroxy groups of hydroxy acids. Martell [458] found that in the reaction of Al(III) with different hydroxycarboxylic acids (among them GlcA and saccharic acid) 1:1 species were formed, containing the ligands in different protonation states. Recently, it was proved that Al(III) prefers to displace the hydroxy protons from sugar acids (GlcA and LacbA) already in acidic and even in alkaline media (preventing the hydrolysis of the metal ion), while Ga(III) and In(III) formed hydroxo complexes on increasing pH. On the basis of ^{13}C-NMR measurements the carboxylate and the three neighbouring alcoholic hydroxy oxygens were suggested to be the metal ion binding sites [459]. The mixed metal, Al(III)–aldarate–Ca(II) complexes (Fig. 19) have been characterized by multinuclear NMR spectroscopy by van Bekkum et al. The Ca(II) sites of all the complexes are the free carboxylate groups and, additionally, the free or the Al(III)-bonded hydroxy groups [457]. X-ray crystallography showed that in the bis complexes of Taci both ligands were coordinated via the oxygen donor groups to Al(III), and via the amino groups to Tl(III), while one ligand was coordinated by the alkoxo groups, and the second by amino groups in the Ga(III) complex. The equlibria in aqueous solution were also studied by pH metric titrations [45].

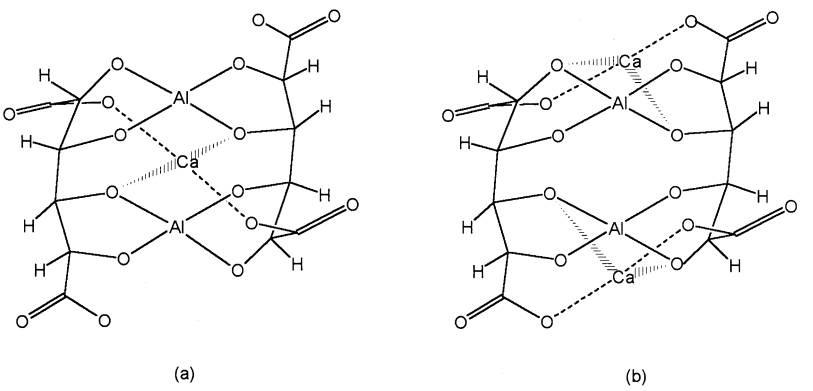


Fig. 19. The proposed structure of Al(III)–glucarate–Ca(II) 2:2:1 (a) and 2:2:2 (b) complexes [457].

Tonkovic et al. [460,461] investigated the structure of incorporated Fru, Sacc, Glc and GlupA into an aluminium hydroxide matrix. In all cases aluminium was found to be octahedrally coordinated, similarly to Al(III) raffinose, Mal, GlcA, and LacbA complexes [462]. It was found that Glc is bonded to the metal ion via the hydroxy groups on C(4) and C(6) atoms in both α- and β-pyranose forms. GlupA bound via the carboxylate and the C(4)–OH group. The formation of homoleptic diacetoneglucose complex of organo-aluminium has also been reported [463]. Tl(I) influenced the sugar conformation in mononucleotides, however the sugar residue suggested to remain uncoordinated, the main binding sites being the base nitrogen and the phosphate groups [464].

4.8. Organotin(IV) complexes

It is well known that organotin(IV) compounds have strong biological activity. The moieties $R_nSn^{(4-n)+}$ ($n = 2$ or 3) may be bonded to proteins and glycoproteins of cell membranes, as well as to cellular proteins: e.g. Et_2Sn^{2+} to ATPase and hexokinase [465], Bu_2Sn^{2+} or Bu_3Sn^{+} to ATPase and acetylcholine esterase of human erythrocyte membrane [466,467] and Bu_2Sn^{2+} to skeletal muscle membranes. Some organotin(IV) compounds have shown antitumour activity [468]. The organotin(IV) compounds have also been used widely in synthetic carbohydrate chemistry [11,469–475].

