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Carbonic Anhydrase Inspired Phosphatase Model Complexes Derived from the Tripodal Ligand Tris(hydroxy-2-benzimidazolyl)amine: The Hydrolysis of p-nitrophenyl Acetate

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Carbonic Anhydrase Inspired *Phosphatase* Model Complexes Derived from the Tripodal Ligand Tris(hydroxy-2-benzimidazolyl)amine: The Hydrolysis of *p*-nitrophenyl Acetate

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The water soluble ligand tris(hydroxyl-2-benzimidazolyl)amine NTB_{OH} was used for the preparation of a series of aqua transition metal complexes and their hydroxo derivatives of the types [NTB_{OH}-M(OH₂)]²⁺ 1-3 and [NTB_{OH}-M(OH)]⁺ 4-6 ($M^{2+} = Zn^{2+}$, Cu^{2+} , and Co^{2+}]. Solid state studies of these model complexes were investigated using FT-IR spectroscopy, elemental analysis, and thermal analysis. Solution studies have also been carried out to investigate the coordination behavior of the ligand towards the metal ions as well as the evidence for the protonation/deprotonation of the coordinated water molecules. The effect of these model complexes as potential catalysts, especially the nature of metal ions on the hydrolysis of *p*-nitrophenyl acetate (NA), has also been investigated. The results indicate that copper(II) complex 3 is the most active hydrolytic catalyst among complexes 1–3, presumably a reflection of the effective electron-withdrawing as well as the greatest electrophilicity of cobalt(II) ion.

Keywords carboxylate ester hydrolysis, thermal analysis, transition metal complexes, water soluble ligand

INTRODUCTION

The use of tripod-like ligand, tris(2-benzimidazolylmethyl)amine, NTB^[1], (Scheme 1) with hydrophobic benzene rings can provide protected 'pockets' for metal ions. It was successfully utilized for the preparation and isolation of different structural zinc(II) enzyme model complexes^[2–6] and was also suitable for the synthesis of biomimetic coordination compounds having *superoxide dismutase*^[7,8] and *carbonic anhydrase* activities.^[1,9–11]

Since the catalytic activity of the "biological zinc" cannot only be understood as a result of hydrophobic effects but also

of hydrophilic interactions of the substrates with polar protein side chains and water molecules in the active site of the enzyme. Therefore, a further development of the ligand NTB to provide a hydrophobic cavity within a hydrophilic system bearing Hbonding groups on the benzimidazole rings and being soluble in aqueous solution has been recently done. First attempts were the synthesis of the water soluble ligand NTB_{sulf}(Scheme 1) was recently made.^[10,11] The insertion of the hydrophilic anionic sulfonate groups (SO_3^-) on the neutral ligand NTB allowed the isolation of zinc complexes very stable towards hydrolysis and soluble in water polar solvents like wet methanol. This ligand afforded the desired N₄-coordination array around zinc, which was more appropriate biomimetic zinc compound in aqueous solution. This model complex showed the largest rate constant among them carbonic anhydrase model compounds reported so far^[11] towards the hydration of CO_2 .

Due to the anionic charge effect of NTB_{sulf} , another new water soluble ligand, namely tris(hydroxy-2benzimidazoly1)amine NTB_{OH} , has been obtained by the introduction of the phenolic OH group on each benzimidazole ring of NTB.^[11] This new ligand with the hydrophilic OH groups afforded new water zinc model complexes, and structurally and functionally mimicked the active site of *carbonic anhydrase*, which has (i) pseudotetrahedral structure around zinc, (ii) hydrohibic environment around zinc-bound H₂O / OH⁻, (iii) the solubility in both water and organic solvents, and (iv) neutral ligand to prevent the charge effect on the enzymatic reaction. The phenolic groups in NTB_{OH} could increase the solubility and recognize the water molecules through hydrogen bond in solution.

