J|A|C|S
ARTICLES
Published on Web 08/30/2003

A Sugar Discriminating Binuclear Copper(II) Complex

Susanne Striegler* and Michael Dittel

Contribution from the Division of Inorganic Chemistry II, University of Ulm, Albert-Einstein-Allee 11, D-89069 Ulm, Germany

Received April 10, 2003; E-mail: susanne.striegler@chemie.uni-ulm.de

Abstract: We investigated the complex formation between various underivatized carbohydrates and the binuclear copper(II) complex **1**, Cu_2(bpdpo). A combined approach of UV/vis and CD spectroscopic investigations shows a large discrimination ability of **1** for structurally closely related monosaccharides in alkaline solution. The dominating form of the binuclear copper(II) complex consists of a $[Cu_2L_{-H}(OH)_2]^+$ species between pH 11 and 13, as determined from pH-dependent spectrophotometric titration experiments. The binding strengths of the 1:1 sugar−**1** complexes, derived from the biologically important monosaccharides D-mannose (**3**) and D-glucose (**5**), is about 1.5 orders of magnitude different at pH 12.40. Moreover, a blue- or a red-shift of the absorption maximum of **1** accompanies the sugar binding and highlights the ability of **1** to discriminate carbohydrates. This phenomenon is due to the number of hydroxyl groups of the particular monosaccharide involved in chelation to the binuclear metal complex.

Introduction

Metal coordination of natural carbohydrates in aqueous solution has been shown to play a central role in many biochemical processes, such as signal transfer, cell−cell recognition, or fertilization.[1] Although coordination chemistry is of fundamental importance to these events, investigations on the structures and characteristics of carbohydrate coordination compounds are often limited to complexes derived from sugars with strong coordinating amino groups.[2] In contrast, carbohydrate−metal assemblies based on sugar-type ligands with weak coordinating alcoholic, aldehyde, or ketone oxygen donor atoms remain poorly understood.[3] Due to the low stability of the complexes in neutral or acidic aqueous solution, the characterization of the equilibria occurring during coordination is difficult and often reaches experimental limitations.[2a] We report here a set of spectroscopic experiments highlighting the remarkable selectivity observed during coordination of underivatized monosaccharides to the binuclear copper(II) complex *N*,*N*′-{1,3-bis[(pyridin-2-ylmethyl)amino]propan-2-ol}ato dicopper(II) (μ-acetato) diperchlorate **1**, Cu_2(bpdpo), under strong binding conditions in alkaline solution.

Results and Discussion

The synthesis of the binuclear copper complex **1** has been conducted for the first time almost twenty years ago.[4] Following this procedure by slight modifications, we obtained **1** as crystalline solid. The free amino ligand *N*,*N*′-1,3-bis[(pyridin-2-ylmethyl)amino]propan-2-ol, bpdpo, and its precursor ligand are characterized here more comprehensively. Assuming that binuclear copper(II) complex **1** and its derivatives **2** exhibit the same carbohydrate coordination behavior, we chose easily accessible **1** for the investigation of the sugar binding ability prior to the preparation of an immobilizable derivative **2**. Compound **1** is very soluble in polar solvents, such as water,[4] methanol,[4] acetonitrile,[4] dimethylformamide,[4] dimethyl sulfoxide, and pyridine. The titration of **1** with carbohydrates in CH_3CN, DMSO, DMF, or pyridine did not result in monosaccharide−**1** complexes as concluded from the nonshifted absorption maxima of **1** during a UV/vis spectroscopic investigation and the lack of saturation of **1** upon monosaccharide addition. Subsequently, alkaline aqueous solutions were used for further investigations of the complex formation ability.[5] During the course of our study, Gajda and co-workers reported investigations on the composition of **1**, derived from the corresponding hydrochloride of the amino ligand, in aqueous solution at up to pH 11 and in solid state.[6] As the number of hydroxyl groups coordinated to the metal centers in the binuclear copper(II) complex in aqueous solution above pH 11 remained unclear, however, and as we plan to use strong carbohydrate binding during the preparation of sugar selective receptors at even higher pH,[7] we used the spectrophotometric titration method developed by Zuberbühler and co-workers to determine the distribution of species related to **1** from multiwavelength spectroscopic data

(1) Sears, P.; Wong, C. H. *Angew. Chem.* **1999**, *111*, 2446−2471; *Angew. Chem., Int. Ed.* **1999**, *38*, 2301−2324.
(2) (a) Gyurcsik, B.; Nagy, L. *Coord. Chem. Rev.* **2000**, *203*, 81−149. (b) Piarulli, U.; Floriani, C. In *Progress in Inorganic Chemistry, Vol 45*; John Wiley & Sons Inc: New York, 1997; Vol. 45, pp 393−429. (c) Angyal, S. J. *Adv. Carbohydr. Chem. Biochem.* **1989**, *47*, 1−43. (d) Yano, S. *Coord. Chem. Rev.* **1988**, *92*, 113−156. (e) Whitfield, D. M.; Stojkovski, S.; Sarkar, B. *Coord. Chem. Rev.* **1993**, *122*, 171−225.
(3) (a) Junicke, H.; Bruhn, C.; Kluge, R.; Serianni, A. S.; Steinborn, D. *J. Am. Chem. Soc.* **1999**, *121*, 6232−6241. (b) Alekseev, Y. E.; Garnovskii, A. D.; Zhdanov, Y. A. *Russ. Chem. Rev.* **1998**, *67*, 649−669.
(4) Mazurek, W.; Kennedy, B. J.; Murray, K. S.; O'Connor, M. J.; Rodgers, J. R.; Snow, M. R.; Wedd, A. G.; Zwack, P. R. *Inorg. Chem.* **1985**, *24*, 3258−3264.
(5) For a detailed discussion on carbohydrate stability at pH 12.40, see: (a) Striegler, S.; Tewes, E. *Eur. J. Inorg. Chem.* **2002**, 487−495. (b) Striegler, S. *Bioseparation* **2001**, *10*, 307−314.
(6) Gajda, T.; Jancsó, M. S.; Lönnberg, H.; Sirges H. *J. Chem. Soc., Dalton Trans.* **2002**, 1757−1763.

