

Carbohydrate–Metal Interactions Shaped by Supramolecular Assembling**

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The most abundant biomolecules, the carbohydrates, can form stable complexes with metal ions in aqueous solution, provided that (multiple) deprotonation of the sugars is supported by a sufficient degree of Lewis acidity of the metal center. The first transition row of the periodic table contains the most important biometals. Of these, all divalent ions except copper(II) are so weakly acidic that stable carbohydrate complexes are known only in higher oxidation states (Mn, Fe, Co) or in the presence of ancillary ligands (Ni). Both iron and manganese, in their higher oxidation states +III (Mn and Fe) and +IV (Mn), are sufficiently acidic to stabilize multiply deprotonated carbohydrate ligands which, in turn, form complexes of such a high stability that precipitation of even some of the least soluble (hydr)oxides, namely, $\text{Fe}(\text{OH})_3/\text{FeO}(\text{OH})$, $\text{Mn}(\text{OH})_3/\text{MnO}(\text{OH})$, and MnO_2 , is prevented in the presence of some carbohydrates. Hence the monosaccharide mannose, being a particularly well-suited ligand in terms of the O_5 pattern of its β -furanoside isomer, forms dinuclear Fe_2^{III} , Mn_2^{III} , and $\text{Mn}^{\text{III}}\text{Mn}^{\text{IV}}$ complexes in the neutral or alkaline pH region with two entirely deprotonated mannosefuranose anions as the only ligands.^[1,2] Deprotonated carbohydrate ligands are apparently present in the active centers of carbohydrate-directed metal enzymes as well. The most important example, economically, is xylose isomerase which is used to convert D-glucose into D-fructose on a commercial scale.^[3,4] The active site contains two metal ions (manganese, magnesium, or cobalt) which are divalent, and thus are of lower Lewis acidity. With the exception of the enzyme's pocket, an aqueous carbohydrate chemistry of divalent manganese, as well as divalent iron, ions does not appear to exist in terms of stable, structurally characterized complexes. The addition of iron(II) or manganese(II) salts, for example, to aqueous alkaline carbohydrate solutions, results in precipitation of

the respective hydroxide only—compare this behavior with that of copper(II), the strongest Lewis acid among the M^{2+} ions of the first transition row which forms deep blue complexes in alkaline solutions of various carbohydrates, such as monosaccharides^[5] and glycosides including cyclodextrins.^[6]

Herein we demonstrate that the formation of supramolecular assemblies, other than the preorganized pattern of ligands in the active site of an enzyme, can add additional stability to the carbohydrate complexes of the divalent ions of iron and manganese. The supramolecular aspects of carbohydrate–metal chemistry appeared in outline during a particularly simple observation: with α -cyclodextrin (α -CD), the cyclic α -1,4-linked hexamer of glucose, clear solutions form instead of a hydroxide precipitate when lithium salts are added to $\text{Fe}(\text{OH})_2/\alpha$ -CD/NaOH slurries—or, more directly, when lithium hydroxide is used instead of sodium hydroxide. Crystallization and X-ray analysis of the individual compounds revealed the same structure for iron(II) and manganese(II). Figure 1 (left) shows the structural principles for the iron compound $\text{Li}_5[\text{Li}_6(\text{H}_2\text{O})_6\text{Fe}_3(\text{H}_2\text{O})_3(\alpha\text{-CDH}_{-7.5})_2\text{H}_{-2}]\cdot 56\text{H}_2\text{O}$ (**1a**); a very similar molecular structure is observed with manganese(II).^[7] Three five-coordinate iron centers form aqua–bis(diolato) moieties—which are not stable as complexes with isolated glucose residues, such as, with glucose itself or an alkylglucopyranoside as the ligand. In **1a** however, the glucose units are not isolated but there are several stabilizing structural fragments which are all formed according to the rules of pattern recognition, that is, according to principles of supramolecular chemistry.^[8]