The presence of organic ligands, among them carbohydrates in organotin(IV) complexes modifies their biological properties [476]. For example the triaryltin(IV)–Sacc conjugates have been shown to be effective in marine antifouling paints [477]. This can be a reason for the increasing interest in interaction between organotin(IV) compounds and carbohydrate derivatives [11].

According to our knowledge there are only few papers in the literature on equilibrium studies of organotin(IV)–carbohydrates or carbohydrate derivatives. A recent work [478] demonstrated that the coordination of dimethyltin(IV) caused the deprotonation of the first two alcoholic OH groups of Fru in the — for such a system unusually low — pH interval 4–6, (see Fig. 20 for the species distribution curve) owing to the favourable steric arrangements of the hydroxy groups of the molecule. The coordination is not anomer selective.

^{13}C-NMR spectroscopic measurements showed that trialkyltin(IV)-GlupA complexes were formed upon reaction of GlupA with bis(tri-*n*-butyltin) oxide, but surprisingly not with tri-*n*-butyltin(IV)- or trimethyltin(IV) chlorides in DMSO or with trimethyltin(IV) chloride in water. Primarily the C(4)–OH hydroxy and to a smaller extent the ring oxygen at C(1) coordinated to the organotin(IV) cation [479].

The diethyltin(IV) cation coordinated to the *N*-D-gluconyl-α-aminoacids via the carboxylate, the deprotonated amide and the adjacent alcoholic hydroxy groups in the $[MLH_{-2}]^{-}$ complexes as proved by ^{13}C-NMR measurements. In contrast to this, the β-alanine derivative bound through the carboxylate and deprotonated hydroxy groups with the amide group remaining uncoordinated [480]. The structure of the species formed have been determined in quick frozen solution by Mössbauer

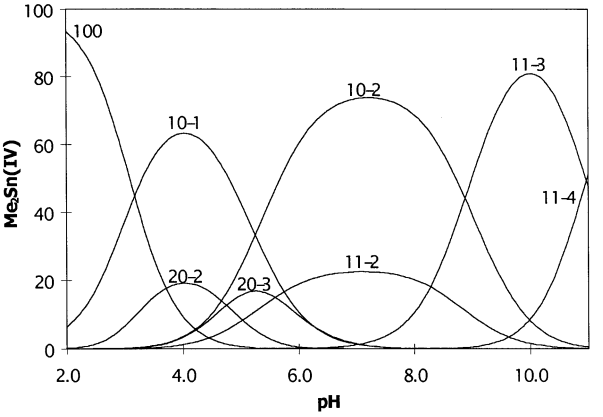


Fig. 20. The species distribution diagram in the dimethyltin(IV):Fru = 1:2 system ($c'_M = 0.01$ M; the complexes are denoted as *pqr* according to the formula $[M'_p(Fru)_qH_r]$, $M' = Me_2Sn(IV)$) [478].

measurements. The interaction of diethyltin(IV) dichloride and PHTAc derivatives led to the formation of $[MLH]^{2+}$, $[ML]^{+}$ and [ML(OH)] complexes, parallel with the formation of the hydrolysis products of organotin(IV) cation [481]. The ligands bound in amino acid type coordination, while the polyhydroxyalkyl substituents did not show direct coordination to dialkyltin(IV), they exerted steric effects only. Mössbauer titration was performed in di- and trimethyltin(IV) D-ribose-5-phosphate system, by changing the ligand to metal ratio and the coordination of the phosphate moiety alone was established at pH 7.4 [482]. Potentiometric and ^{1}H- and ^{31}P-NMR studies on the coordination of dimethyltin(IV) to nucleic acid fragments and related ligands, among them Rib and dRib showed that in acidic medium, up to pH 7, the phosphate groups can provide suitable sites for the metal ion, while the hydroxy groups started to coordinate only above pH 8 [483].