10.1021/ja035561f CCC: $25.00

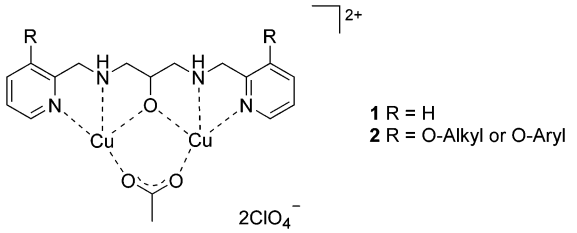


Figure 1. Chemical structure of binuclear copper(II) complex Cu_2(bpdpo) (**1**) and its *O*-alkyl or *O*-aryl derivatives (**2**).

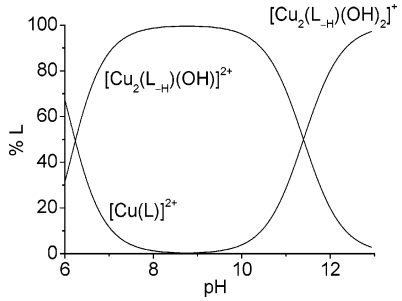


Figure 2. Distribution of species at pH 6−13 related to the binuclear copper(II) complex Cu_2(bpdpo) **1**, calculated from measured UV/vis spectra, recorded in dependence of the pH.

up to pH 13.[8,9] Upon addition of aqueous sodium hydroxide solution to the amino ligand bpdpo in the presence of twice the molar amount of copper(II) acetate at constant ion strength, two species of the binuclear complex **1** are formed. In a pH range of 7.0 to 11.4, a doubly deprotonated species $Cu_2(L)H_{-2}$ (L = bpdpo) dominates the distribution of compounds, which has been already ascribed to a $[Cu_2(L_{-H})(OH)]^{2+}$ complex based on potentiometric titration results.[6] Thus, we attribute the additional compound, detected at even higher pH (11.4 to 13.0), to a $[Cu_2(L_{-H})(OH)_2]^{+}$ species (Scheme 1).

The calculation of species distribution from the experimentally determined pH-dependent UV/vis spectra furthermore suggests that more than 91% of the ligand forms the binuclear complex $[Cu_2(L_{-H})(OH)_2]^{+}$ at pH 12.40, whereas the rest of the amino ligand remains as $[Cu_2(L_{-H})(OH)]^{2+}$ species. Mononuclear copper(II) complexes, free copper(II) ions, nonbound ligand, or binuclear copper(II) complexes, which coordinate more than two hydroxyl groups, were not observed above pH 9 (Figure 2).

Discrimination of Carbohydrates. The binuclear copper(II) complex **1** discriminates between various monosaccharides in alkaline solution, which is in contrast to several previously investigated mononuclear complexes.[5a] Only 1:1 complexes between **1** and a sugar are formed even if a large excess of the carbohydrate is applied. This has been concluded from the determination of the number of spectroscopic states and from saturation binding isotherm plots.[10] The apparent binding

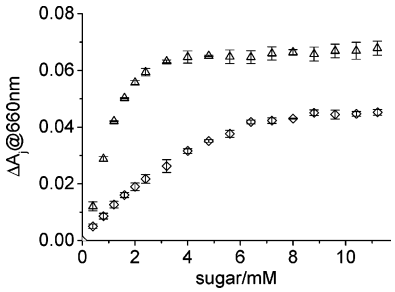


Figure 3. Binding isotherm plot observed during titration of **1** (2 mM) with D-mannose (**3**) (△) and D-glucose (**5**) (◇) in 18 aliquots (0−11 mM); $\Delta A_j = A_1 - A_j$, for j = **3** or **5**.[12]

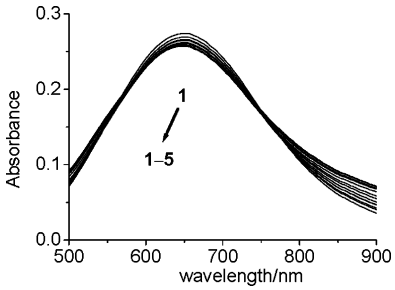


Figure 4. Selected UV/vis spectra observed during titration of binuclear copper(II) complex **1** (2 mM) with D-glucose (**5**) (0−12 mM).[12,13]

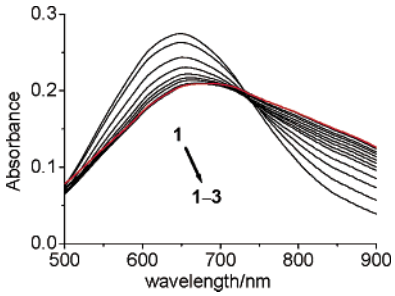


Figure 5. Selected UV/vis spectra obtained during titration of binuclear copper(II) complex **1** (2 mM) with D-mannose (**3**) (0−8 mM).[12,13]

constants ($pK_{app} = -\log K_{app}$) of the sugar−**1** complexes were determined from the UV/vis titration experiments by the method of Rose and Drago.[10] The binuclear copper complex **1** shows a strong preference for D-mannose (**3**) over D-galactose (**4**) and D-glucose (**5**), as well as for D-ribose (**6**) over D-xylose (**7**) and D-arabinose (**8**) (Table 1).

The largest differentiation upon coordination of carbohydrates to the binuclear copper(II) complex **1** (about 1.5 orders of magnitude) is observed with the monosaccharides D-mannose (**3**) and D-glucose (**5**), which differ in the configuration of the hydroxyl group at C-2 only. This observation is in strong contrast to previously investigated mononuclear copper(II) complexes and their ability to bind **3** or **5**.[5a] Saturation of **1** upon glucose binding is reached after addition of a 5-fold molar excess of **5**, while saturation of **1** with mannose requires addition of a 2-fold molar amount of **3** only (Figure 3). Interestingly, a blue-shift of the absorption maximum of **1** (λ_{max}(**1**) = 654 nm) upon glucose binding (λ_{max}(**1**−**5**) = 649 nm, Figure 4) and a red-shift during mannose coordination (λ_{max}(**1**−**3**) = 679 nm, Figure 5) accompanies the chelation of these two biologically important monosaccharides.