To unravel the various factors which contribute cooperatively to the overall stability of the assembly in **1a**, a step-by-step approach has been chosen which, of course, may not reflect the true formation mechanism. A structural description may thus start with three iron(II) atoms that assemble two CD tori to a $(\text{CD})_2$ double torus. The six diol functions of one torus now face the six diol groups of the other, and, after 12-fold deprotonation, three of the six diol pairs bind the iron(II) atoms to give three bis(diolato)iron centers. The deprotonated sites are stabilized by shortening some of the intramolecular $\text{O}2\cdots\text{O}3'$ hydrogen bonds of each torus. Since the typical hydrogen-bonded $\text{O}2\cdots\text{O}3'$ distance between the glucose units of an α -CD torus is about 2.8 Å, those glucose units that do not bind to iron are tilted towards one of their two neighboring iron-binding glucose units to shorten the respective hydrogen bond. This feature is depicted in Figure 2: the upper non-iron-binding glucose shortens the $\text{O}\cdots\text{O}$ distance to the left diolate, the lower to the right one. The remaining two hydroxy functions of the non-metallized glucoses reorientate their hydrogen bonds. The intratorus hydrogen bonds are lost and a new, short, intertorus bond is established. Considering both the short $\text{O}\cdots\text{O}$ separation and the balance of charges, monodeprotonation of this site should be assumed (Figure 2). Having established these three hydrogen bonds per non-metallized glucose pair, two optimal binding sites for lithium counterions result in this part of the double torus, that is, six sites in the entire assembly. These sites resemble O_3 basal planes of LiO_4 tetrahedra. The remaining coordination sites at Li point inside the double

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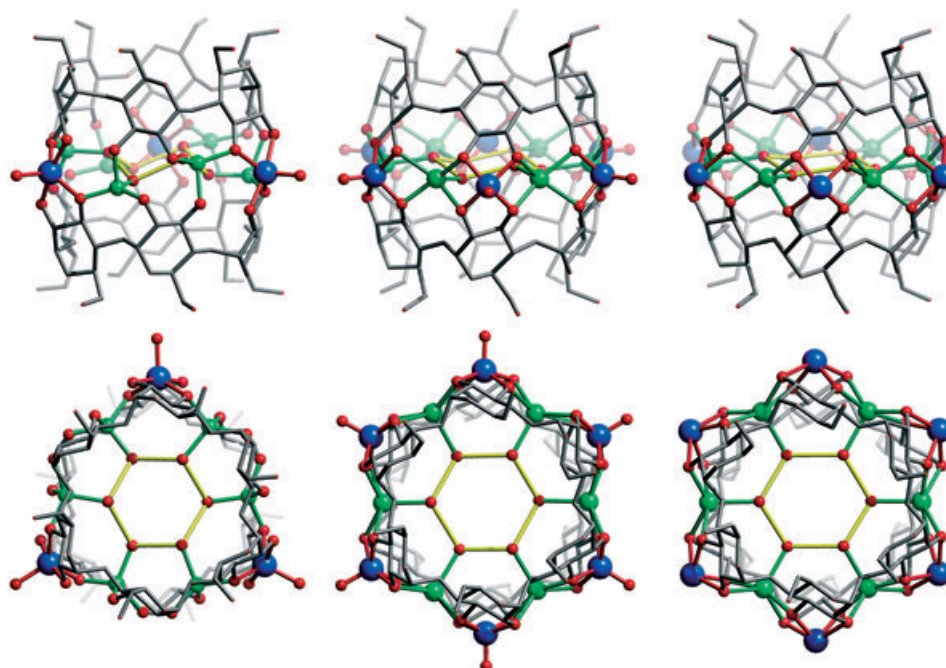


Figure 1. X-ray crystal structures of the C_3 -symmetric ferrate(II) unit in **1a** (left), the C_3 -symmetric oxo-vanadate(IV) unit in **2** (middle), and the C_2 -symmetric, electroneutral bismuth(III) aggregate in **3** (right). Top: view onto the cylinder; bottom: view through the cylinder. Blue Fe, V, or Bi; red O; green counterion; yellow bonds represent hydrogen bonds between water molecules. For comparison, all structures are drawn to the same scale.