The ultimate aim of this work was to show how the ligand NTB_{OH} may assume, upon complexation with metal ion, a basket-like structure, bind substrates in water, and eventually, cleavage them under physiological conditions. Therefore our target was (i) the synthesis of a series of water soluble aqua metal (Zn^{2+} , Cu^{2+} , and Co^{2+}) complexes and their hydroxide

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SCH. 1. The ligand NTB_{OH} and its metal complexes 1-3.

derivatives (Scheme 2) as structural and functional models of the active site of *hydrolase* enzymes, (ii) analysis and characterization of the obtained compounds in the solid state using FT-IR spectroscopy, elemental analysis, and thermal analysis, (iii) solution studies of the metal-ligand interactions for determining the stoichiometry and the pK_a value of the coordinated water molecule using complexometric titration by using ¹H NMR and UV-visible spectroscopies, and (iv) application of the obtained metal complexes as structural and functional catalyst towards the hydrolytic reactions using UV-visible spectroscopy.

EXPERIMENTAL

Materials and General Methods

The ligand tris(hydroxyl-2-benzimidazolyl)amine, NTB_{OH}, and its aqua and hydroxo zinc complexes [NTB_{OH}Zn(OH₂)]·(ClO₄)₂·6H₂O **1** and [NTB(OH)](ClO₄)·1.5 H₂O **4**, respectively, have been previously synthesized and described.^[6] The IR absorption spectra (Figure 1) were recorded using FT-IR Bruker Vector 22 Spectrometer, Germany in the range of 400–4000 Cm⁻¹. The ¹H NMR measurements were recorded by using Mercury-300 BB 'NMR300' and Gemini-200 'NMR'. All UV-visible measurements were recorded by UV-240 Shimadzue, Japan and quartez cuvette.

Thermal Analysis

Thermogravimetric analyses (Figures 2 and 3) were performed using Shimadzu Stand-Alone Thermal Analyzer Instruments (TGA-50H) Japan. About 5 mg of pure sample was subjected to dynamic TGA scans at a heating rate of 10° C / min in the temperature range of ambient to 800° C under a dynamic atmosphere of dry nitrogen gas (flow rate = 10 ml/min). The kinetic parameters of the dehydration and decomposition steps were determined from the TGA thermograms using the Coats-Redfern^[12] equations in the following form:

$$\log\left[\frac{1-(1-\alpha)^{1-n}}{T^2(1-n)}\right] = \log\frac{\mathrm{AR}}{\mathrm{qE}_a}\left[1-\frac{2\mathrm{RT}}{\mathrm{E}_a}\right] - \frac{\mathrm{E}_a}{2.3\,\mathrm{RT}}$$

Where α is the fraction of the sample decomposed at time t, T is the derivative peak temperature (K), n is the order of reaction, A is the frequency factor, R the molar gas constant, E_a is the activation energy. A plot of log[-log(1- α)T²] versus 1/T gives the slope for evaluation of the activation energy. The thermodynamic parameters, Δ H, Δ S, and Δ G were computed using the relationships^[13]: Δ H = E – RT, Δ S = R[ln(Ah/kT)⁻¹], and Δ G = Δ H – T Δ S where k is Boltzmann's constant and h is the Planck's constant.

UV-visible Measurements

The stoichiometry of ligand-metal complexes were calculated by applying the "mole ratio" method. The stoichiometric ratios between ligand and metal ions for NTB_{OH} with Zn(ClO₄)₂·6H₂O, Cu(NO₃)₂·3,5H₂O and Co(NO₃)₂·6H₂O with (1×10^{-4}) mole/L in aqueous methanolic solution (50%, v/v). The pk_a of the coordinated water molecules of the obtained aqua metal complexes **1–3** has been determined by recording the absorbance of the generated hydroxo complexes at different pH values. The measurements have been carried out in aqueous ethanol (50%, v/v) and the pH values were adjusted by using dilute solutions of NaOH and HNO₃.

Syntheses

$[NTB_{OH}Cu(OH_2)](NO_3)_2 3H_2 OCH_3 OH 2$

TBA_{OH} (0.103 g, 0.20 mmol) in methanol (10 ml) was added to a stoichiometric amount of Cu(NO₃)₂·3.5 H₂O (0.05 g, 0.2 mmol) in methanol (10 ml). The mixed solution was stirred for around 2 h. A dark brown precipitate was formed formed, filtered off, washed with diethyl ether, and dried in vacuo. Yield 114 mg (78 %), m. p. 265°C. Anal. calcd. for C₂₅H₃₃O₁₄N₉Cu



SCH. 2. The hydrolysis reaction of p-nitrophenylacetate by using the hydroxo metal complexes [NTB_{OH}-M(OH)]* 4-6.





