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New Dinuclear Cobalt(II) and Zinc(II) Complexes of a Carboxylate-Rich Dinucleating Ligand: Synthesis, Structure, Spectroscopic Characterization, and Their Interactions with Sugars

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Supporting Information

ABSTRACT: Sugar–metal ion interactions in aqueous medium are involved in many biochemical processes such as the transport and storage of metals, the function and regulation of sugar-metabolizing metalloenzymes, the mechanism of action of metal-containing pharmaceuticals, and toxic metal metabolism. To understand such interactions we synthesized and fully characterized two new dinuclear cobalt(II) and zinc(II) complexes as carbohydrate binding models for xylose/glucose isomerases (XGI). Synthesis of the dicobalt complex, $Na_3[Co_2(ccdp)(\mu\text{-}HCO_2)]\text{-}BF_4\cdot 9H_2O\cdot 2CH_3OH$ (**1**), was performed in methanol with stoichiometric amounts of $Co(BF_4)_2\cdot 6H_2O$ and the dinucleating ligand, H_5ccdp (H_5ccdp = *N*,*N*′-bis[2-carboxybenzomethyl]-*N*,*N*′-bis[carboxymethyl]-1,3-diaminopropan-2-ol), in the presence of NaOH at ambient temperature in an argon glovebox. Similarly, the dizinc complex, $[NMe_4]_2[Zn_2(ccdp)(\mu\text{-}OAc)]\cdot CH_3OH$ (**2**), was synthesized from $Zn(OAc)_2\cdot 2H_2O$ and H_5ccdp in the presence of NMe_4OH at ambient temperature in methanol. Binding of the complexes with carbohydrates was investigated under different reaction conditions. In aqueous alkaline media, complexes **1** and **2** showed chelating ability towards the biologically important sugars, D-glucose and D-xylose, and a polyalcohol enzyme inhibitor (xylitol). In solution, each complex forms a 1:1 complex-substrate bound product with specific binding constant values. Synthesis, characterization details, and substrate binding using spectroscopic techniques and single-crystal X-ray diffraction are reported.

INTRODUCTION

Carbohydrates form the most abundant group of natural products and are found in all classes of living organisms. They serve as a direct link between the energy of the sun and the metabolic energy that sustains life. Carbohydrates also play several other roles in biological functions. Thus, considerable effort has been directed toward carbohydrate recognition, by synthetic receptors, in relation to the important roles that carbohydrates serve in biological processes.[1,2] Examples of recognition can be observed in intercellular recognition, signal transduction, and fertilization and as targets of bacterial or viral infections of cells, to name a few.[1−3] In this regard, the interactions between metal ions and carbohydrates remain one of the main objectives of carbohydrate coordination chemistry.[4−11] Although metal–carbohydrate 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.[12−14] In contrast, carbohydrate–metal assemblies based on sugar-type ligands with weak coordinating alcoholic, aldehyde, or ketone oxygen donor atoms remain poorly understood.[15,16] Due to the low stability of the complexes in neutral or acidic aqueous solution, characterization of the equilibria occurring during coordination is difficult and often reaches experimental limitations.[12] In the past several years, Rao and co-workers contributed immensely to the understanding of transition metal–carbohydrate interactions in chemistry and biology.[17] Synthetic strategies have been developed for VO^{2+}, Cr^{3+}, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and MoO_2^{2+}. Furthermore, the biologically relevant aspects of carbohydrate complexes of Cr^{3+},[18] VO^{2+},[19,20] and Zn^{2+}[21] have also been studied.

To understand the enzymatic processes, a wide variety of synthetic complexes have been prepared and reported in the literature as structural or/and functional models.[22−25] It has also been elucidated that carboxylate-bridged divalent dinuclear complexes with Mg^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, and Zn^{2+} are involved in many enzymatic but nonredox active processes. Included in this list is the biological transfer reactions of phosphoryl, acyl, and other carbonyl groups promoted by phosphatases, nucleases, amidases, peptidases, etc.[26−35] However, unlike the

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case with various other metalloenzymes, study of metalloenzymes involved in carbohydrate metabolism using synthetic models is largely unexplored. Xylose glucose isomerase, XGI, is an example of a metalloenzymes which catalyzes aldose−ketose interconversion by utilizing Mg^{2+}, Mn^{2+}, and Co^{2+} dinuclear active sites.[36−39] Enzymatic conversion is from glucose and xylose to fructose and xylulose, respectively. The XGI enzyme has undergone a considerable expansion in the industrial market in recent years and offers several cost-saving advantages. However, neither the mode of substrate binding nor the mechanistic role of the active site is fully understood.

The focus of this paper is on a carboxylate-rich dinucleating ligand, *N*,*N*′-bis[2-carboxybenzomethyl]-*N*,*N*′-bis-[carboxymethyl]-1,3-diaminopropan-2-ol (H_5ccdp), which incorporates two acetate and two benzoate functionalities (Figure 1).[40] Synthesis of the H_5ccdp ligand and its derivative along

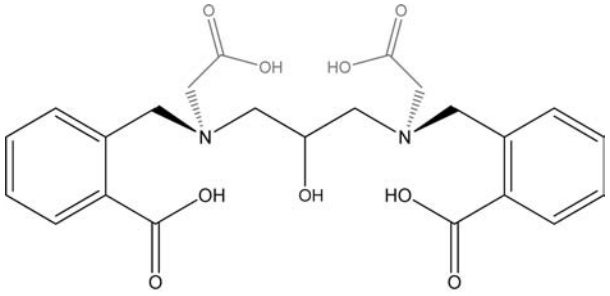

Figure 1. Chemical structure of the ligand H_5ccdp.

with a discussion of the flexibility to bind divalent cobalt(II) and zinc(II) metal centers to yield mono-, tetra-, hexa-, and heptanuclear complexes under various reaction conditions is reported elsewhere.[40−43] Presently, we report the synthesis and characterization of a new dinuclear cobalt(II) complex (**1**) and a new dinuclear zinc(II) complex (**2**) and their binding interactions with different physiologically important substrates, D-glucose and D-xylose. Additionally, xylitol was used as an open ring model of the carbohydrates under investigation since appreciable amounts of open ring forms of carbohydrate is generally unattainable in aqueous solutions.