In the reaction of vicinal diols with dialkyltin oxide [481,484–491] or dialkyltin diethoxide [492–494] under conditions of azeotropic dehydration cyclic dialkoxides, dialkyl-1,3,2-dioxastannolanes, are formed. Such complexes [495] have been studied by ^{1}H- and ^{13}C-NMR [490,496] and by multinuclear NMR (^{119}Sn, ^{1}H, ^{13}C) [497–499] spectroscopy and were shown to be present in solution as dimers and/or higher oligomers in which the tin central atoms are penta- or hexacoordinated. Both the ^{119}Sn chemical shift intervals (from -100 to -150 ppm for the pentacoordinated and from -230 to -300 ppm for the hexacoordinated tin nuclei with respect to tetramethyltin in solution [499,500]) and the ^{119}Sn-NMR spin-lattice relaxation rates in 2,2-di-*n*-butyl-1,3,2-dioxastannolanes proved to be characteristic for the geometry of the coordination sphere [498,501,502].

A crystallographic study by David et al. [503] showed that the di-*n*-butylstannolane derivative of 4,6-*O*-benzylidene-α-D-glucopyranoside had a dimeric structure corresponding to the dimerization scheme in Fig. 23a., in which each tin atom showed distorted trigonal bipyramidal geometry. Later the structure of the same complex was redetermined by Cameron et al. [504]. The result showed, that the tin

atoms were pentacoordinated in severely distorted trigonal bipyramids, indeed. The butyl carbon atoms were equatorial but the average C–Sn–C bond angle is large (131.0°). Each of the *n*-butyl groups adopted different conformations and were still significantly disordered even at −70°C. The Sn–O bond lengths inside the monomer units were shorter (average 207 pm) than those between monomer units (average 223.7 pm). Contrary to these results, Holzapfel et al. [485] reported that the corresponding Man derivative had a pentameric structure (see the oligomerization scheme in Fig. 23b) containing two five- and three six-coordinated Sn(IV) central atoms. The Sn-O distances within a pentacoordinated monomeric unit (209 pm) and the 'intermonomeric' Sn–O distances (223 pm) for these units were similar to the above results. The average Sn-O distance to hexacoordinated tin between the monomeric units was 248 pm. On the basis of Mössbauer measurements on 2,2-di-*n*-butyl-mannose-stannolane, Davis et al. [487] have shown the presence of five- and six-coordinated tin atoms in 3:2 ratio. The degree of oligomerization was discussed in terms of the interaction between the sugar moieties. While in the Glc derivative the pyranose ring was in the plane of the dimeric unit preventing further association, in the Man derivative the pyranoside units projected perpendicularly from this plane, allowing the association to proceed as far as a pentamer. In the dioxastannolane derivative where no such pendant group is present (e.g. with ethyleneglycol) an infinite ribbon polymer has been formed. X-ray crystallographic data for the latter compound showed an average Sn–O bond length of 204 pm within the monomer units, and 251 pm between the units, the endocyclic O–Sn–O angle was found to be 79.9°, and the exocyclic C–Sn–C angle was 138.6° (Fig. 21).

Mössbauer spectroscopy revealed that the usual magnitude of the QS was ca. 2,90 mm s^{-1} for dialkyltin(IV) derivatives of carbohydrates in solid state, indicating a coordination number greater than four, usually five- or six-coordinated Sn(IV) surroundings in the oligomeric or polymeric complexes [481,487–489,491,505–507]. The comparison of the experimental quadrupole splitting values with those calculated on the basis of the partial quadrupole splitting (PQS) concept revealed that the complexes formed belong to one of the three types with central diethyltin(IV) and di-*n*-butyltin(IV) present: (a) in purely trigonal bipyramidal; (b) in purely octahedral surrounding; and (c) in both octahedral and trigonal bipyrami-

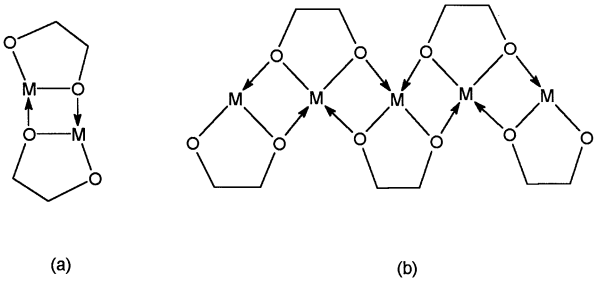


Fig. 21. The di- and oligomerization scheme for the 2,2-di-*n*-butyl-1,3,2-dioxastannolanes derived from carbohydrate ligands (M denotes Bu_2Sn(IV)).