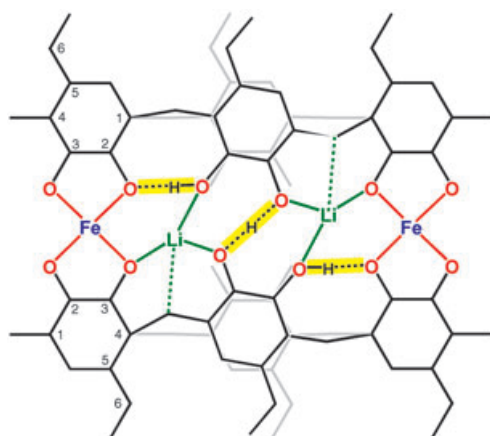


Figure 2. Hydrogen bonds in the cylinder wall in **1a**: shown here is the front part of the cylinder shown in Figure 1, top left. The two middle glucose units are tilted out of their undistorted position, which is shown in gray. O–O separations in the highlighted hydrogen bonds are between 2.45 and 2.55 Å. Glucose-atom-numbering scheme also shown on the left side; in this scheme, centers without a number are oxygen atoms.

torus. Owing to the aqueous reaction medium, these positions are occupied by six water molecules, which, because of the overall dimensions of α -cyclodextrin, find themselves at an optimum distance to establish a homodromic (H_2O)₆ cycle (yellow hexagon in Figure 1a, homodromic = hydrogen bonds all run in the same direction). Owing to its chairlike structure, the water hexamer resembles the basic building block of cubic ice I_c . Along with other water oligomers, the chair hexamer

has been recognized as one of the more stable conformations of this basic motif.^[9,10] As a result, there are many factors that, though too small to establish isolated structural fragments of a similar kind, such as diolato ferrates derived from simple diols or highly lithiated α -CD salts, nevertheless contribute to the total energy of the entire supramolecular assembly. These factors are: 1) aqua–diolato–ferrate(II) formation, 2) intramolecular hydrogen-bond strengthening, 3) counterion aggregation, 4) counterion hydration, and 5) formation of a cooperative hydrogen-bond system in the cyclic water hexamer. From the viewpoint of carbohydrate–iron complexation, points 2–5 represent a supramolecular support that resembles the three-dimensional pre-orientation of the ligating protein side-chains in a metal enzyme, such as xylose isomerase.

The significance of the supramolecular contributions is particularly clear if the scope of the investigation is extended to stronger Lewis acidic metal ions that stabilize deprotonated diol functions more efficiently. Though supramolecular support is not necessary for carbohydrate complexation in these cases, the respective α -CD complexes show in their cooperative features a surprising persistency, which strongly underlines the significance of the supramolecular factors mentioned. As a result, metal ions of very different kinds lose their individuality of behavior when forming an assembly with α -CD tori. This principle is demonstrated by two metals of otherwise different chemistry, one a hard Lewis acid and the other a soft Lewis acid: oxo-vanadium(IV) and bismuth(III).

Owing to their higher Lewis acidity than iron, metal-bonding and the formation of intramolecular hydrogen bonds do not compete in the case of oxo-vanadium(IV) ions, VO^{2+} .

Hence each of the six facing bis(diols) moieties of a hypothetical (α -CD)₂ double torus transforms into a bis(diolato)oxo-vanadium center on the reaction of α -CD, an oxo-vanadium salt, and sodium hydroxide. Blue crystals of Na₆[Na₆(H₂O)₆(VO)₆(α -CDH₋₁₂)₂] \cdot 59 H₂O (**2**) contain double-toroidal anions (Figure 1; middle). Again, the principle of pattern recognition is adequate to comprehend the structure. As a result of the entire deprotonation and metalation of each of the diol functions, no intramolecular hydrogen bonding has to be considered—and hence no deformation of the tori with respect to a glucose tilt such as that shown in Figure 2. Instead, between the glucose units, that is, between each of the bis(diolato)vanadium moieties, an almost square O₄ pattern is present, which is optimally suited to coordinate a larger counterion than the lithium-binding O₃ pattern in **1**. Six sodium ions are thus found per double torus. The side of the square is not long enough to accommodate the sodium ions into the square plane, thus they are located outside the plane. Of the two possible orientations (inside and outside the double torus), the inside-the-double-torus arrangement is realized and the homodromic hexaqua cycle can form as well. Note that in **1** the stabilizing factors may partly be compensated by the energy that is required for the glucose tilt described above. With **2**, we do not find any destabilizing contributions of steric origin.