FIG. 1. IR spectra of the ligand NTB_{OH} and its zinc(II), copper(II), and cobalt(II)-bound hydroxo complexes 1–3.

(746.54): C, 41.17; H, 4.52; N, 16.87. Found: C, 40.33; H, 5.25; N, 16.94. FT-IR (KBr): ν (cm⁻¹): 1156 (m, C-N, R), 1353 (s, NO₃-), 1484 (m), 1450 (m, C=C), 1545 (m), 1599 (m), 1634 (m, C=N), and 3217cm⁻¹ (b, OH).

$[NTB_{OH}Co(OH_2)](NO_3)_2 \cdot H_2O \cdot CH_3OH 3$

 TBA_{OH} (103 mg, 0.20 mmol) in methanol (10 ml) was added to a stoichiometric amount of $Co(NO_3)_2 \cdot 6H_2O$ (60 mg, 0.2

FIG. 2. TGA-DTG curves of (a) Zinc(II) complex **1**, (b) Copper(II) complex **2**, and (c) Cobalt (II) complex **3** in the temperature ranges 25–800°C.

mmol) in methanol (10 ml). The mixed solution was stirred for around 3 h. A pinkish white precipitate was formed formed, filtered off, washed with diethyl ether, and dried in vacuo. Yield 123 mg (89%), m. p. > 300° C (decomp.). Anal. calcd. for C₂₅H₂₉O₁₂N₉Co (705.933): C, 42.49; H, 4.10; N, 17.84. Found: C, 40.21; H, 3.59; N, 17.34. FT-IR (KBr): ν (cm⁻¹): 1157 (m, C-N, R), 1354 (m), 1381 (s, NO₃⁻), 1481 (m), 1449 (m, C=C), 1545 (w), 1603 (m), 1634 (s, C=N), and 3379 cm⁻¹ (b, OH).



FIG. 3. TGA-DTG curves of (a) Zinc(II) complex **4**, (b) Copper(II) complex **5**, and (c) Cobalt (II) complex **6** in the temperature ranges 25–800°C.

$[NTB_{OH}Cu(OH)](NO_3) \cdot 4H_2O5$

The copper hydroxo complex **5** was precipitated by stirring methanolic solutions of the aqua copper(II) complex **2** (0.0479 mmol) in ethanol (15 ml) and sodium methoxide (0.0479 mmol) for 24 hours. Filtered, washed with ethanol and dried in vacuo. Yield 1.9 mg (59 %). m. p. > 300° C (decomp.). Anal. calcd. for C₂₄H₃₁O₁₁N₈Cu (670.54): Calc.: C, 42.95; H, 4.62; N, 16.70. Found: C, 41.21; H, 4.57; N, 16.12. IR (KBr): $\nu = 1161.2$ (m, C-N R), 1381.1(s, NO₃), 1443.7 (m), 1479 (m, C=C), 1544.3 (m), 1631.3 (m, C=N), 2926.3 (w, C-H), 3380.2 (b, OH).

$[NTB_{OH}Co(OH)](NO_3) \cdot 6H_2O 6$

The cobalt(II) hydroxo complex **6** was precipitated by stirring ethanolic solutions of the aqua cobalt complex **3** (0.0255 mmol) and sodium methoxide (0.0255 mmol) for 24 hours. Filtered, washed with diethyl ether, dried in vacuo and weighted as violet powder. Yield 12 mg (63%). m. p. > 300°C (decomp.). Anal. calcd. for C₂₄H₃₄O₁₃N₈Co (700.93): Calc.: C, 41.08; H, 4.85; N, 15.97. Found: C, 41.21; H, 4.33; N, 15.74. IR (KBr): $\nu =$ 1159.4 (m, C–N, R), 1356.4 (s, NO₃⁻), 1446.9 (m), 1475.6 (m, C=C), 1543.6 (w), 1631.2 (m, C=N), 2924.8 (m, C–H), 3219.1 (b, OH), 3379.1 (b, NH).