RESULTS AND DISCUSSION

Synthesis and Characterization of the Complexes. The symmetric carboxylate-rich dinucleating ligand, H_5ccdp, with a central pendant alcoholic arm has been synthesized according to our previously published procedure.[40] We chose the carboxylate-rich dinucleating ligand system for this investigation to better understand the sugar binding ability and mode of binding because there are many sugar-metabolizing metalloenzymes, like xylose/glucose isomerases which consist of a dimetallic Mg^{2+}, Mn^{2+}, or Co^{2+} active site having carboxylate-rich coordination environments.[36−39] Besides, the carboxylate-rich ligand complexes were found to be water soluble, which has allowed us to study the binding interaction in aqueous medium. The central pendant alcoholic arm of the ligand acts as a spacer and bridging unit for the metals. The ligand is fully characterized using analytical techniques such as elemental analysis, FTIR, and ^{1}H and ^{13}C NMR spectroscopic analyses. Reaction of $Co(BF_4)_2{\cdot}6H_2O$ with the H_5ccdp ligand in a 2:1 molar ratio in the presence of NaOH in methanol at ambient temperature in an argon glovebox for 2 h resulted in a dark pink solid product that was easily crystallized into a new dinuclear complex, $Na_3[Co_2(ccdp)(\mu\text{-}HCO_2)]\text{-}BF_4{\cdot}9H_2O{\cdot}2CH_3OH$ (**1**). The exogeneous bridging formate group in complex **1** is achieved via a known mechanism that involves oxidation of methanol to formic acid, catalyzed by cobalt(II)[44−46] in solution, in the presence of dioxygen. Although not the aim of this study, it is worthy to make a note that similar results have been obtained when oxygen is deliberately added during synthesis of the complex. Reaction of $Zn(OAc)_2{\cdot}2H_2O$ with H_5ccdp in a 2:1 molar ratio in the presence of NMe_4OH in methanol at ambient temperature in air for 2 h afforded a colorless crystalline powder that was easily crystallized into a new dinuclear complex $[NMe_4]_2[Zn_2(ccdp)\text{-}(\mu\text{-}OAc)]{\cdot}CH_3OH$ (**2**). Molecular structures of the complexes have been established using techniques such as FTIR, UV−vis, ^{1}H and ^{13}C NMR, and single crystal X-ray structure determination.

Complexes are investigated for their binding interaction with biologically important sugars (D-glucose and D-xylose) and a polyalcohol (xylitol) in aqueous medium at pH ≈ 12.5. Accordingly, we checked their stability and the possibility of OH^- ion coordination at such a high pH. We ran the UV−vis spectra of complex **1** in aqueous medium in the absence of NaOH (pH ≈ 8) and in the presence of NaOH (pH ≈ 12.5). The two spectra obtained remain identical (Figure S1, Supporting Information). Again, we performed ^{13}C NMR experiments of complex **2** in D_2O in the absence of NaOH (pH ≈ 8) and in the presence of NaOH (pH ≈ 12.5). In both the two cases, the ^{13}C NMR spectra remain the same without any shift of the signal positions (Figure S2, Supporting Information). From the above observations, it can be suggested that the complexes are stable and there is no possibility of OH^- ion coordination in solution, even at high pH (pH ≈ 12.5).

Spectroscopic Studies of the Complexes. In complexes **1** and **2**, the different modes of carboxylate binding, namely, monodentate terminal coordination of acetate and benzoate groups and syn−syn bidentate bridging coordination of exogeneous formate or acetate groups, have been established by the FTIR spectra. Deacon and Phillips carefully examined the FTIR spectra of many metal−carboxylate complexes with known X-ray crystal structures and drawn useful conclusions for the correlations between carboxylate stretching frequencies and their geometries.[47] In the FTIR spectra of complex **1**, two strong asymmetric $\nu_{as}(COO^-)$ vibrations were observed at 1586 and 1557 cm^{-1} and two strong symmetric $\nu_s(COO^-)$ vibrations were observed at 1425 and 1390 cm^{-1}. The significantly higher difference, Δ ($\Delta = \nu_{as(COO-)} - \nu_{s(COO-)}$), of ∼196 cm^{-1} between the asymmetric and the symmetric stretching vibrations is attributed to the monodentate terminal coordination of carboxylate.[48] The lower value of Δ at ∼132 cm^{-1} between the asymmetric and the symmetric stretching vibrations is indicated by the syn-syn bidentate bridging ($\eta^1{:}\eta^1{:}\mu_2$) of the exogenous formate group.[48] The characteristic acetate frequencies at 1581 and 1547 cm^{-1} correspond to two strong asymmetric stretches, and 1405 and 1398 cm^{-1} correspond to two strong symmetric stretches which are observed in the FTIR spectra of complex **2**. The significantly higher value of Δ at ∼183 cm^{-1} frequently indicates the monodentate terminal coordination of carboxylate. Again, the lower value of Δ at ∼159 cm^{-1} is characterized by the syn-syn bidentate bridging ($\eta^1{:}\eta^1{:}\mu_2$) of the exogeneous acetate group.

Electronic spectra of complex **1** in aqueous solution indicates one weak band at 721 nm (ε, 18 L $mol^{-1}cm^{-1}$) and a broad

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intense band at 532 nm (ε, 80 L mol^{-1}cm^{-1}) due to the d−d transitions. A charge transfer transition is also observed at 268 nm (ε, 2427 L mol^{-1} cm^{-1}).

Crystal and Molecular Structures. Crystallographic data and refinement details for complexes **1** and **2** are summarized in Table 1. Selected bond distances and bond angles for complexes **1** and **2** are given in Table 2.

Table 1. Crystal Data and Structure Refinement for 1 and 2[a]

	1	2
empirical formula	$C_{26.85}H_{49.70}N_2O_{22}BF_4Na_3Co_2$	$C_{34}H_{52}N_4O_{12}Zn_2$
fw	1026.27	873.75
cryst syst	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$
a, Å	9.5203(11)	12.4123(7)
b, Å	19.953(2)	10.5098(5)
c, Å	22.273(3)	29.2654(16)
α, deg	90	90
β, deg	97.053(5)	97.206(3)
γ, deg	90	90
vol., Å^3	4198.9(8)	3787.5(3)
Z	4	4
density (calcd), Mg/m^3	1.623	1.472
wavelength, Å	0.71073	0.71073
temperature, K	100(2)	100(2)
F(000)	2115	1760
abs coeff, mm^{-1}	0.922	1.332
wR (F^2 all data)	0.1181	0.0994
R (F obsd data) [$I > 2\sigma(I)$]	0.0428	0.0409
goodness-of-fit on F^2	1.027	1.151
largest diff. peak and hole, e Å^{-3}	1.309 and −1.017	1.808 and −0.545

[a] $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$, $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.