dal arrangements in approximately 1:1 ratio [489]. In case of di-*n*-butyltin(IV) cation tetrahedral complex of D-mannitol is also detectable [491]. Different structural isomers were distinguished (equatorial or axial arrangements of two organo substituents) for diethyltin(IV)- [489,491], di-*n*-butyltin(IV)- [491,508] and dibenzyltin(IV)-carbohydrates [507] and di-*n*-butyltin(IV)–PHTAc [481] and -flavonoid glycosides (Rutin, hesperidin etc) [509] complexes. The formation of different structural isomers have been discussed in terms of different steric requirements of organo substituents. The Goldanskii–Karyagin effect for di-*n*-butyltin(IV) complexes have also been observed and discussed [491].

Since no single crystals suitable for X-ray diffraction measurements were obtained so far for the organotin(IV) complexes of unprotected sugars, the first structural information for this type of solid complexes by means of EXAFS was published by Nagy et al. [510]. The results showed that the diethyltin(IV) units were associated into an infinite ribbon polymer, in which Sn(IV) bound to two carbon atoms and to three or four oxygen atoms. Within each unit the average Sn–O and Sn–C bond lengths in the first coordination shell were 206–210 and 213 pm, while these bond distances between units showed somewhat larger variation (246–255 pm) similarly to the X-ray diffraction data obtained for complexes of protected sugars and discussed above. The Sn···C and Sn···Sn distances in the third and fourth shells are in the range of 277–323 and 324–362 pm, respectively. The endocyclic Sn–O–Sn angles fall in the range 80–98° and are comparable with the value of 79° published in Ref. [487]. These EXAFS investigations have proved the correctness of structural information, derived from Mössbauer studies based on the PQS concept, on the symmetry and configuration of the coordination sphere of diorganotin(IV) complexes.

Wardell et al. prepared some C-stannylated carbohydrate derivatives with protected sugars and determined the structure of these by means of X-ray crystallography, ^{1}H-, ^{13}C- and ^{119}Sn-NMR spectroscopy [511–515]. Studies on the alkyl or aryl tin bond cleavage by iodine showed that the β-hydroxy group is in ideal position to aid the above process by nucleophylic assistance. It was found that in the 1,2:5,6-di-*O*-isopropylidene-3-C-methyl-α-D-allofuranose triphenyltin(IV) derivative the tin atoms are in a slightly distorted tetrahedral environment (d(Sn–O) = 301 pm), but distorted trigonal bipyramidal arrangement of the di-*n*-butyltin(IV) compound with iodine and oxygen in axial positions (d(Sn–O) = 268 pm) has been observed [512].

4.9. Lanthanide and actinide complexes

Lanthanides showed very strong preference for oxygen donor atoms, consequently water is a strong ligand for them. The difficulty that competing ligands experience in attempting to dislodge water molecules from the coordination sphere severely restricts the types of ligands, which can interact with these cations in aqueous solution. Although lanthanides have a very low affinity for simple uncharged carbohydrates, their interaction could be detected by NMR and Tb(III) CPL spectroscopy. One of the first studies of this kind were done by Angyal [516].

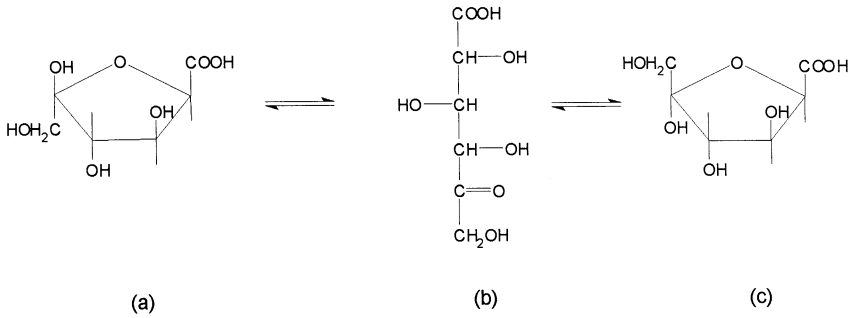


Fig. 22. The schematic structure of D-*xylo*-5-hexulosonic acid: 1-α (a), keto (b) and 1-β (c) forms.