$[NTB_{OH}Zn(OPO(OC_6H_4-p-NO_2)_2)](ClO_4) 3H_2O7$

Complex was prepared by the reaction 7 of $[NTB_{OH}Zn(OH_2)] \cdot (ClO_4)_2 \cdot 6H_2O \ 1 \ (169 \ mg, \ 0.2 \ mmol)$ in methanol (10 ml) with a stoichiometric amount of bis(pnitrophenyl)phosphate (82 mg, 0.039 mmol) in methanol (10 ml) at pH = 9. After several days, colorless crystals were formed, filtered, and dried in vaccuo. Yield 61%, m.p. 136°C. Anal. calcd. for C₃₆H₃₅O₁₇N₉ZnPCl (996.53): Calc.: C, 43.39; H, 3.54; N, 12.65 %. Found: C, 43.11; H, 3.60; N, 12.58 %. ¹H NMR, δ_H (DMSO-d₆): 8.09 (d, 4H, -C₆H₄-NO₂), 7.47 (d, 3H C₆H₃), 7.42 (s, 3H C₆H₃), 7.34 (d, 4H, -C₆H₄-NO₂), 6.93 (d, 3H C₆H₃), and 4.53 ppm (s, 6H, -CH₂-). IR (KBr): $\nu = 855$ (m, C-N for C-NO₂), 1089 (s, ClO₄⁻), 1219 (m, P-O-C), 1253 (m, P=O), 1348 (s, NO₂), 1453 (m), 1488 (s), 1517 (s, C=C), 1593 (m), 1616 (m), 1637 (m, C=N), 2926 (m, C-H), 3413 (b, OH).

Kinetic Studies for the Hydrolysis Reactions of the Carboxy Ester p-nitrophenyl Acetate (NA)

The hydrolysis rates of both *p*-nitrophenyl acetate (NA) in aqueous methanol (40% v/v)) by using the obtained model complexes 1-3 were measured by recording the increase in 402 nm absorption of the released yellow *p*-nitrophenolate as a hydrolyzed product.^[11,14-17] The mixed solvent (CH₃OH / H₂O, 40%) was used to prevent precipitation of the metal complex as well as increasing the solubility of the substrates. The pH value of each sample was adjusted by using a concentrated solutions of NaOH (1M) or HNO₃ (1M), and not by using buffers. In the course of hydrolysis, the pH value of each sample was checked and was found that the difference compared to the adjusted pH value at the beginning of hydrolysis was not larger than 0.3. The measurements of the hydrolysis reactions were carried out at $25\pm 0.2^{\circ}$ C. Release of only one pnitrophenolate per the substarte NA molecules was considered. The catalytic reaction was initiated by rapid injection of 0.3 ml acetonitrile solution of both NA (3 \times 10⁻⁴ mol/L) into 2.7 ml of the metal complex (72 \times 10⁻⁶ mol / L) in quartez covette 3 ml. The UV absorption increase was recorded immediately, the concentration of p-nitrophenolate was measured at intervals of times. Reaction rates are corrected by blank experiments that were made up similarly but without the presence of metal complexes.

RESULTS AND DISCUSSION

Characterization of the Model Complexes 1-7

Complexation of transition metal cations is favored by the presence of soft donor atoms such as nitrogen or sulfur, but also ligands containing the harder oxygen atoms can bind these cations. We examined the complexation of both Zn(II), Cu(II) and Co(II) ions with the ligand NTB_{OH} and their complex structures as well as the determination of the pk_a values for the coordinated water molecules. The ligand NTB_{OH} has three benzimidazole nitrogen atoms and on tertiary amine nitrogen atom, allowing them to act as tetradentate donors. The agua metal(II) complexes $[NTB_{OH}-M(OH_2)]^{2+}$ 1-3 (M = Zn, Cu, and Co) were obtained by the reaction of the ligand NTB_{OH} with equimolar amounts of Zn(ClO₄)₂, Cu(NO₃)₂, and (Co(NO₃)₂, respectively, in absolute methanol. Analogous to zinc (II) complex 1 (Figure 1),^[11] the IR spectra (Figure 1) of both copper(II) complex 2 and cobalt(II) complex 3 showed very broad OH absorption bands around 3217 and 3279 cm⁻¹, respectively. They also showed ν (NO) absorption bands of the nitrate anion at 1353 and 1354 cm^{-1} , respectively. These complexes were also characterized using elemental analysis, in which the observed values were in good fits with the calculated ones. Attempts to propose the structure of the isolated aqua copper(II) complex come from the investigation using thermal analysis studies in its solid state as well as from the solution studies using UV-visible spectroscopy. Attempts to prepare the metal-bound hydroxo complexes of the formula [NTB_{OH}MOH]⁺ 4-6 in methanol solution using Me₄NOH·5H₂O condition similar to those utilized for the preparation of the monomeric hydroxide complexes of similar ligand system^[18] failed to give clean crystalline product. However, using sodium methoxide, MeONa as a base, treatment of the ligand NTB_{OH} with equimolar amounts of the perchlorate or nitrate salts of metal ions $(Zn^{2+}, Cu^{2+}, and Co^{2+})$ and MeONa under an aerobic conditions, then followed by workup and crystallization from MeOH/CH₂Cl₂ yielded the monomeric hydroxide complexes as crystalline solid with good yields. The chemical characterization of these hydroxide derivatives was determined by ¹H NMR and FT-IR spectroscopices as well as elemental and thermal analyses.