As the energy gain from counterion binding and the fitting of the hexaqua hexagon may be substantial, the structure of the electroneutral bismuth compound [Na₆(H₂O)₆Bi₆(α -CDH₋₁₂)₂] \cdot 47 H₂O (**3**) is as expected (Figure 1, right). Owing to its +III oxidation state, a stereochemically active lone pair takes the place of the oxo ligand in **2** and the aqua ligand in **1**. The larger bismuth atoms stretch the double torus to a greater degree than the smaller iron and vanadium atoms. Thus the cone angle of each α -CD torus is smaller and the hexaqua hexagon is pulled flatter, but despite these marginal differences the similarity of the two structures **2** and **3** is striking and demonstrates their conditioning by supramolecular control.

The structures of compounds **2** and **3** demonstrate particularly that use of the principle of pattern recognition in synthetic work opens the door to a variety of low-dimensional oxo-metal compounds. The use of carbohydrates in bioinorganic chemistry as decisive building blocks could thus make a contribution to materials science. Although α -cyclodextrin molecules are not strictly rigid,^[11] double tori composed of them appear as reliable building units with predictable binding properties for this new class of compounds. The rules of metal assembling through carbohydrate-based nucleation, however, are still largely unexplored; even in cyclodextrin–metal chemistry there are open questions. A problem regarding the planned synthesis of these materials is presented by the preparation of **1–3**: what are the products of the reaction of oxo-vanadium and bismuth salts with α -cyclodextrin and lithium hydroxide? We will contribute descriptions of how nature accommodates a mismatch of one component in due course.

In conclusion, the synthetic principles reported herein open avenues towards molecular materials of the oxo-metalate class based on a biomolecule backbone. Supramolecular

and bioinorganic chemistry interact in this approach to provide a new synthetic strategy towards nanometer-scaled metalates for materials science.

Experimental Section

All compounds were prepared from alkaline aqueous solutions. Details for the synthesis of **1a** are given as an example. To prevent formation of iron(III), all operations were carried out under nitrogen. A suspension of iron(II) chloride tetrahydrate (0.255 g, 1.28 mmol) and α -cyclodextrin (0.629 g, 0.647 mmol) in water (5 mL) was slowly dropped into a suspension of lithium hydroxide monohydrate (1.355 g, 32.3 mmol) and α -cyclodextrin (0.605 g, 0.622 mmol) in water (5 mL). A clear, pale blue solution formed. On controlled diffusion of acetone vapors into the filtered solution, needles of **1a** formed in the course of 3 days. Colorless crystals of Li₇[Li₆(H₂O)₆Mn₃(H₂O)₃(α -CDH_{-7.5})₂H₋₄] \cdot 41 H₂O \cdot 2.5 EtOH (**1b**) are prepared by a similar procedure. For the manganese preparations, successful exclusion of oxygen is monitored with particular ease as the presence of even traces of oxygen lead to the solutions turning intensely blue owing to the formation of trivalent manganese. Compounds **2** and **3** are prepared similarly except that no inert gas is needed.