(7) The material will be prepared at highly alkaline pH to ensure strong carbohydrate coordination, but it will be investigated and used under weak sugar coordination conditions at neutral pH in aqueous solution ("bait-and-switch" approach). For further information on the method, see: (a) Janda, K. D.; Weinhouse, M. I.; Schloeder, D. M.; Lerner, R. A.; Benkovic, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 1274−1275. (b) Plunkett, S. D.; Arnold, F. H. *J. Chromatogr., A* **1995**, *708*, 19−29. (c) Striegler, S. *Tetrahedron* **2001**, *57*, 2349−2354.

(8) Gampp, H.; Maeder, M.; Meyer, C. J.; Zuberbühler, A. D. *Talanta* **1986**, *33*, 943−951.

(9) Binstead, R. A.; Jung, B.; Zuberbühler, A. D. *SPECFIT/32 Global Analysis System*; version 3.0; Spectrum Software Associates: Marlborough, MA, 2000.

(10) Connors, K. A. *Binding constants − The measurement of molecular complex stability*; John Wiley & Sons: New York, 1987; Chapter 4.

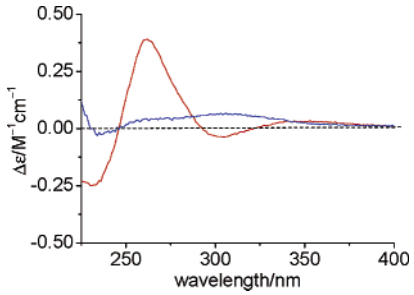


Figure 6. CD spectra of the complexes **1**−**3**, red line, and of **1**−**5**, blue line, formed from Cu_2(bpdpo) (**1**) and D-mannose (**3**), or D-glucose (**5**), in nonbuffered water at pH 12.40 and 20 °C.

The wavelength shifts in opposite directions reflect a different coordination sphere around the metal ions upon binding of **3** or **5** to **1**. Subsequently, we investigated the origin of this phenomenon, which may result from a different number and/or position of the sugar hydroxyl groups involved in complex formation, from dissymmetric δ- or λ-conformations of the chelate ring formed during complexation or from distortion in the resulting carbohydrate−**1** complex.

Structure of Sugar−1 Complexes. Circular dichroism (CD) spectroscopy has become an invaluable tool in chemistry to characterize coordination compounds in solution. The technique rapidly provides not only detailed information on the electronic origin of optical activity but also structural information without resorting to full X-ray structural determination.[14] Consequently, we characterized the complex formation between the binuclear copper(II) complex **1** and mannose (**3**) or glucose (**5**) by CD spectroscopy. The binuclear copper(II) complex **1** itself is not CD-active, whereas alkaline solutions containing **3** or **5**, respectively, show a strong absorption band at 205 nm with a positive Cotton effect for **5** and a negative one for **3** without further perceptible bands above 350 nm (see Supporting Information). It has been shown that the sign of the Cotton effect strongly depends on the configuration of the epimeric C-2 carbon of the sugar, which is the only structural difference between **3** and **5**.[15] Mirrorlike CD spectra of sugar containing coordination compounds with Cotton effects are reported for carbohydrates with identical binding sites, when epimeric centers or other sources of optical activity are not involved in complex formation.[16] On contrast, the corresponding **1**−**3** and **1**−**5** complexes show CD spectra, which differ in wavelength, intensity, and number of the absorption maxima (Figure 6). Thus, the overall structure of both complexes, **1**−**3** and **1**−**5**, is clearly different, which has to be related to a different number and/or position of hydroxyl groups involved in chelating **1**, rather than to identical binding sites combined with a subsequent distortion or dissymmetric conformation effect.

Table 1. Stability Constants for Monosaccharide−**1** Complexes, Determined in Aqueous Solution at pH 12.40 ± 0.01 and 25 °C[11]

hexose	$pK_{app} \pm \Delta pK_{app}$	pentose	$pK_{app} \pm \Delta pK_{app}$
D-mannose (**3**)	4.06 ± 0.03	L-ribose (**9**)	4.11 ± 0.03
L-mannose (**21**)	3.98 ± 0.03	D-ribose (**6**)	4.07 ± 0.02
L-rhamnose (**22**)	3.75 ± 0.03	D-lyxose (**10**)	3.75 ± 0.04
D-fructose (**11**)	3.33 ± 0.04	L-lyxose (**12**)	3.75 ± 0.05
D-galactose (**4**)	3.02 ± 0.05	L-xylose (**13**)	3.58 ± 0.04
D-glucose (**5**)	2.56 ± 0.03	D-xylose (**7**)	3.55 ± 0.03
3-*O*-methyl-glucose (**19**)	2.52 ± 0.02	D-arabinose (**8**)	2.64 ± 0.02
		L-arabinose (**14**)	2.64 ± 0.03