The of recognition coordination and bis(pnitrophenyl)phosphate (BNPP⁻) in complex 7 was reaction the possible by the of aqua complex $[NTB_{OH}Zn(OH_2)] \cdot (ClO_4)_2 \cdot 6H_2O$ **1**^[11] with an equivalent amount of the deprotonated form of bis(pnitrophenyl)phosphate in water. It was isolated analytically pure with a good yield. Its chemical characterization showed absorption of $\nu(\text{ClO}_4^-)$ at 1089 cm⁻¹ and absorptions of 1253 cm^{-1} (s, P=O) and 1219 cm^{-1} (s, P-O-C), and are typical characterization bands of coordinated phosphate to metal complexes.^[15-20]



FIG. 4. ¹H NMR spectra of the ligand NTB_{OH} and its zinc(II)-bound aqua and zinc(II)-bound hydroxo complexes in DMSO- d_6 at 25°C.

Solution Studies

The binding ability of NTB_{OH} with these metal ions was spectroscopically examined in aqueous methanol using ¹H NMR and UV-visible spectroscopies.

In order to get a better insight into the complex species formed in NTB_{OH} / Zn²⁺ system, ¹H NMR study was carried out for the free ligand, its aqua zinc(II) complex, and its hydroxo zic(II) complex **4**. The ¹H NMR spectrum of zinc(II) complex **1** (Figure 4) showed that the proton signals of the methylene and benzimidazolyl protons were shifted down filed compared to those found for the free ligand, indicating the formation of zinc(II) complex **1**. The observed ¹H NMR spectrum for the zinc(II) complex **4** showed that the chemical shifts of the methylene and benzimidazolyl protons were shifted upfield. This shift is not found in the ligand itself, indicating the formation of zinc(II)-bound hydroxo complex **4**.

The spectra of NTB_{OH} with Co(II) ions in aqueous methanol (33%, v/v) show d-d absorptions at 539 nm, which suggests that cobalt ions have the characteristics of a penta- coordinate complex with distortion.^[21] As can be seen from Figure 5, an increase in absorbance is observed upon addition of increasing quantities of cobalt(II) ions to the ligand solution, whereas the absorption intensity changes as a function of the $[Co^{2+}]/[NTB_{OH}]$ mole ratio. These changes could be attributed to the complexation between the ligand and copper(II) ions. From the inflection point in the absorbance/mole ratio plots at $[Co^{2+}]/[NTB_{OH}]$ values between 0.8 and 1.0, it can be inferred that 1:1 complex species are formed.

FIG. 5. UV study for NTB_{OH} (1 \times 10⁻⁴ M) with different ratio of Cu(NO₃)₂ $3.5H_2O(1 \times 10^{-4} \text{ M})$ in aqueous MeOH (33%, v/v) at I = 0.1 M NaNO₃ and 25°C.