His generally accepted rule (the most stable complexes are formed with sugars containing three -OH in *ax–eq–ax* configuration in at least one chain conformational anomer) was confirmed by the results of the Tb(III) CPL investigations [517]. ^{1}H- [518] and ^{13}C-NMR [519] studies on the lanthanide induced NMR shift of alditols also supported the conformational preferences discussed in the general properties. The results also showed that Yb(III) ion was superior to La(III), Pr(III) and Eu(III) in shifting the ^{13}C resonances of D-sorbitol. The shift data suggested a tridentate complex, with Yb(III) resting 230 pm from C(2)–O, C(3)–O, and C(4)–O. [519]. Among the alditols studied, D-mannitol is the one of the weakest binders. Consistent with this interpretation, Gd(III) was shown to broaden the ^{13}C resonances of C(2), C(3) and C(4) or C(5) [520]. The stability constant calculated from the ^{139}La chemical shift was 2.8 M^{-1} for the La(III) Rib complex, while complexation with D-arabinose was almost not detectable [521]. A recent multinuclear NMR investigation showed that La(III) may force D-glucitol, to obtain a suitable conformation to provide three hydroxy groups for the coordination [522].

Introducing a carboxyl group greatly increases the affinity of carbohydrates for lanthanides. In a series of papers Anthonsen et al. have reported on the interaction of lanthanide(III) ions with carbohydrate derivatives (among them GlupA and GalpA) to understand the gelation of poly-(1,4-hexuronates) induced by metal ions. They observed that three consecutive hydroxy functions with an *ax–eq–ax* arrangement provide a favourable binding site. In some cases the stability constants of the lanthanide(III) complexes have also been determined e.g. $K = 350$, 160 and 6.5 M^{-1} for Eu:GalpA = 1:3, 1:2 and 1:1 species, respectively suggesting some kind of cooperativity in the binding [523–528]. However, Izumi [529] and Angyal [530] have suggested a bidentate coordination mode via the carboxylate and the ring oxygen of the α-anomer. The same binding sites have been found in the chondroitin sulphate Yb(III) complex by De Bolster et al. [531]. Stereoselectivity of the Gd(III) ions on the relaxation properties of ^{13}C and ^{1}H nuclei of some aldohexuronic acids was observed for the α-anomers of these ligands [532].

D-*xylo*-5-hexulosonic (5-oxo-GlcA, see Fig. 22) acid has found various applications, e.g. as a browning agent for food and as a precursor of the meat flavour dihydro-4-hydroxy-5-methyl-3-furanose. Gd(III) bound preferentially to the keto

tautomer of this ligand in a bidentate fashion via the carboxylate oxygen and the C(2)–OH at pD = 7. The first coordination sphere of Gd(III) in this complex is completed by furanose forms of the ligand bound in bidentate manner via the two carboxylate oxygens [533]. Gd(III) coordinated to a unique binding site of three alcoholic hydroxy groups in gluconamides, while Mn(II) binding was nonspecific according to ^{13}C-NMR measurements [534].

On the basis of a CD study on a series of polyhydroxy acids with Pr(III) and Eu(III) ions the presence of 'acidic' and 'neutral' complexes has been suggested in aqueous medium with the carboxylate and α-, and with the carboxylate and γ-hydroxy groups in the coordination sphere, respectively [535–537].

A series of lanthanide(III) complexes formed with D-aldonic and D-alduronic acids have been prepared and characterized by Edelmann et al. [538]. It was found that in most cases the carboxylate group coordinated in monodentate manner. Beside the carboxylate the α- and sometimes the β-alcoholic hydroxy groups were also bonded to the central metal ions according to the general ionization scheme for polyhydroxy carboxylic acids discussed by van Bekkum et al. [35].