Binding Sites in the Sugar−1 Complexes. To support the conclusions from the CD-spectroscopic investigation, we determined which hydroxyl groups of **3** and **5** are involved in complex formation with the binuclear copper(II) complex **1** using UV/vis spectroscopy. Toward this end, we used an indirect chain of evidence and characterized the coordination ability of **1** to derivatized sugars including α-methyl-D-glucopyranoside (**15**), α-methyl-D-galactopyranoside (**16**), α-methyl-D-mannopyranoside (**17**), and 2-desoxy-D-glucose (**18**).[17] The sugars **15**−**18** cause, as **5**, a small blue-shift of the absorption maximum of **1** upon chelation. This shift is common for an $n \rightarrow \pi^*$ transition resulting from complex formation in a polar solvent, such as water at alkaline pH.[18] The apparent binding constants for the resulting sugar−**1** complexes (sugar = **15**−**18**) were not determined due to the very weak binding interaction, which is slightly above the experimental error of the UV/vis spectroscopic investigation. Thus, blocking the hydroxyl group at C-1 in **3**, **4**, or **5** or removing the hydroxyl group at C-2 does not result in complex formation but shows on the other hand that the hydroxyl groups at C-1 and C-2 of **3** and **5** are involved in chelation to the metal complex **1**. Methylation of **3** and **5** at C-3, as investigated by titrating **1** with 3-*O*-methyl-D-glucose (**19**) and 3-*O*-methyl-D-mannose (**20**), reduces the coordination ability of **20** in comparison to **3**, whereas the apparent binding constants of the glucose derived complexes **1**−**5** and **1**−**19** are of the same order of magnitude (Table 1). This demonstrates that the *cis*-diol group consisting of the hydroxyl group at the anomeric carbon and at C-2 of **5** chelates **1**, whereas the hydroxyl group at C-3 of **5** does not significantly contribute to the complex formation with **1**. A similar coordination behavior has been observed between **5** and several mononuclear copper-(II) complexes.[5a] Additionally, CD spectra obtained from the complexes **1**−**5** and **1**−**19** show a high degree of similarity and thus give further evidence for an identical binding mode of **5** and **19** upon chelating **1** (see Supporting Information). On contrast, the interaction between the mannose derivative **20** and the binuclear copper complex **1** is very weak, which underlines the participation of the underivatized hydroxyl group at C-3 of mannose in formation of the strong **1**−**3** complex. The number of hydroxyl groups of **3** or **5** involved in complexation of **1** at pH 12.40 is clearly different, which drastically influences the coordination sphere around the copper(II) centers in the complexes. Judging from the results of the CD- and UV/vis-spectroscopic investigation, the different numbers of the sugar hydroxyl groups involved in complex formation have to be

(11) The error of the mean of the apparent binding constants (ΔpK_{app}) is given as a 95% confidence limit determined from 53 data points obtained from two independent measurements using six different wavelengths between 615 and 640 nm each; see also ref 18, Appendix A.
(12) The titration experiments were conducted at least in duplicate at pH 12.40, 25 °C, V_t = 1 mL. The variation of absorbance was equal or less than 0.005 absorption units for all experiments.
(13) The arrow indicates the direction of the wavelength shift of the absorption maximum during sugar binding.
(14) Kuroda, R.; Saito, Y. In *Circular Dichroism − Principles and Application*; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCH Publishers: Weinheim, 1994; Chapter 9, pp 217−258.
(15) Hayward, L. D.; Angyal, S. J. *Carbohydr. Res.* **1977**, *53*, 13−20.
(16) Tsukagoshi, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4089−4091. Takeuchi, M.; Imada, T.; Shinkai, *S. Bull. Chem. Soc. Jpn.* **1998**, *71*, 1117−1123 and reference citations therein.
(17) Desoxy-D-glucose and 2-desoxy-D-mannose are equivalent names for the same monosaccharide.
(18) Skoog, D. A.; Leary, J. J. *Instrumental Analysis*; Springer: Berlin, 1996; Chapter 8.

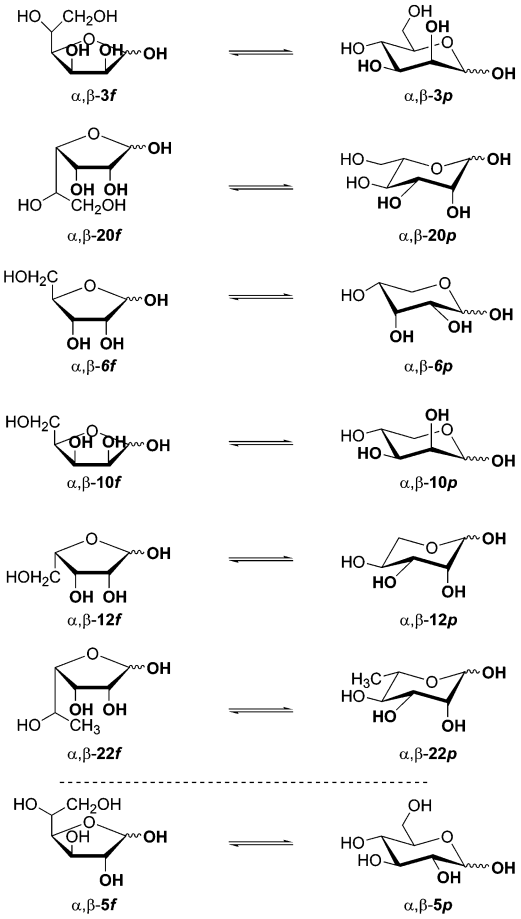


Figure 7. Furanose and $^4C_1$ pyranose equilibrium structures of carbohydrates causing a red-shift of the absorption maximum of binuclear copper(II) complex **1** during complexation: D-mannose (**3**), L-mannose (**21**), D-ribose (**6**), D-lyxose (**10**), L-lyxose (**12**), and L-rhamnose (**22**), in contrast to the structures of D-glucose (**5**), which causes a blue-shift of the absorption maximum of **1**. Hydroxyl groups involved in complexation are shown in bold. f = furanose, p = pyranose.

related to the blue- or red-shift of the absorption maximum of **1** upon chelation of **3** or **5**.