500.00

λ(nm)

0.6

0.4 Absorbance

0.2

0.0

0.0

0.8 0.4

R = [C 0] / [N TB03]

600.00

700.00

1.2 1.6

The generation of the hydroxo complexes $[NTB_{OH}-M(OH)]^+$ 4-6 (M = Zn, Cu, and Co) were also investigated in solution by determining the pk_a values of the coordinated water molecule of their aqua complexes 2 and 3. The absorbance of these complexes has been measured at different pH values in aqueous methanol (33%, v/v). The pH values were adjusted by using dilute solutions of HNO₃ and NaOH. The obtained UV-Vis spectra in solution for cobalt(II) complex are shown in Figure 6 as an representative example. The copper(II) complex $[NTB_{OH}-Cu(H_2O)]^{2+}$ 3 is characterized by a visible band at 639 nm, which can be assigned to the A' \rightarrow E" transition for a five-coordinate D3h Cu(II) complex.^[22-24] A new band gradually appeared at 349 nm on increasing the pH. This indicates that the geometry distorts from trigonal bipyramidal to a square pyramidal/octahedral structure due to the formation of





FIG. 8. Hydrolysis rate constant, k_{obs} of *p*-nitrophenyl acetate (3 × 10⁻⁴) M) catalyzed by using complexes 1-3 (72×10^{-6} M) at different pH values in aqueous methanol (33%, v/v) at I = 0.1 M NaNO₃ and 25°C.

8.0

8.5

pH

9.0

9.5





M) catalyzed by copper(II) complex 2 (72×10^{-6} M) at pH = 8.5 in aqueous

 $[NTB_{OH}-Cu(OH)]^+$.^[19] The absorbance indicates a sigmoidal

change in the pH range 8 to 9, which corresponds to a change

from [NTB_{OH}-Cu(H₂O)]²⁺to [NTB_{OH}-Cu(OH)]⁺. From the fit-

ting curve, the obtained pk_a value for the coordinated water

The TGA curve of complex 1 (Figure 2a) shows four de-

composition steps within the temperature range 40-900°C. The

methanol (33%, v/v) at I = 0.1 M NaNO₃ and 25°C.

molecule of complex **3** is $ca 8.86 \pm 0.1$.

Thermogravimetric Analysis

0.0

7.0

7.5



1.500

1.000

0.500

-0.020

300.00

400.00

Absorbance



SCH. 3. Proposed mechanism for the hydrolysis of p-nitrophenylacetate by using the hydroxo-bound zinc(II), copper(II), and cobalt(II) complexes 1-3.

steps of the decomposition within the temperature range 330-734°C, corresponding to the loss of the perchlorate anions and the organic part of the complex with a mass loss of 77.46% (calcd 77.36%). The final residue within the temperature range 734-900°C corresponded to (Zn) metal with a mass loss of 7.703% (calcd 7.732%). The TGA curve of complex 2 (Figure 2b) shows four decomposition steps within the temperature range 25-900°C. The first step of the decomposition within the temperature range 25-100°C corresponded to the loss of three water molecules of lattice with a mass loss of 7.368% (calcd 7.55%). The second step within the temperature range 120-220°C corresponded to the loss of coordinated water molecule with a mass loss of 2.32% (calcd 2.5%). The third and the fourth steps of the decomposition within the temperature range 222-497°C corresponded to the loss of the nitrate anions and the organic part of the complex with a mass loss of 75.89% (calcd 75.433%). The final residue within the temperature range 497– 900°C corresponded to (CuO + 2C) with a mass loss of 14.41% (calcd 14.49%). The TGA curve of complex **3** (Figure 2c) shows four decomposition steps within the temperature range 30–90°C (Scheme 3). The first step of the decomposition within the temperature range 30-100°C corresponded to the loss of one water molecule of lattice with a mass loss of 2.711% (calcd 2.67%). The second step within the temperature range 260–278°C corresponded to the loss of 2.513% (calcd 2.67%). The third and the fourth steps of the decomposition within the temperature range 282–515°C corresponded to the loss of nitrate anions and the organic part of complex with a mass loss of 76.57% (calcd 76.42%). The final residue within the temperature range 515–900°C corresponded to (CoO + 4C) with a mass loss of 18.21% (calcd 18.19%).