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- [7] Stoe IPDS, Mo_{K α} . **1a**: C₇₂H₂₃₃Fe₃Li₁₁O₁₂₅, M_r = 3343.432 g mol⁻¹, almost colorless needles, 1.30 × 0.05 × 0.05 mm³, trigonal, P321, a = 29.322(3), c = 15.8374(13) Å, V = 11 792.7(19) Å³, Z = 3, ρ = 1.4124(2) g cm⁻³, T = 200(2) K, μ (Mo_{K α}) = 0.395 mm⁻¹, θ range: 1.4–20.7°, 32 193 reflections, 8062 independent and used in refinement, 3936 with I ≥ 2 σ (I), R_{int} = 0.1564, mean σ (I)/I = 0.2348, 468 parameters, R(F_{obs}) = 0.0933, R_w(F²) = 0.2346, S = 0.885, Flack parameter: 0.01(5), min. and max. residual electron density: -0.487, 0.790 e Å⁻³. **1b**: C₇₇H₂₂₈Li₁₃Mn₃O_{118.5}, M_r = 3305.610 g mol⁻¹, colorless platelet, 0.46 × 0.39 × 0.06 mm³, orthorhombic, P2₁2₁2₁, a = 15.632(3), b = 25.561(4), c = 35.086(5) Å, V = 14 019(4) Å³, Z = 4, ρ = 1.5662(4) g cm⁻³, T = 200(2) K, μ (Mo_{K α}) = 0.393 mm⁻¹, θ range: 1.7–24.0°, 45 176 reflections, 19 395 independent and used in refinement, 11 327 with I ≥ 2 σ (I), R_{int} = 0.0531, mean σ (I)/I = 0.1032, 904 parameters, R(F_{obs}) = 0.0758, R_w(F²) = 0.2261, S = 0.968, Flack parameter: -0.01(2), min. and max. residual electron density: -0.757, 0.978 e Å⁻³. To obtain electroneutrality, two deprotonated sites are required for **1a** and four for **1b**, which, however, have not been located. The metal-bonded aqua ligands and the O6 hydroxy groups appear as candidates. **2**: C₇₂H₂₂₆Na₁₂O₁₃₁V₆, M_r = 3770.013 g mol⁻¹, blue prism, 0.34 × 0.22 × 0.10 mm³, trigonal, P312 (close to P622, twin refinement with trigonal symmetry, [010] considered as the twin axis), a = 17.8985(13), c =

31.066(3) Å, $V = 8618.8(12)$ Å³, $Z = 2$, $\rho = 1.4527(2)$ g cm⁻³, $T = 200(2)$ K, $\mu(\text{Mo}_{\text{K}\alpha}) = 0.457$ mm⁻¹, θ range: 1.5–23.9°, 53404 reflections, 8842 independent and used in refinement, 5616 with $I \geq 2\sigma(I)$, $R_{\text{int}} = 0.0960$, mean $\sigma(I)/I = 0.1041$, 348 parameters, $R(F_{\text{obs}}) = 0.0909$, $R_w(F^2) = 0.2733$, $S = 0.988$, Flack parameter: $-0.03(7)$, min. and max. residual electron density: -0.637 , 1.640 e Å⁻³. **3**: C₇₂H₂₀₂Bi₆Na₆O₁₁₃, $M_r = 4268.13$ g mol⁻¹, colorless prism, $0.25 \times 0.23 \times 0.15$ mm³, orthorhombic, $C222_1$, $a = 40.292(8)$, $b = 25.814(4)$, $c = 15.442(2)$ Å, $V = 16061(5)$ Å³, $Z = 4$, $\rho = 1.7651(5)$ g cm⁻³, $T = 293(2)$ K, $\mu(\text{Mo}_{\text{K}\alpha}) = 6.676$ mm⁻¹, θ range: 3.7–24.1°, 48016 reflections 12159 independent and used in refinement, 11523 with $I \geq 2\sigma(I)$, $R_{\text{int}} = 0.0799$, mean $\sigma(I)/I = 0.0464$, 460 parameters, $R(F_{\text{obs}}) = 0.0423$, $R_w(F^2) = 0.1126$, $S = 1.047$, Flack parameter: $-0.020(7)$, min. and max. residual electron density: -1.938 , 1.139 e Å⁻³. CCDC 234016 (**1a**), CCDC 234017 (**1b**), CCDC 234018 (**2**), and CCDC 234015 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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