Structure and dynamics of some lanthanide complexes with sugar based DTPA-bis(amides) (Fig. 23) have been determined by multinuclear NMR [539]. Octadentate coordination of the organic ligand via amino, amide and carboxylate groups was observed. The sugar moiety did not influence significantly the coordination mode.

Ce(IV) ion has been proved to be an efficient catalyst in the hydrolysis of disaccharides [540]. The monosaccharide complexes of this ion were found to promote DNA hydrolysis [66].

According to the results of FTIR measurements, GlupA forms two types of complexes with hydrated uranyl salts: $[UO_2(L)X]\cdot 2H_2O$ and $[UO_2L_2]\cdot 2H_2O$ (where $X = Cl^-$, Br^- or NO_3^-) [541]. Hexacoordinated UO_2^{2+} ion was found, with bipyramidal geometry, where the equatorial coordination occurred preferentially through the two ionized carboxylate C(6)–O and C(6′)–O′ oxygens, parallel with the binding of only one of the oxygens of each carboxylate and one hydroxy or ring

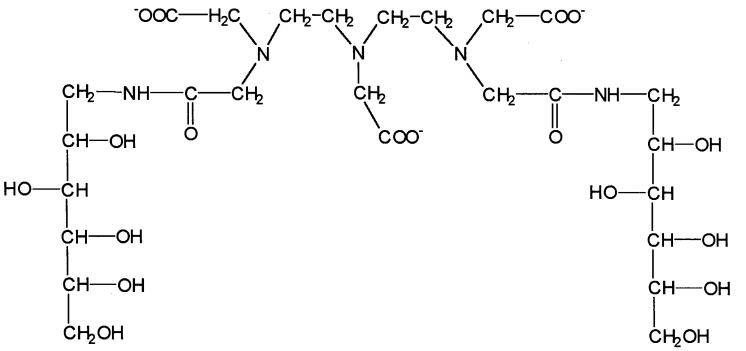


Fig. 23. The schematic structure of the DTPA-bis(glucamide) ligand, (DTPA = diethylenetriamine-*N*,*N*′,*N*″,*N*″-pentaacetate) [539].

oxygen of each sugar ring. Fru forms only one complex with the composition $[UO_2(L)X_2]\cdot 2H_2O$ ($X = Cl^-$, Br^-, NO_3^- or 1/2 SO_4^{2-}), with the UO_2^{2+} cation bonded to the sugar moiety via two *cis* hydroxy groups [542]. The binding of the metal ion can occur both with D-fructofuranose and D-fructopyranose. Further studies on the complexation of UO_2^{2+} to various monosaccharides and related compounds in aqueous solution have been performed by Geraldes et al. [543] by means of ^1H- and ^{13}C-NMR method. Similarly to the results published in Ref. [542], it was found that complexation occurred above pH 10 with both pyranose and furanose forms of Man and Rib coordinated in various *cis*-diol modes. In the case of sugar derivatives like D-ribose-5-phosphate or mononucleotides, polynuclear complexes were formed above pH 11 involving the coordination of uranyl cation both by the sugar hydroxy and the phosphate groups, whereas below pH 10 only the phosphate group reacted [544].

5. Concluding remarks

This overlook on the literature data, with the emphasis on the last two decade has confirmed that the field of metal ion-sugar type complexes became quite extensive. In spite of this still a large part of experimental work should be performed. The introduction of recently developed sophisticated experimental methods (e.g. EXAFS, electrospray mass spectrometry), or the developments in the already used methods (NMR, FTIR, EPR, equilibrium measurements, etc.) largely accelerate the progress. The development of new carbohydrate type chelators by the introduction of anchoring donor groups provide new complexes of medicinal, pharmaceutical, agricultural and chemical use. The study of the biological systems containing carbohydrate type complexes and of the biological effects of the synthetized complexes in more detail is warranted to get a better view into the mechanism of the action.

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