A red-shift of the absorption maximum of **1** is also observed upon interaction with L-mannose (**21**), D-ribose (**6**), D-lyxose (**10**), L-lyxose (**12**), or L-rhamnose (**22**). The saturation of sugar binding is reached at a 2-fold molar excess of the carbohydrate concentration in respect to **1**. Among these monosaccharides, only D-ribose (**6**) exists in aqueous solution at equilibrium effectively in furanose form (6.5% α-furanose, 13.5% *β*-furanose), while the other saccharides mainly exist as pyranoses (Figure 7).[19]

However, pyranoses can easily convert into furanose or acyclic structures upon coordination to a metal complex. Resulting binuclear sugar−metal complexes with a furanose form of an underivatized carbohydrate are known for complexes derived from several metal ions, such as Fe(III), V(III), Cr(III), Al(III), or Ga(III).[20] The rearrangement of a pyranose to a furanose structure has also been discussed for diboronic acid

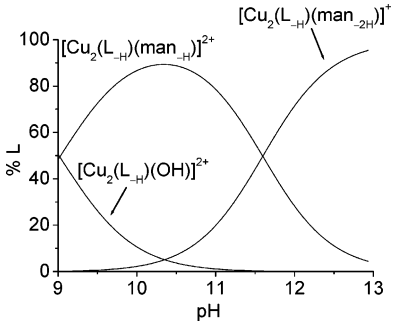


Figure 8. Distribution of species at pH 9−13 for a 1:5 molar ratio of the binuclear copper(II) complex Cu_2(bpdpo) **1** and mannose (**3**).

esters of carbohydrates.[21] Both, the furanose and the pyranose form of the carbohydrates causing a red-shift potentially enable coordination to the binuclear copper(II) complex **1** via a *cis,cis*-triol at C-1, C-2, and C-3, whereas sugars causing a blue-shift allow chelation via a *cis*-diol only.[22,23]

Carbohydrate Deprotonation during Complex Formation. Multiple deprotonation of metal-bound carbohydrates is a well-known phenomenon in the solid state, particularly when complexes are obtained from highly alkaline solutions.[20a] However, the system under investigation here is different in several aspects, namely the aggregation state discussed, the concentration of the compounds, the nature, number and charge of the metal ions, and the nature of the metal ion binding ligand. Thus, we used the procedure of Zuberbühler and co-workers described above to assign the protonation state of the sugar hydroxyl groups in solution from experimentally determined pH-dependent UV/vis spectra.As noted earlier, complex **1** consists predominantly as a $[Cu_2L_{-H}(OH)_2]^+$ species at pH 12.40, which may release two water molecules and two hydroxyl groups upon coordination of a sugar (Scheme 1). Similarly, the distribution of species obtained from titrating solutions containing copper(II) acetate, the bpdpo ligand, and **3** or **5** with aqueous sodium hydroxide gives evidence for chelation of a doubly deprotonated sugar anion, when the pH value exceeds 11.5 (Figure 8 and Supporting Information). We therefore propose equilibrium structures with doubly deprotonated sugar anions for the complexes **1**−**3** and **1**−**5** at pH 12.40 taking into account that the *cis,cis*-triol at C-1, C-2, and C-3 is involved in coordination of **3**, whereas **5** chelates **1** with a *cis*-diol at C-1 and C-2 only (Scheme 2).

The assumption of higher deprotonation of **3** as a result of coordination to the binuclear metal complex implies either protonation of the bpdpo ligand or a release of protons from the coordinated sugar. As a consequence of the protonation of the bpdpo ligand, a mononuclear instead of a binuclear copper(II) complex would be favored, which is not supported by our experimental data or other reported investigations.[6] As a consequence of the second assumption, further deprotonation of mannose at the hydroxyl group at C-3 in a **1**−**3** complex should result in a measurable release of molar amounts of

(19) Collins, P.; Ferrier, R. *Monosaccharides − Their chemistry and their roles in natural products*; John Wiley & Sons: Chichester, 1995; Chapter 2.4, p 41.

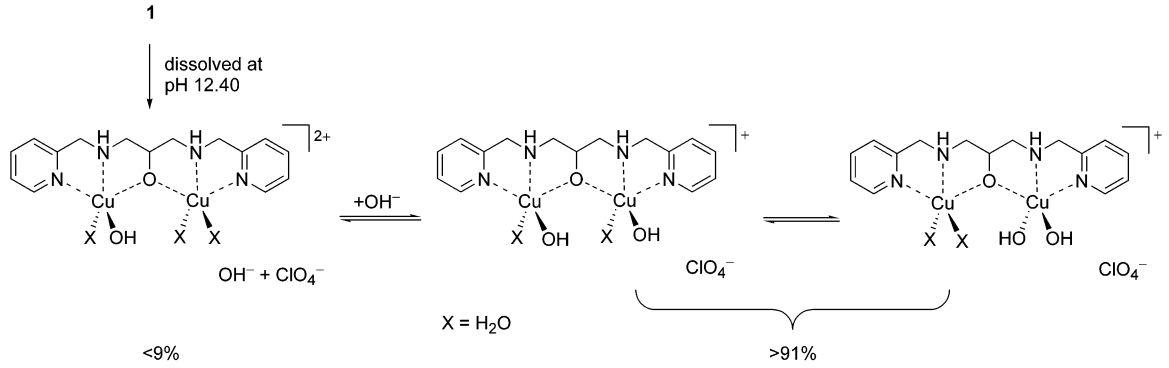
(20) (a) Burger, J.; Gack, C.; Klüfers, P. *Angew. Chem.* **1995**, *107*, 2950−2951; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2647−2649. (b) Burger, J.; Klüfers, P. *Z. Anorg. Allg. Chem.* **1997**, *623*, 1547−1554.

(21) (a) Norrild, J. C.; Eggert, H. *J. Am. Chem. Soc.* **1995**, *117*, 1479−1484. (b) Bielecki, M.; Eggert, H.; Norrild, J. C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 449−455. (c) Eggert, H.; Frederiksen, J.; Morin, C.; Norrild, J. C. *J. Org. Chem.* **1999**, *64*, 3846−3852. (d) Norrild, J. C.; Sotofte, I. *J. Chem. Soc., Perkin Trans. 2* **2002**, 303−311.