The TGA curve of complex 4 (Figure 3a) shows five decomposition steps within the temperature range $40-900^{\circ}$ C. The

					1	I I I I I		
Complex	Step	T(k)	А	r	$\Delta E^{\#}$	$\Delta H^{\#}$	$\Delta S^{\#}$	$\Delta G^{\#}$
	1st	338	1.6×10^{12}	0.977	91.26	88.34	-0.021	95.43
	2nd	563	719416	0.912	20.89	17.97	-0.146	100.16
1	3rd	638	183×10^{7}	0.979	77.81	74.89	-0.082	127.20
	4th	798	22×10^{6}	0.994	161.93	159.01	-0.120	254.77
	1st	317	1.49×10^{10}	0.825	101.56	98.64	0.036	87.01
	2nd	398	2018.2	0.992	44.84	21.92	-0.192	78.33
2	3rd	513	1.87×10^{8}	0.982	219.76	216.85	0.130	150.07
	4th	612	5.06×10^{10}	0.985	298.94	296.02	-0.054	329.06
	1st	323	2.42×10^{10}	0.958	123.65	120.73	0.078	95.27
3	2nd	533	95×10^{4}	0.965	23.74	20.82	-0.143	97.03
	3rd	583	119×10^{7}	0.996	128.19	125.27	-0.076	169.57
	4th	658	1.5×10^{9}	0.998	339.33	336.41	0.203	202.82

 TABLE 1

 Kinetic and thermodynamic parameters of the aqua metal(II) complexes 1–3

first step of the decomposition within the temperature range 40– 70°C corresponds to the loss of one and half water molecules of lattice with a mass loss of 3.91% (calcd. 4.11%). The second step within the temperature range 180–280°C corresponds to the loss of hydroxo group with a mass loss of 2.989 % (calcd. 2.59 %). The third, fourth and fifth decomposition steps of the decomposition within the temperature range 300–820°C corresponded to the loss of organic part of complex with a mass loss of 75.22% (calcd. 75.39%). The final residue within the temperature range 820–900°C corresponds to a mixture of zinc oxide and carbon, ZnO + 3C with a mass loss of 18.15% (calcd. 17.89%). The TGA curve of **5** (Figure 3b) shows four decomposition steps within the temperature range 31–900°C. The first step of the decomposition within the temperature range 31– 200°C corresponds to the loss of four water molecules of lattice with a mass loss of 10.909 % (calcd. 10.737 %). The second step within the temperature range $205-225^{\circ}C$ corresponds to the loss of hydroxo group with a mass loss of 2.8% (calcd. 2.53%). The third and fourth steps of the decomposition within the temperature range $250-550^{\circ}C$ corresponds to the loss of organic part of complex with a mass loss of 73.76% (calcd 74.86%). The final residue within the temperature range $550-900^{\circ}C$ corresponded to CuO with a mass loss of 12.528% (calcd. 11.86%). The TGA curve of **6** (Figure 3c) shows five decomposition steps within the temperature range $50-89^{\circ}C$ corresponds to the loss of 15.928% (calcd. 15.41%). The second step within the temperature range 200-242°C corresponds to the loss of hydroxo group with a mass loss of 2.473% (calcd. 2.43%).

TABLE 2
Kinetic and thermodynamic parameters of the metal-bound hydroxo complexes $4-6$

Complex	Step	T(k)	А	r	$\Delta E^{\#}$	$\Delta H^{\#}$	$\Delta S^{\#}$	$\Delta G^{\#}$
	1st	318	13095.2	0.982	8.28	5.36	-0.174	60.69
	2nd	503	26635.4	0.922	13.5	10.58	-0.172	97.48
4	3rd	621	98715.7	0.991	14.14	11.22	-0.163	112.44
	4th	742	2.6×10^{9}	0.957	225.11	222.19	-0.004	225.15
	5th	889	2.6×10^{10}	0.978	362.03	359.11	-0.062	415.02
	1st	353	1.09×10^{11}	0.899	106.91	103.99	0.014	99.02
	2nd	513	15063.04	0.968	10.09	7.17	-0.177	97.97
5	3rd	568	7.07×10^{10}	0.995	298.88	295.96	0.235	161.94
	4th	648	40×10^{4}	0.977	106.02	103.11	-0.152	201.60
	1st	347	2.2×10^{11}	0.977	101.52	98.6	0.001	98.25
	2nd	477	1900.7	0.925	5.25	2.33	-0.194	94.86
6,	3rd	586	5.3×10^{10}	0.996	320.43	317.51	0.029	200.51
	4th	677	2.2×10^{9}	0.958	361.91	359	0.226	205.53
	5th	828	4.388	0.991	38.23	35.31	-0.249	241.48