$Na_3[Co_2(ccdp)(\mu\text{-}HCO_2)]BF_4\cdot 9H_2O\cdot 2CH_3OH$, 1. A view of the anion of compound **1** is depicted in Figure 2. Two methanol and nine water molecules cocrystallized with the complex. The deprotonated ligand, ccdp^{5-}, acts as a dinucleating ligand coordinated to the two cobalt(II) ions. Both cobalt(II) ions adopt a five-coordinate trigonal bipyramidal geometry, each provided by the two carboxylate oxygens, one tertiary amine nitrogen, one bridging alkoxo oxygen of the ligand, and the bridging formate group. The exogenous formate group binds two cobalt(II) ions in μ-*syn-syn*-η^1:η^1-fashion. This type of carboxylate bridging in the syn-syn bidentate mode is common in dicopper,[49−51] diiron, and dimanganese complexes[52−54] and also found in dinuclear cobalt(II) complexes.[55] The cobalt(II) ions at the core are bridged to each other by O(1) of the deprotonated alcohol and the O(10) and O(11) of the formate group. Co−O bond distances to nonbridging carboxylates are shorter than those to the bridging formate, while the bridging Co−O_{alkoxo} bonds have intermediate values. The trigonal bipyramidal geometry around Co(1) is defined by the O(1), O(2), and O(4) atoms at the equatorial position and N(1) and O(10) at the axial position. Similarly, the trigonal bipyramidal geometry around Co(2) is defined by the O(1), O(6), and O(8) atoms at the equatorial position and N(2) and O(11) at the axial position. These two trigonal planes meet at 124.75(9)° between each other. The exhibited sharp angle between these two planes indicates the flexibility of the ligand to accommodate the two metal centers in such proximity. The deviation of the metals from the equatorial planes is 0.179 (Co1) and 0.194 Å (Co2). The Co−O_{alkoxo} and Co−$O_{formate}$ distances indicate that these bridges are close to symmetric (Co(1)−O(1), 1.961(1) Å; Co(2)−O(1), 1.960(4) Å; Co(1)−O(10), 2.070(2) Å; Co(2)−O(11), 2.050(2) Å). The Co−Co separation in the complex **1** is 3.475(4) Å, which is comparable to a reported dinuclear cobalt(II) complex containing phenoxo−O and acetate bridges[55] but is larger than other reported dinuclear cobalt(II) complexes containing only a phenoxo−O bridge.[56]

Table 2. Selected Bond Lengths and Angles in 1 and 2

1		2	
bond lengths [Å]			
Co(1)−O(1)	1.9611(16)	Zn(1)−O(1)	1.9509(11)
Co(1)−O(2)	2.0205(17)	Zn(1)−O(2)	1.9641(12)
Co(1)−O(4)	2.0243(17)	Zn(1)−O(4)	2.0009(12)
Co(1)−O(10)	2.0664(17)	Zn(1)−O(11)	2.0198(12)
Co(1)−N(1)	2.1994(19)	Zn(1)−N(1)	2.2228(13)
Co(2)−O(1)	1.9604(16)	Zn(2)−O(1)	1.9504(12)
Co(2)−O(6)	2.0327(17)	Zn(2)−O(9)	1.9635(13)
Co(2)−O(8)	2.0404(17)	Zn(2)−O(6)	1.9784(13)
Co(2)−O(11)	2.0493(18)	Zn(2)−O(10)	2.0499(13)
Co(2)−N(2)	2.2084(19)	Zn(2)−N(2)	2.2496(14)
bond angles [deg]			
O(1)−Co(1)−O(2)	127.67(7)	O(1)−Zn(1)−O(2)	112.47(6)
O(1)−Co(1)−O(4)	110.99(7)	O(1)−Zn(1)−O(4)	111.73(5)
O(2)−Co(1)−O(4)	118.96(7)	O(2)−Zn(1)−O(4)	33.93(6)
O(1)−Co(1)−O(10)	99.82(7)	O(1)−Zn(1)−O(11)	100.37(5)
O(2)−Co(1)−O(10)	88.37(7)	O(2)−Zn(1)−O(11)	93.21(6)
O(4)−Co(1)−O(10)	97.83(7)	O(4)−Zn(1)−O(11)	91.16(5)
O(1)−Co(1)−N(1)	81.67(7)	O(1)−Zn(1)−N(1)	82.63(5)
O(2)−Co(1)−N(1)	81.45(7)	O(2)−Zn(1)−N(1)	92.27(5)
O(4)−Co(1)−N(1)	92.67(7)	O(4)−Zn(1)−N(1)	81.02(5)
O(10)−Co(1)−N(1)	168.00(7)	O(11)−Zn(1)−N(1)	172.18(5)
O(1)−Co(2)−O(6)	123.98(7)	O(1)−Zn(2)−O(9)	111.68(5)
O(1)−Co(2)−O(8)	112.43(7)	O(1)−Zn(2)−O(6)	119.52(6)
O(6)−Co(2)−O(8)	120.81(7)	O(9)−Zn(2)−O(6)	126.80(6)
O(1)−Co(2)−O(11)	98.61(7)	O(1)−Zn(2)−O(10)	95.63(5)
O(6)−Co(2)−O(11)	94.29(7)	O(9)−Zn(2)−O(10)	94.99(6)
O(8)−Co(2)−O(11)	93.72(7)	O(6)−Zn(2)−O(10)	93.59(6)
O(1)−Co(2)−N(2)	81.31(7)	O(1)−Zn(2)−N(2)	81.59(5)
O(6)−Co(2)−N(2)	80.84(7)	O(9)−Zn(2)−N(2)	93.71(5)
O(8)−Co(2)−N(2)	91.91(7)	O(6)−Zn(2)−N(2)	80.76(4)
O(11)−Co(2)−N(2)	173.92(7)	O(10)−Zn(2)−N(2)	171.29(5)

$[NMe_4]_2[Zn_2(ccdp)(\mu\text{-}OAc)]\cdot CH_3OH$, 2. Single-crystal X-ray structure analysis reveals that compound **2** consists of two zinc(II) ions, one ccdp^{5-} ligand, one bridging acetate group,

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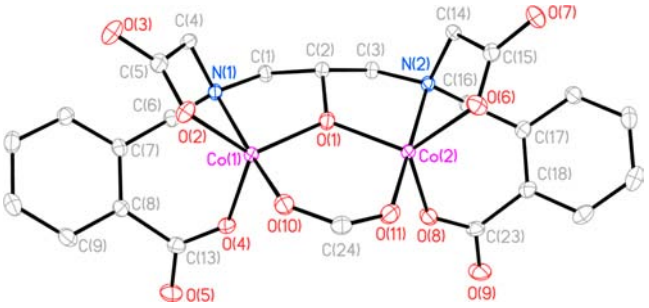