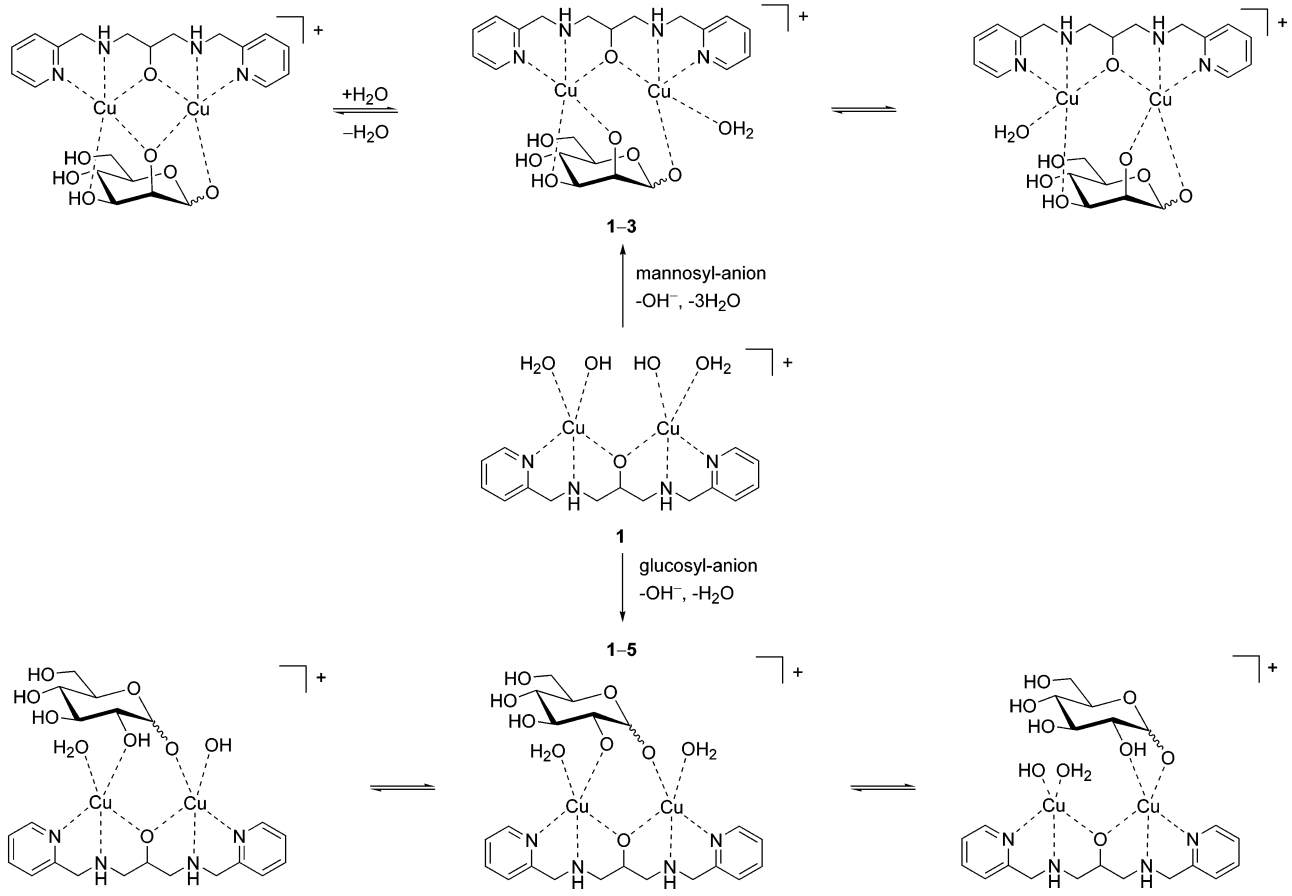
(22) The hydroxyl groups of the saccharides involved in complexation are shown in bold (Figure 7).

(23) Keeping in mind that the monosaccharides may be coordinated to **1** in several equilibria structures, we used the predominant pyranose form to describe the structures of the carbohydrate−**1** complexes.

Scheme 1. Equilibrium Species Derived from **1** in Aqueous Solution at pH 12.40



Scheme 2. Proposed Equilibrium Structures of the Complexes **1**−**3** and **1**−**5**, Derived from the Binuclear Copper(II) Complex (**1**), Cu_2(bpdpo), and D-Mannose (**3**), or D-Glucose (**5**), at pH 12.40[a]



[a] The perchlorate counter ions of the complexes are omitted for clarity.

protons in respect to the amount of carbohydrate bound. We prepared separate solutions of **1** and **3** at pH 12.40 each and measured the pH of the resulting solution after mixing. We observed a very small drop of equal or less than 0.10 pH units, which is by far less than the drop of 0.35 pH units related to a release of molar amounts of protons that has been calculated applying the Hendersson−Hasselbalch equation (see Supporting Information). Thus, a release of molar amounts of protons due to complex formation between **1** and **3** is not apparent from the experimental results at all. On the other hand, the pK^H values of **3** (p$K_3{}^H$ = 12.08)[24] is much lower than the pH value used throughout our investigation and therefore nonbound **3** exists for the most part as a singly deprotonated species in a solution at pH 12.40.[25] As we used a 5-fold molar excess of **3** in respect to **1**, the slight decrease in pH can be related to the amount of protons released from noncoordinated sugar molecules, which restore the equilibrium balance between the monoanionic and the neutral carbohydrate form after disturbance of the equilibrium by chelation.

Conclusions

We studied the coordination of various natural, underivatized sugars to binuclear copper(II) complex **1** in aqueous solution

(24) Martell, A. E.; Smith, R. M. NIST − Critically selected stability constants of metal complexes database; U. S. Department of Commerce, National Institute of Standards and Technology: Gaithersburg, MD, 1998.

