

## Carbohydrates and Related Compounds as Ligands: Complexes and Applications

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Recently, there has been an increased interest in the field of inorganic carbohydrate chemistry due to developments in various areas involving their coordination as ligands. It is not surprising, considering the abundance of electronegative functional groups in carbohydrates, that they readily react with metal cations.

Complex formation between salts and carbohydrates is not a new subject. Crystalline adducts of sugars with inorganic salts have been studied since 1825 when an adduct of D-glucose with NaCl was first described [1]. For the next 150 years, however, little was published on the subject. Although crystalline adducts of sugars and alkali and alkaline earth metals were studied to prove the existence of such compounds [2], little was done to confirm coordination geometries of the compounds and there was doubt as to their existence in solution. In 1961, the first proof of metal-sugar interactions in solution was noticed--by accident [3]. A study to test sugar acidity in basic solutions by paper electrophoresis revealed that, surprisingly, the sugars migrated even at pH 7 and toward the cathode. It was concluded that the sugars must be interacting and migrating with the cations in the solution. It was not until 1971 that the first paper discussing the relationship between structure and complex-formation of neutral carbohydrates was published [4].

To a large extent, the conformations of carbohydrates determine their ability to form complexes. In general, sugars that can complex a metal center as a triol bind more strongly than sugars that can only complex as a diol; in addition, binding is strongest if these hydroxyl groups are arranged at the corners of an equilateral triangle. The strongest complexation is exemplified by the 1,3,5-*syn*-triaxial sequence of hydroxyl groups in *cis*-inositol [5]. The next most favorable arrangement is the axial-equatorial-axial sequence as seen in *epi*-inositol [6].

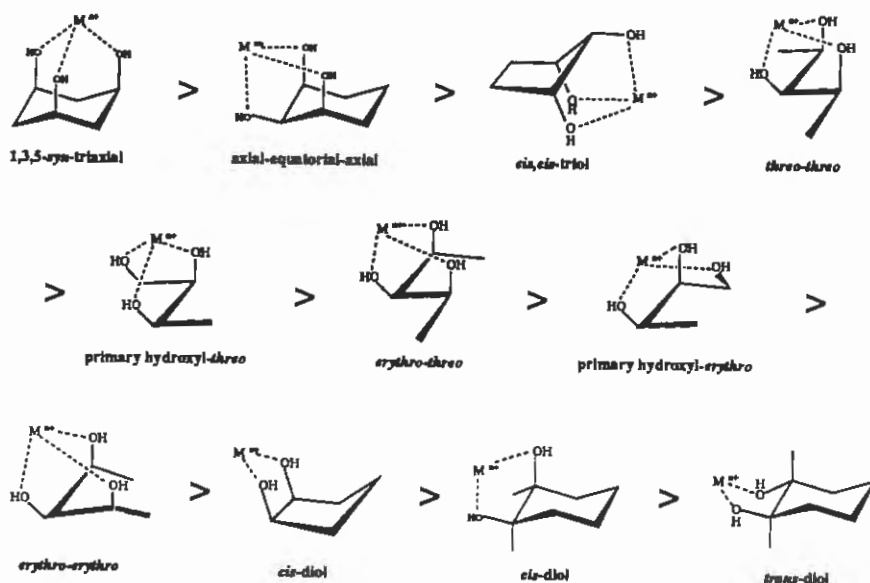


Figure 1. Relative strengths of complexation for polyol arrangements in aqueous solution

Five-membered cyclic triols will only bind if they possess a *cis,cis*-triol sequence. This arrangement follows the two previously mentioned in strength of complexation [7]. Acyclic triols, in general, bind less strongly than cyclic triols. All acyclic sequences can form triangular coordination sites, but their strength of complexation depends on whether or not there are unfavorable interactions within the carbon chain. Their effectiveness as complexing sites are, in descending order: *threo-threo*, primary hydroxyl-*threo*, *erythro-threo*, primary hydroxyl-*erythro*, and *erythro-erythro* [8]. Finally, the best ligand diols are found on five-membered rings in a *cis*-arrangement, then followed by *cis*- and *trans*- arrangements, respectively, on six-membered rings [9]. *Trans*-diols on five-membered rings do not coordinate to any significant extent in solution.