Figure 2. Thermal ellipsoid (50%) drawing of the molecular structure of the dianionic complex of $Na_3[Co_2(ccdp)(\mu\text{-}HCO_2)]\cdot BF_4\cdot 9H_2O\cdot 2CH_3OH$ (**1**). Hydrogen atoms omitted for clarity.

and two tetramethylammonium ions as counter cations. One methanol molecule cocrystallized with the complex. A structural view of the anion of compound **2** is shown in Figure 3. The anionic part of the compound **2** is isostructural to that of

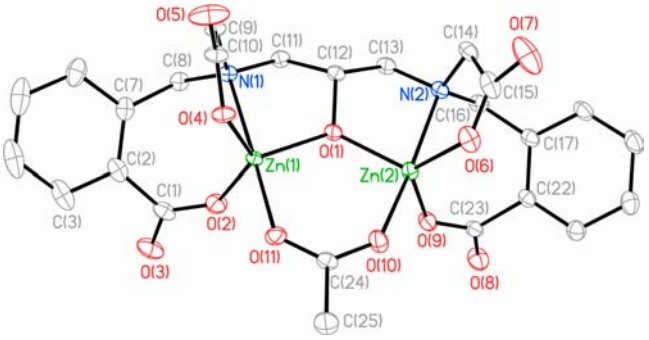

Figure 3. Thermal ellipsoid (50%) drawing of the molecular structure of the dianionic complex of $[NMe_4]_2[Zn_2(ccdp)(\mu\text{-}OAc)]\cdot CH_3OH$ (**2**). Hydrogen atoms omitted for clarity.

compound **1**, except the exogeneous carboxylate bridging group. In compound **2**, the exogenous acetate group binds two zinc(II) ions in μ-*syn-syn*-η^1:η^1-fashion.[57,58] The coordination geometry around the Zn(1) center is best described by a trigonal bipyramidal geometry, surrounded by a bridging alkoxo oxygen (O1), a monodentate aliphatic carboxylate oxygen (O4), a monodentate aromatic carboxylate oxygen (O2), a tertiary amine nitrogen (N1) of the $ccdp^{5-}$ ligand, and an exogeneous bridging acetate oxygen (O11). The Zn(2) center also adopts a trigonal bipyramidal geometry consisting of a bridging alkoxo oxygen (O1), a monodentate aliphatic carboxylate oxygen (O6), a monodentate aromatic carboxylate oxygen (O9), a tertiary amine nitrogen (N2) of the $ccdp^{5-}$ ligand, and an exogeneous bridging acetate oxygen (O10). The Zn−O (bridging alkoxo) bond distances are within the range of previously reported alkoxo-bridged dinuclear and hexanuclear zinc systems at ∼1.951 Å.[40,59,60] The $Zn-O_{bridging\ alkoxo}$ bond distances indicate that the Zn−O alkoxo bridge is very close to symmetric [Zn1−O1, 1.9509(11) Å; Zn2−O1, 1.9504(12) Å]. The Zn−O (monodentate carboxylate) bond distances are shorter than the Zn−O (bridging carboxylate) bond distances. The Zn−O (bridging carboxylate) bond distances also indicate that the Zn−O acetate bridge is close to symmetric [Zn(1)−O(11), 2.0198(12) Å; Zn(2)−O(10), 2.0499(13) Å). The Zn−Zn separation in complex **2** is 3.500(1) Å, which is comparable to a reported dinuclear zinc(II) complex containing alkoxo−O and acetate bridges.[57,58,61−63]

UV−Vis Titration and Substrate Binding with Complex 1. The interactions between substrate and complex **1** were measured using UV−vis spectrometry. UV−vis spectra obtained during titration of the dinuclear cobalt(II) complex **1** (M) with D-glucose (G) are shown in Figure 4. Titration

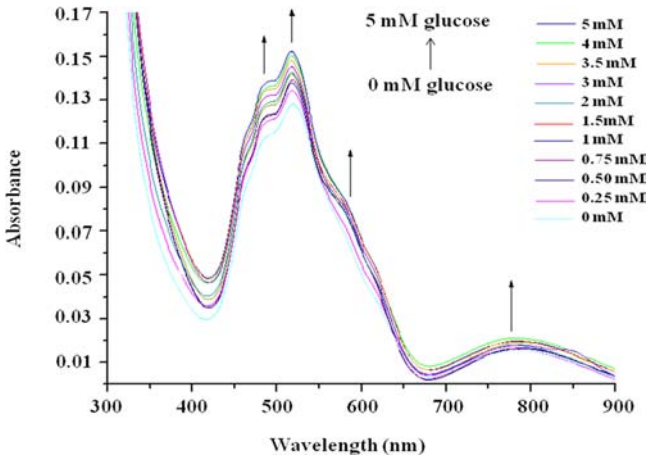

Figure 4. Selected UV−vis spectra observed during titration of dinuclear cobalt(II) complex (**M**) (1 mM) with D-glucose (**G**) at 25 °C in unbuffered, aqueous solution at pH = 12.5; the concentration of **G** were varied from 0 to 5 mM.

resulted in a significant blue shift of the absorption maximum of complex **1** (λ_{max}(M) = 532 nm) as aliquots of D-glucose were added (λ_{max}(MG) = 522 nm), which confirms the chelation of this biologically important sugar. The interesting feature of this spectrum is absorption increases until 1:1 binding stoichiometry is reached. Two methods were used to determine this binding stoichiometry, Rose−Drago and Job's Methods.[64]

Since addition of D-glucose produced a ligand field change around the dicobalt, we sought to find the number of spectroscopic states in equilibrium of MG. We used the Rose−Drago method presented by Connor to determine if a single absorbing species was present or multiple absorbing species were present.[64] The mathematical justification for this method is given in the Supporting Information. This method determines the number of absorbing complexes formed in the system. The reaction is described by eq i, its apparent binding constant $pK_{MG} = \log(K_{MG}^{-1})$, whereas K_{MG} is defined by eq ii.[64]

$$M + G \leftrightarrow MG \quad \text{(i)}$$

$$K_{MG} = \frac{[MG]}{([M]\cdot[G])} \quad \text{(ii)}$$

When a two-state system is considered, the only absorbing species being unbound will be the dinuclear cobalt(II) complex (M) and D-glucose-bound dinuclear cobalt(II) complex (MG). A two-state system can be demonstrated by plotting the change in absorption at a specific wavelength, of different concentrations, versus a different wavelength of the original concentrations $\{(A_{1j} - A_{1k})$ versus $(A_{2j} - A_{2k})$, where concentration $j \neq$ concentration $k\}$. When one absorbing complex is present (only M) only one slope will result. However, if multiple spectroscopic states exist (M plus MG) more than one slope will be evident in the graph. Applying this procedure to the data in Figure 4, the plots of Figure 5 are generated. The linear fit of dinuclear cobalt(II) complex (M)