(25) pH = p$K_{sugar}{}^H$ + log([sugar$_{-H}$]/[sugar]). The calculation suggests that 69.6% of **3** is monodeprotonated in stock solutions at pH 12.40.

under strong binding conditions, that is at highly alkaline pH, with a set of UV/vis and CD spectroscopic experiments. Complex **1** differentiates structurally closely related monosaccharides, for example, D-glucose and D-mannose. The binding strengths of both 1:1 sugar−**1** complexes are about 1.5 orders of magnitude different. Moreover, a blue- or a red-shift of the absorption maximum of the metal complex occurs during carbohydrate binding highlighting the sugar discrimination ability of **1**. This phenomenon is related to the particular number of sugar hydroxyl groups chelating **1**. The wavelength of the absorption maximum of **1** is red-shifted, when the chelating sugar enables a coordination by a *cis*,*cis*-triol at C-1, C-2, and C-3, and is blue-shifted, when the saccharide is binding through a *cis*-diol at the anomeric carbon and at C-2 only. Our results imply that the similarity of saccharides does not necessarily resemble in transition metal−saccharides complexes. Combining the determined selectivity with a chemical transformation property in a macromolecular metal complex is a topic of ongoing work.

Experimental Section

General Remarks. Methanol, ethanol, chloroform, pyridine-2-carbaldehyde, D-arabinose (**8**), l-arabinose (**14**), D-mannose (**3**), D-galactose (**4**), silica gel (60 Å), and sodium sulfate were purchased from Merck Eurolab; 1,3-diaminopropan-2-ol, copper(II) acetate monohydrate, sodium perchlorate, 2-desoxyglucose (**18**), and 3-*O*-methylglucose (**19**) were obtained from Aldrich; d-ribose (**6**), D-xylose (**7**), L-ribose (**9**), L-lyxose (**12**), methyl-α-D-glucopyranoside (**15**), methyl-α-D-galactopyranoside (**16**), methyl-α-D-mannopyranoside (**17**), sodium hydroxide, and sodium borohydride were purchased from Fluka; D-glucose (**5**), D-lyxose (**10**), L-xylose (**13**), l-mannose (**21**), and D-fructose (**11**) were purchased from Sigma; L-rhamnose (**22**) was purchased from Roth, and 3-*O*-methylmannose (**20**) was prepared as described.[26] Pyridine-2-carbaldehyde was distilled in a vacuum immediately prior to use. All other reagents and solvents had reagent grade quality or better and were used without further purification.

The melting points are uncorrected and were measured with a Büchi B-540. The IR spectra were obtained on a Bruker IFS 133V as thin films or KBr pellets; ν in cm^{-1}. The microanalysis was performed on a Elementar Vario EL. The mass spectra (EI) were obtained using a Varian Saturn GC/MS 2000 equipped with a DB5 MS column, 30 m × 0.25 nm × 0.25 μm. The FABMS spectra were obtained using a Finnigan MAT SSQ 7000. The NMR experiments were performed on a Bruker DRX 400 (^{1}H, 400.1 MHz; ^{13}C, 100.6 MHz) at 300 K; $CDCl_3$ or acetone-d_6 were used as solvents; residual $CHCl_3$ or CD_2HCOCD_3 were used as internal standard ($CHCl_3$: $\delta(^1H)$ 7.24; $\delta(^{13}C)$ 77.0. CD_2HCOCD_3 $\delta(^1H)$ 2.05; $\delta(^{13}C)$ 30.5). Chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane, and scalar coupling constants J, in Hz.

UV/vis Spectroscopy. All experiments were performed on an UV/vis J&M TIDAS spectrophotometer (software SPECTRALYS version 1.55) with Suprasil standard cells (200−2000 nm) of 10 mm thickness and 700 μL volume at 25.0 ± 0.1 °C over a range of 200−900 nm. All experiments were done in unbuffered, degassed Nanopure water, in which pH was adjusted to pH 12.40 with NaOH prior to use for each set of titrations. Typically, 2.5 mM stock solutions of **1** and 80 mM stock solutions of the carbohydrates were prepared separately and kept at 25 °C. The total concentration of **1** ($V_1 = 800$ μL; $M_t = 2$ mM) and the total volume of the resulting solutions ($V_t = 1$ mL) were kept constant during the titration experiments ($V_{sugar} = 0-200$ μL) by adding an appropriate amount of water. The UV/vis absorbances and the pH meter readings of the resulting mixtures were measured immediately after mixing.

Circular Dichroism (CD) Spectroscopy. The CD spectra were recorded on a JASCO J-715 spectropolarimeter at 20 °C in the spectral range of 200−600 nm in 100 μL Suprasil standard cuvettes fixed in a path length of 10 mm. All experiments were done in unbuffered, degassed Nanopure water, in which pH was adjusted freshly to pH 12.40 with NaOH. The concentrations of **1** ($V_1 = 1000$ μL; $M_t = 1$ mM) and of the sugar S ($V_S = 100$ μL; $S_t = 10$ mM), as well as the total volume of the resulting solutions ($V_t = 1250$ μL) were kept constant for all measurements by adding an appropriate amount of water. Additionally, solutions consisting of a 1:15 molar ratio between **1** ($V_1 = 1000$ μL; $M_t = 1$ mM) and glucose (**5**) or 3-*O*-methylglucose (**19**) were prepared.

Species Distributions. All experiments were done in aqueous solution, in which ionic strength was maintained constant with 0.1 M $NaClO_4$. The UV/vis spectra were recorded on a UV/vis J&M TIDAS spectrophotometer (software SPECTRALYS version 1.55) with Suprasil standard cells (200−2000 nm) of 10 mm thickness and 4.5 mL volume at 25.0 ± 0.1 °C over a range of 200−900 nm. The pH value was measured with a Beckman Φ 250 pH meter equipped with a refillable long combination Futura pH electrode of 0.7 mm thickness. Typically, 2 mL of stirred solutions containing copper(II) acetate (4 mM), purified bpdpo ligand (2 mM) and carbohydrate (2 or 10 mM) were titrated with freshly prepared 0.3 M aqueous NaOH. The UV/vis spectra were recorded in dependence of the pH value measured in the reaction vessel after equilibration. The spectral data were computed by the fitting procedures provided by the program Specfit.[8]