The strength of the metal-sugar interaction in solution is also dependent on the nature of the metal cation. Generally, univalent cations all complex weakly, divalent cations complex better, and trivalent cations form the strongest complexes. The ionic radius of the metal is crucial. At first it was believed that the best radius for complex-formation was 1.00-1.10 Å ( $\text{Na}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{La}^{3+}$ ) [10]. This estimate has been further refined to 0.95-0.98 Å as shown in a recent study of carbohydrate-lanthanide metal complexes [11].

Monosaccharides can be modified such that their hydroxyl groups are exchanged with either amino groups or primary and secondary amines to give amino-sugars and glycosylamines, respectively. Both types of compounds will coordinate to metal cations. D-glucosamine has been complexed as a bidentate ligand to Co(III) [12]. Glycosylamines have been used with nickel(II) as tri- and tetra-dentate ligands [13,14], as bridging ligands in binuclear complexes [15], and as ligands which exhibit intramolecular sugar-sugar interactions [16].

Since carbohydrates constitute the majority of the biomass, they could be convenient starting materials for the production of synthesis gas. Synthesis gas, a mixture of CO and  $\text{H}_2$ , is a starting point for the bulk synthesis of many organic chemicals, but thus far, a conversion of carbohydrates to synthesis gas has yet to be realized. Currently, reactions of transition metal organometallic complexes with carbohydrates are being investigated with the goal of discovering and understanding reactivity patterns that might ultimately serve as a basis for new, chemical approaches to biomass conversion [17-20].

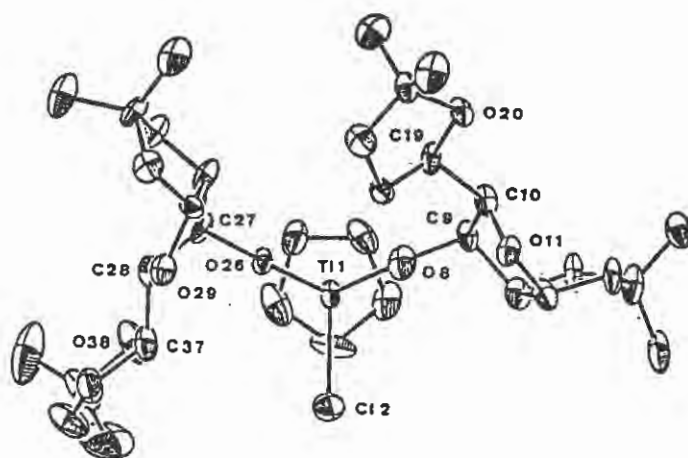


Figure 2. ORTEP of Chloro(cyclopentadienyl)bis(1,2:5,6-di-O-isopropylidene-a-D-glucufuranos-3-O-yl) Titanate [25]

Due to the wealth of possible stereochemistries which carbohydrates may assume, they are ideal ligands for asymmetric synthesis. This application is recognized in a homoleptic vanadium(III) complex in which diacetone glucose residues are monodentate to form a chiral Lewis acid [21]. Also, this synthetic strategy is currently utilized with a Ti(IV)-carbohydrate complex in the enantioselective allyl and ester enolate additions to aldehydes [22-25].

Carbohydrates and their related compounds have been very successful ligands in complexes used in the pharmaceutical industry. Cisplatin (an anti-tumor agent) derivatives have been synthesized in which the neutral ammonia ligands are replaced by amino-sugars [26-27]. These ligands tend to increase the solubilities and decrease the toxicities normally found for cisplatin derivatives. They also exhibit anti-tumor activities that are comparable to those of other, more commonly used, anti-cancer drugs. Another pharmaceutical application of metal-sugar complexes which has been quite effective is chrysotherapy. Gold-sugar complexes have long been known to be effective in the treatment of arthritis [28-29].

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