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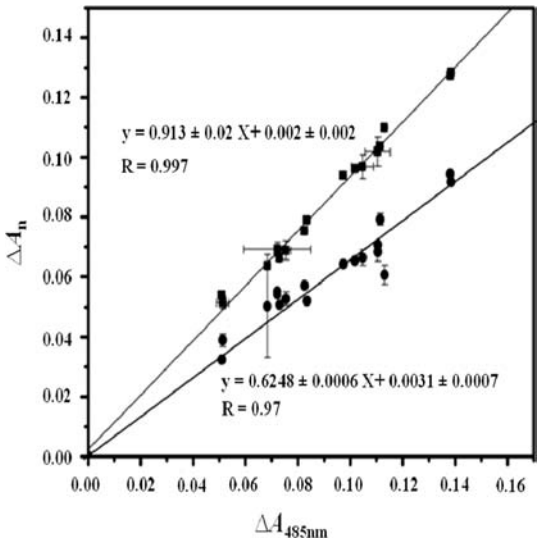

Figure 5. Plot of differences in absorbance $\Delta A_n = (A_{n,j} - A_{n,k})$ over $\Delta A_{485nm} = (A_{485nm,j} - A_{485nm,k})$ from titration of dinuclear complex (**M**) with D-glucose (**G**) at n = 520 (■) and 575 nm (●) for solution j containing **M** and **G** and solution k containing **M** at pH = 12.5, 25 °C.

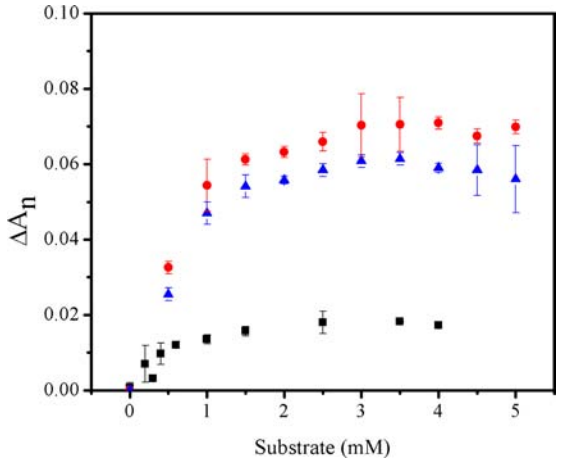

Figure 6. Binding isotherms for D-xylose, D-glucose, and xylitol. Binding isotherm plot observed during titration of complex **1** (M) (1 mM) with D-xylose (●), D-glucose (▲), and xylitol (■) (0 − 5 mM); n = wavelength chosen, 490 nm for D-xylose, 485 nm for D-glucose, and 515 nm for xylitol. Data collected in unbuffered aqueous solution at pH = 12.5 and 25 °C.

binding with D-glucose (G) at pH =12.5 is a nice fit for 1:1 complex/substrate-bound product, which results in a two-state system. Following the same procedure, UV−vis titration experiments of the dinuclear cobalt(II) complex **1** (M) with D-xylose and xylitol have been executed. The UV−vis spectrum indicates that there is a significant blue shift of the absorption maximum of complex M (λ_{max}(M) = 532 nm) upon D-xylose binding (λ_{max} = 515 nm) and a blue shift upon xylitol binding (λ_{max} = 525 nm), see Figures S3 and S5 in the Supporting Information for details. The 1:1 stoichiometry of the D-xylose- and xylitol-bound dinuclear cobalt(II) complexes was determined using the same procedure above and given, see Figures S4 and S6 in the Supporting Information for details. A representative Job plot obtained from the titration data of complex M and D-xylose is shown in Figure S7 (see Supporting Information). This finding is consistent with several previously investigated mononuclear and dinuclear copper(II) complexes.[9−11] When the system contained only one absorbing species (i.e., M), no complex/substrate-bound product formation would have taken place and the slopes of the linearly fitted data for corresponding wavelength pairs in systems containing M or M and G would be identical. This is not observed here; therefore, the binding between M and G takes place and D-glucose-bound cobalt(II) complex is formed. From the linear fit of the data, the current system can be described as a two-state system, based on 1:1 complex formation, Figure 5.[64]

Additionally, only 1:1 complexes between dinuclear cobalt(II) complex (M) and substrate are formed even if excess substrate was added. This has been concluded from the determination of the number of spectroscopic states and from the combined saturation binding isotherm plot shown in Figure 6. Saturation of complex M upon substrate binding was reached after addition of a 2-fold molar excess of D-glucose, 3-fold molar excess of D-xylose, and 1-fold molar excess of xylitol. The method of continuous variation (Job's method) has also been applied to confirm 1:1 binding interactions between complex M and substrates. Accordingly, the concentrations of complex M and the substrates were varied, keeping the total concentration of the substrates and the metal complex constant.

The apparent binding constants [pK at pH = 12.5] of the substrate-bound cobalt(II) complexes were determined from the UV−vis titration experiments by the method of Rose and Drago[64] and are shown in Table 3. From the value of the

Table 3. Apparent Binding Constants (pK_{app}) for Substrate-Bound Cobalt(II) Complexes Formed from Dinuclear Cobalt(II) Complex (1) with the Substrates at pH = 12.5

substrates	$pK_{app} \pm \Delta pK_{app}$
D-glucose	2.59 ± 0.19
D-xylose	2.93 ± 0.11
xylitol	2.45 ± 0.04

binding constants, it can be concluded that D-xylose interacts more strongly with complex M compared to that of D-glucose, whereas the interaction of xylitol is weaker than that of both D-glucose and D-xylose. The difference in binding strength between D-glucose and D-xylose is most likely due to structural differences. D-Glucose is more sterically hindered at its C-5 position with a CH_2OH group, whereas D-xylose has a smaller H atom at C-5. Xylitol, being a polyalcohol and its alcoholic hydrogens are weakly acidic, interacts very weakly with complex M, even at higher pH. This interaction was expected based on work by Norkus et al. on formation of a copper(II)−xylitol complex in aqueous alkaline solution.[6]