1,3-Bis[(pyridin-2-ylmethylene)amino]propan-2-ol. Typically, pyridine-2-carbaldehyde (10.7 g, 0.1 mol) and 1,3-diaminopropan-2-ol (4.5 g, 0.05 mol) were dissolved in methanol (40 mL) at ambient temperature and stirred overnight. The mixture was diluted to 100 mL with methanol and used as raw product for subsequent synthesis. During distillation, column chromatography (neutral or basic Al_2O_3) as well as for prolonged standing at ambient temperature, decomposition of the raw product was observed. TLC analysis on aluminum backed silica gel plates ALUGRAM SIL G/UV_{254} (Machery−Nagel) using chloroform as mobile phase and UV absorption for detection as well as GC−MS analysis of the raw product indicate that the major impurity consists of nonreacted pyridine-2-carbaldehyde. However, the obtained material was sufficiently pure to allow characterization by NMR spectroscopy as well as by GC−MS (EI). Yellowish oil. GC−MS (EI): *m*/*z* (%) 268 (98, M^+), 252 (19), 145 (55), 119, (63), 92 (100). ^{1}H NMR (acetone-d_6) δ 8.62 (ddd, $J = 4.9, 1.8, 0.9$, 2H), 8.48 (s, 2H), 8.05 (ddd, $J = 8.0, 1.3, 0.9$, 2H), 7.79 (ddd, $J = 7.4, 4.9, 1.3$, 2H), 7.37 (ddd, $J = 7.4, 4.9, 1.3$, 2H), 4.41 (m, 1H), 4.02 (ddd, $J = 12.0., 4.7, 1.4$, 1H), 3.84 (ddd, $J = 12.0, 6.7, 1.1$, 1H), 3.36 (s, 2H). ^{13}C NMR (acetone-d_6) δ 164.7, 155.7, 150.4, 137.9, 126.2, 122.2, 71.6, 66.5.

1,3-Bis[(pyridin-2-ylmethyl)amino]propan-2-ol, bpdpo. Sodium borohydride (2.8 g, 0.1 mol) was added in small quantities to a solution of 1,3-bis[(pyridin-2-ylmethylene)amino]propan-2-ol in methanol at room temperature. The resulting mixture was refluxed for 3 h, and the solvents were evaporated. The residue was dissolved in chloroform (100 mL) and washed 4 times with equal amounts of water. The organic layer was separated and dried with anhydrous sodium sulfate. Filtration and subsequent removal of the solvent yielded the bpdpo ligand as a bright yellow oil, which was used for the preparation of **1** without further purification. Yield: 13 g. An analytical sample of the amine ligand was purified using column chromatography on silica gel using methanol as mobile phase. Colorless oil. SiO_2, MeOH, $R_f = 0.22$. GC−MS (EI): *m*/*z* (%) 272 (23) [M^+], 194 (42), 182 (100), 121 (91), 93 (63). IR (thin film) ν/cm^{-1} 3259, 2920, 2824, 1592, 1570, 1474, 1434, 1050, 756, 624. ^{1}H NMR (CD_3OD) δ 8.48 (ddd, $J = 4.9, 1.8, 0.9$, 2H), 7.79 (m, 2H), 7.45 (m, 2H), 7.29 (ddd, $J = 7.6, 4.9, 1.1$, 2H), 3.89 (dd, $J = 22.2, 14.3$, 2H), 3.88 (m, 1H), 2.69 (dd, $J = 12.2, 4.1$,

(26) (a) Oshitari, T.; Shibasaki, M.; Yoshizawa, T.; Tomita, M.; Takao, K.; Kobayashi, S. *Tetrahedron* **1997**, *53*, 10993-11006. (b) Tian, X.-X.; Li, A.; Farrugia, I. V.; Mo, X.; Crich, D.; Groves, M. J. *Carbohydr. Res.* **2000**, *324*, 38−44.

2H), 2.61 (dd, J = 12.2, 7.8, 2H). ^{13}C NMR (CD_3OD) δ 160.3, 149.8, 138.75, 124.19, 123.7, 70.1, 55.3, 54.4.

N,N′*-{1,3-Bis[(pyridin-2-ylmethyl)amino]propan-2-ol}ato Dicopper(II) (μ-Acetato) Diperchlorate (1), Cu_2(bpdpo).** The complex was prepared as described,[4] recrystallized twice from water, washed with acetone, and air-dried to yield blue crystalline **1**. Overall yield: 7.8 g (24%). Mp: ***CAUTION, explosive decomposition occurred during heating at 290 °C. IR (KBr): ν/cm^{-1} 3264, 1563, 1516, 1483, 1446, 1100, 1048, 951, 771, 621. FABMS: Cu^{65}/Cu^{63} isotopes (%/%), m/z = 557/555 (100/95) $[M - ClO_4^-]^+$, 498/496 (16/29), 458/456 (12/17), 397/395 (32/25), 335/333 (43/49). Microanalysis calcd for $C_{17}H_{22}Cl_2Cu_2N_4O_{11}$: C, 31.11; H, 3.38; N, 8.54. Found: C, 31.04; H, 3.42; N, 8.54. UV λ_{max} (H_2O): 324 nm, 654 nm.

Acknowledgment. The authors gratefully acknowledge a fellowship in the Margarete von Wrangell habilitation program, Baden-Württemberg state, Germany (S.S.) and a fellowship from the Landesgraduiertenkolleg, Baden-Württemberg state, Germany (M.D.). The authors also thank Professor D. Hilvert, Laboratory of Organic Chemistry, Swiss Federal Institute of Technology, Zurich, Switzerland for providing the equipment for CD measurements.

Supporting Information Available: Figures showing FABMS, EIMS, IR, and ^{1}H, ^{13}C NMR spectra of binuclear copper(II) complex **1** and its precursor ligands, figures showing CD spectra of **3**, **5**, **1**−**5**, and **1**−**19** as well as a figure showing the change in pH upon formation of **1**−**3** and **1**−**5** complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

JA035561F