The binding constant values of substrate-bound cobalt(II) complexes are comparable to the reported dinuclear and mononuclear cobalt(II) and copper(II) complexes.[6,9,10,65] From the comparison of the binding constant values with the literature data, it can be suggested that the substrate-bound cobalt(II) complexes are reasonably stable in solution. Comparing with the binding constant values of reported D-mannose-bound dinuclear cobalt(II) and copper(II) complexes, it is clear that the binding of D-mannose is much more stronger than that of both D-glucose and D-xylose, most possibly because of the difference in the configuration of the hydroxyl group at the C-2 position.[9,10,65]

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^{13}C NMR Spectroscopy and Substrate Binding with Complex 2. To further understand the modes of substrate binding we synthesized a new dinuclear zinc(II) analog complex, **2**, and investigated its binding interaction with the substrates. The dinuclear zinc(II) complex, **2**, competetively binds D-glucose, D-xylose, and xylitol in alkaline solution (pH 12.5). Figure 7 shows a representative ^{13}C spectrum of pure

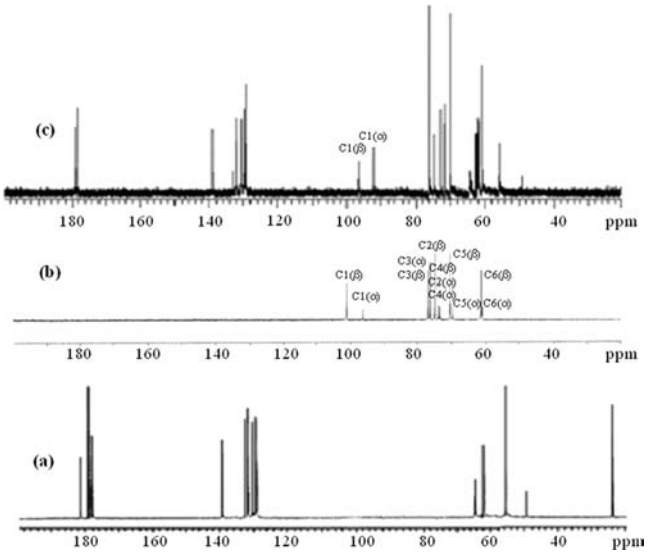

Figure 7. ^{13}C NMR spectra of a solution of (a) dinuclear zinc(II) complex, **2**, (b) free D-glucose at pH 12.5, and (c) D-glucose-bound dinuclear zinc(II) complex **2** at pH 12.5. Concentration of complex **2** is 20 mM. Ratio of complex/D-glucose is 1:1.

complex **2**, pure D-glucose, and the combination of **2** and D-glucose. The best resolution in the spectra of the D-glucose bound dinuclear zinc(II) complex was obtained using 3:1 molar ratio of complex **2** to D-glucose. The assigned chemical shifts and integrations in Figure 7b are typical for ^{13}C NMR spectra of α- and β-D-glucopyranose in aqueous alkaline solution.[66] The most surprising feature is seen when comparing Figure 7b with 7c. The intrinsic equilibrium between α and β forms at the anomeric carbon is disrupted, which results in a α/β population inversion upon coordination to complex **2**. In addition to anomeric inversion, the binding sites of D-glucose are indicated by a characteristic "coordination-induced shift" (CIS), which is an upfield shift of about 2−5 ppm for those carbon atoms that are bonded to zinc-coordinating oxygen atoms (Table 4). The upfield shift is partly due to conformational changes of the carbohydrate. Conformational changes (i.e., chair to boat to twist−boat) of the pyranose rings can be induced due to a variety of factors, including metal ion complexation. Recent literature has examples where a single metal ion is interacting with D-glucose and D-xylose; however, no reports, to our knowledge, exist for these carbohydrates interacting with dinuclear complexes. Spectra remain the same for solutions of D-glucose-bound dinuclear zinc(II) complex obtained. Klüfer and co-workers reported single-crystal X-ray structure and ^{13}C NMR spectral characterization of a D-glucose-bound dinuclear palladium(II) complex.[8] According to their research, the spectroscopically determined metal-binding sites were found entirely deprotonated and O1−O4 deprotonated α-D-glucopyranose tetraanion is coordinated as a bis(chelate) ligand to two palladium(II) central atoms.

Coordination behavior has also been observed between complex **2** and D-xylose. Figure S8 (presented in the Supporting Information) shows spectra of a solution of D-xylose-bound dinuclear zinc(II) complex obtained using a 1:1 molar ratio of complex **2** and D-xylose. Xylitol remains the least interacted substrate to the complex **2**, see Figures S9 in the Supporting Information for details. For xylitol, even at higher pH (pH ≈ 13.5), the spectrum remains the same. Hence, xylitol remains the least interacting substrate at all pH's above 12. The percentage distribution of the main equilibrium structures of D-glucose and D-xylose in aqueous solution at pH ≈ 7 at room temperature and the structure of xylitol under investigation are

Table 4. ^{13}C NMR Spectral Data of D-Glucose, D-Xylose, and Xylitol in the Free State at pH 12.5 and in the Dinuclear Zinc(II) Complex, 2

	C1	C2	C3	C4	C5	C6
free α-D-glucopyranose	96.62	73.50	76.29	70.47	70.29	60.97
α-D-glucopyranose in dizinc complex	92.08	72.05	75.10	71.37	69.77	60.74
CIS	4.54	1.45	1.19	−0.90	0.52	0.23
free β-D-glucopyranose	101.34	75.35	77.22	73.39	70.36	61.24
β-D-glucopyranose in dizinc complex	96.25	74.31	76.16	72.52	69.85	60.91
CIS	5.09	1.04	1.06	0.87	0.51	0.33
free α-D-xylopyranose	97.04	73.95	76.69	64.81	57.75	
α-D-xylopyranose in dizinc complex	92.31	71.65	74.10	65.41	57.60	
CIS	4.73	2.30	2.59	−0.60	0.15	
free β-D-xylopyranose	102.50	74.42	77.15	70.41	59.93	
β-D-xylopyranose in dizinc complex	96.73	72.85	75.65	69.59	61.10	
CIS	5.77	1.57	1.50	0.82	−1.17	
free xylitol	63.03	72.58	71.42			
xylitol in dizinc complex	63.16	72.64	71.36			
CIS	0.16	−0.07	0.17			

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shown in Figure 8. Stable metal−xylitol complexes are formed in strongly alkaline solutions, where xylitol is expected to be in

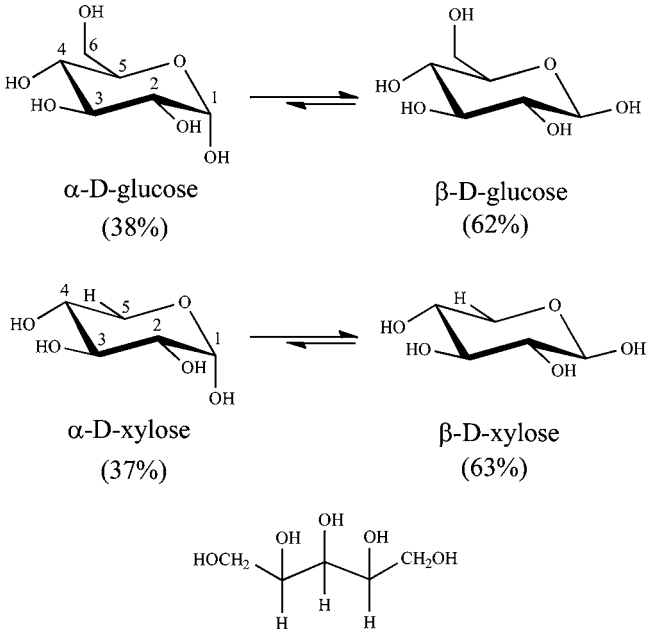

Figure 8. Percentage distribution of the main equilibrium structures of D-glucose and D-xylose in aqueous solution at pH = 7 at room temperature, and the structure of xylitol.

the deprotonated form,[6] since only deprotonated alditols represent rather strong and efficient metal ion binding agents.[67,68] The previously reported pK_a value for xylitol (pK_a = 13.73)[69] was determined electrochemically, and deprotonation of the only OH group was suggested. Deprotonation of all five OH groups has been shown in the copper(II)−xylitol and cobalt(III)−xylitol complexes,[6,70] suggesting that formation of multiple deprotonated xylitol species is also possible. Thus, although xylitol has a potential binding capability toward the transition metal ions in strongly alkaline solution, the present study shows that the interaction of xylitol with dinuclear cobalt(II) and zinc(II) complexes is very weak. This can be explained that the sterically crowded chelation in complexes **1** and **2** provided by the ligand and the exogeneous bridging carboxylate ion are stronger than the chelation provided by xylitol. The ^{13}C NMR spectroscopic technique is now convincingly used to understand the sugar binding ability and modes of their binding.[8] From the characteristic "coordination-induced shift (CIS)" values both the binding ability and the modes of binding are well understood. However, from the ^{13}C NMR data obtained in the present study it is not possible to estimate the association constants. Therefore, we have not been able to compare the binding constants from UV−vis data with the association constants from the NMR data.

CONCLUSIONS

Host−guest behavior is a prevalent theme in biological processes, rather it be for recognition, catalyst, signaling, or a myriad of other cell operations. This has spurred us to synthesize and characterize a new five-coordinate dinuclear cobalt(II) complex (**1**) and a zinc(II) complex (**2**) with carboxylate-rich dinucleating sites for potential binding interactions with substrates, specifically D-glucose, D-xylose, and xylitol. Binding characterizations between the host−guest units have been made. The dinuclear cobalt(II) complex **1** binds substrates in solution in a 1:1 molar ratio as manifested by the UV−vis titration and binding experiments. Binding sites of D-glucose are indicated by their characteristic CIS values in ^{13}C NMR spectra, which is an upfield shift for carbon atoms C1 and C2. As a result, the two oxygen atoms attached to C1 and C2 are bonded to the zinc(II) ions of complex **2**. A similar coordination behavior has been observed between complex **2** and D-xylose. Xylitol remained the least interacted substrate to complexes **1** and **2**. On the basis of the calculated binding constant values and CIS values in ^{13}C NMR spectra, it can be concluded that dinuclear cobalt(II) and zinc(II) complexes **1** and **2** bind D-xylose more strongly than D-glucose, a result that corresponds to the behavior of xylose/glucose isomerases (XGI). The current investigation of the binding interactions between the functional dimers (such as dinuclear cobalt(II) and zinc(II) complexes) and targeted templates (such as sugars) prior to polymerization will positively contribute in the field of carbohydrate recognition in aqueous medium. Additionally, the present study can provide important structural and functional information with relevance to various important sugar-metabolizing metalloenzymes.

EXPERIMENTAL SECTION

General Remarks. All starting materials were purchased from commercial sources and used without further purification. Elemental analyses were determined by Galbraith Laboratories, Inc., Knoxville. FTIR spectra were recorded with a Bruker Vector 22 spectrometer.

UV−Vis Spectroscopy. All experiments were performed on an Agilent 8453 diode array UV−vis spectrophotometer with a 1 cm quartz cell at room temperature over a range of 200−900 nm. An Eppendorf Research micropipet was used to measure volumes. All experiments were done in degassed nanopure water, in which pH was adjusted to pH 12.5 with NaOH prior to use for each set of titrations. Typically, a 1.5 mM stock solution of complex **1** and 15 mM stock solution of each substrate were prepared separately and kept at room temperature. The total concentration of complex **1** ($V_{\text{complex 1}}$ = 2 mL; [Complex **1**]$_t$ = 1 mM) and the total volume of the resulting solutions (V_t = 3 mL) were kept constant during the titration experiments ($V_{\text{substrate}}$ = 0−1000 μL) by adding an appropriate amount of water. UV−vis absorbances and pH meter readings of the resulting mixtures were measured immediately after mixing. Each concentration was made and measured three times, and data points were averaged. Standard deviation was applied to these averages.

NMR Spectroscopy. ^{1}H and ^{13}C NMR spectra of the ligand and complex **2** were obtained in D_2O solution with a Varian Inova 500 NMR spectrophotometer. All ^{13}C NMR experiments for determination of binding interactions were performed on the same NMR spectrophotometer at room temperature. Experiments were done in D_2O solution, for which pH was adjusted to pH 12.5 with NaOH prior to use for each set of NMR titrations. The pH of the resulting solution was measured immediately after mixing

Synthesis of *N,N′*-Bis[2-carboxybenzomethyl]-*N,N′*-bis-[carboxymethyl]-1,3-diaminopropan-2-ol, H_5ccdp. Ligand has been prepared according to our previously published procedure.[40] Product was collected by filtration, washed with water and methanol, and dried at 80 °C. Product was confirmed by elemental analysis, FTIR, and ^{1}H and ^{13}C NMR spectroscopy. Yield: 5.2 g (95%). Anal. Calcd for $C_{23}H_{26}N_2O_9\cdot$2HCl: C, 50.47; H, 5.16; N, 5.12. Found: C, 50.31; H, 5.50; N, 5.06. FTIR (cm^{-1}): ν = 3503(b), 3032(b), 1667(s), 1590(vs), 1562(s), 1440(s), 1392(s), 1264(s), 1160(s), 902(s), 845(s), 788(s). ^{1}H NMR for the sodium salt of the compound (500 MHz, D_2O, 25 °C, δ): 7.51 (d, 2H, J = 7.5 Hz), 7.40 (m, 4H), 7.33 (t, 2H, J = 7.5 Hz), 3.92 (d, 2H, J = 13.5 Hz), 3.82 (d, 2H, J = 13.5 Hz), 3.82 (d, 1H), 3.19 (d, 2H, J = 16.5 Hz), 3.10 (d, 2H, J = 16.5 Hz), 2.62 (d, 1H, J = 3.0 Hz), 2.59 (d, 1H, J = 3.0 Hz), 2.45 (d, 1H, J = 9.0 Hz), 2.42 (d, 1H, J = 9.0). ^{13}C NMR (500 MHz, D_2O, 25 °C, δ): 180.14,

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178.80, 140.58, 134.41, 130.46, 128.48, 127.30, 126.42, 66.27, 58.70, 58.57, 56.68.

Synthesis of $Na_3[Co_2(ccdp)(\mu\text{-}HCO_2)]BF_4\cdot 9H_2O\cdot 2CH_3OH$ (1). In an argon glovebox, to a stirred solution of ligand, H_5ccdp (0.082 g, 0.173 mmol), and NaOH (0.042 g, 1.05 mmol), $Co(BF_4)_2\cdot 6H_2O$ (0.118 g, 0.346 mmol) which was dissolved in another 5 mL methanol was added dropwise. Almost immediately upon addition, a dark pink-violet solution was formed. The pink-violet solution was stirred at room temperature for 2 h and then filtered to remove any solid. X-ray quality single crystals were obtained after 5 days from slow ether diffusion into the filtrate solution. Yield: 0.159 g (90%). Anal. Calcd for $C_{24}H_{32}N_2O_{16}BF_4Na_3Co_2$: C, 32.38; H, 3.59; N, 3.14. Found: C, 31.90; H, 3.23; N, 2.89. FTIR (cm^{-1}): ν = 3373(b), 1586(vs), 1557(s), 1425(s) 1390(s), 1156(s), 1043(s), 910(s), 761(s). UV–vis spectra [λ_{max}, nm (ε, L $mol^{-1}cm^{-1}$)]: (H_2O solution) 721 (18), 532 (80), 485 (37)^{sh}, 268 (2427)^{sh}.

Synthesis of $[NMe_4]_2[Zn_2(ccdp)(\mu\text{-}OAc)]\cdot CH_3OH$ (2). A methanol solution (10 mL) of $Zn(OAc)_2\cdot 2H_2O$ (0.463 g, 2.107 mmol) was slowly added dropwise, at ambient temperature into a 15 mL methanol solution of the ligand H_5ccdp (0.500 g, 1.054 mmol) and NMe_4OH (1.147 g, 6.328 mmol) in a period of 15 min under stirring. The whole reaction mixture was stirred for 2 h. The colorless solution formed was filtered. X-ray-quality colorless plate-shaped single crystals were grown after 3 days from slow ether diffusion into the filtrate solution. Yield: 0.738 g (90%). Anal. Calcd for $C_{33}H_{48}N_4O_{11}Zn_2$: C, 47.08 ; H, 5.74; N, 6.65. Found: C, 46.73; H, 5.16; N, 6.34. FTIR (cm^{-1}): ν = 3040(b), 1581(vs), 1547(s), 1405(s), 1398(s), 1201(s), 1150(s), 907(s), 865(s), 751(s). ^{1}H NMR (500 MHz, D_2O, 25 °C, δ): 1.94 (s, 3H, bridging acetate), 2.65–4.25 (m, 13H, ethylenic), 3.17 (s, 24H, NMe_4), 7.34–7.57 (m, 8H, aromatic). ^{13}C NMR (500 MHz, D_2O, 25 °C, δ): 23.62 (1C, CH_3 of bridging acetate), 49.31 (8C, NMe_4), 55.35 (2C, CH_2), 55.53 (2C, CH_2), 61.77 (2C, CH_2), 64.25 (1C, aliphatic CH), 128.90 (2C, aromatic CH), 129.34 (2C, aromatic CH), 130.29 (2C, aromatic CH), 131.50 (2C, aromatic CH), 131.88 (2C, aromatic CH), 139.07 (2C, aromatic CH), 177.91 (2C, aromatic carboxylate), 178.59 (2C, aliphatic nonbridging carboxylate), 181.18 (1C, bridging carboxylate).

X-ray Crystallography and Data Analysis. Crystal data as well as data collection and refinement for complexes are summarized in Table 1. Pink colored prism-shaped single crystals with approximate dimensions 0.214 × 0.196 × 0.184 mm (**1**) and clear colorless plate-shaped single crystals with approximate dimensions 0.42 × 0.40 × 0.15 mm (**2**) were selected for structural analysis. Intensity data for these compounds were collected using a diffractometer with a Bruker APEX CCD area detector[71,72] and graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). For **1**, a total of 76 308 data were measured in the range 2.24° < θ < 28.03° using ω oscillation frames. Data were corrected for absorption by the semiempirical method,[73] giving minimum and maximum transmission factors of 0.819 and 0.793. Data were merged to form a set of 10 146 independent data with R(int) = 0.0350 and a coverage of 99.6%. The monoclinic space group $P2_1/c$ was determined by statistical tests and verified by subsequent refinement. For **2**, cell parameters were determined from a nonlinear least-squares fit of 9943 peaks in the range 2.6972° < θ < 34.8714°. A total of 16 735 data were measured in the range 1.65° < θ < 35.10° using ω oscillation frames. Data were corrected for absorption by the semiempirical method,[73] giving minimum and maximum transmission factors of 0.6046 and 0.8283. Data were merged to form a set of 14 508 independent data with R(int) = 0.0409. Monoclinic space group $P2_1/c$ was determined by statistical tests and verified by subsequent refinement. Structures were solved by direct methods and refined by full-matrix least-squares methods on F^2.[74,75] Hydrogen atom positions were initially determined by geometry and refined by a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were generated at ideal positions (C–H, 0.96 Å) and fixed with isotropic thermal parameters.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic data in CIF format for complexes **1** and **2**; UV–vis, Jobs graphs, and NMR data and figures of the substrate/complex interactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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