PH	Complex 1 $K_{obs} \times 10^{-4}$	Complex 2 $K_{obs} \times 10^{-4}$	Complex 3 $K_{obs} \times 10^{-4}$	Blank $K_{obs} \times 10^{-4}$
7	2.184	2.570	4.119	_
7.5	2.576	2.833	9.526	1.561
8	3.878	4.167	13.345	3.012
8.5	6.148	9.08	31.378	5.939
9	19.336	55.122	112	8.804
9.5	35.127	91.289	177.8	15

TABLE 3The observed pseudo-first-order rate constants, k_{obs}/s^{-1} for the hydrolysis of NA (3 × 10⁻⁴ M) catalyzed by using complexes1–3 (72 × 10⁻⁶ M) at different pH values in aqueous MeOH (33 %, v/v) at I = 0.1 M NaNO3 and 25°C

The third, fourth and fifth steps of the decomposition within the temperature range $265-600^{\circ}$ C correspond to the loss of organic part of complex with a mass loss of 73.595% (calcd. 73.673%). The final residue within the temperature range 600–900°C corresponds to Co with a mass loss of 8.034% (calcd. 8.4%).

The kinetic parameters ($\Delta E^{\#}$) and thermodynamic parameters $\Delta S^{\#}$, $\Delta H^{\#}$, and $\Delta G^{\#}$ also have been calculated for every step for the decomposition of the aqua complexes **1–3** and their hydroxide derivatives **4–6**. The results are shown in Tables 1 and 2. The low value of *E* for each water molecule in the first dehydration process indicates that the first six water molecules are not coordinated to the zinc metal. Whereas, the relatively high values for the second decomposition step, as well as the third and fourth decomposition steps, indicate that the coordinated water molecule and the organic part of the ligand are strongly coordinated to the zinc(II) ion. The negative values of $\Delta S^{\#}$ in the second and the other following steps indicate that the activated complex have more ordered structure than the reactants and the reactants are slower than the metal.^[25]

Hydrolysis Reactions of p-nitrophenyl Acetate (NA) by Using the Model Complexes 1–3

The hydrolysis reactions of *p*-nitrophenyl acetate (NA) have been examined using the model complexes **1–3**. The hydrolysis reactions were investigated in aqueous methanol (40%, v/v). Upon hydrolysis, NA decompose into *p*-nitrophenolate, (NP⁻) and acetate anions, respectively (Scheme 3). The catalytic reactions were followed by an increase in absorption maximum at 402 nm for generation of *p*-nitrophenolate. The pH of each sample was adjusted by using 1 M NaOH / HNO₃, and not by using buffers in order to avoid any catalytic or inhibition effect. In the course of hydrolysis, the pH of each sample was checked and was found that the difference compared to the adjusted pH value at the beginning of the hydrolysis was not larger than 0.3. Figure 7 shows a absorption intensities of the released *p*-nitrophenolate for the hydrolysis of *p*-nitrophenyl acetate by using copper(II) complex **2** (72×10^{-6} M) as a function of time time at pH = 8.5 in aqueous methanol (33%, v/v) atI = 0.1 M NaNO₃ and 25° C. The pseudo-first-order rate constants, k_{obs} , were obtained from the plot of $\ln(A_{\infty}/A_{\infty} - A_t)$ versus time. The pH-dependence of the observed pseudo-first-order rate constants, k_{obs} studied over the pH range 7.0–9.5 are shown in Table 3 and Figure 8. The cobalt(II) complex **3** was found to be the most effective one towards the hydrolysis of NA. This phenomenon may be due to the higher electrophilic character comparing to the other metal ions.

The pH-rate constant k_{obs} profiles for the hydrolysis reactions displayed sigmoidal curves with inflection points around the p K_a values of the coordinated water molecules in complexes **1–3**. Such pH-rate profile was observed in a number of phosphate ester hydrolysis promoted by using copper(II),^[26] cobalt(II),^[27–29] and zinc(II) complexes,[^{11,15–18,30]} and are indicative of the involvement of metal-hydroxo species in the catalytic process. The pk_a values obtained from these inflection points are in good agreement with the pk_a values determined from the previously mentioned solution studies of these complexes by using UV-visible spectroscopy. Therefore, the metal(II)-bound hydroxo species of these complexes are believed to be active catalyst for hydrolyzing the carboxy ester NA.

On the basis of the above mentioned kinetic studies of the carboxylate ester NA in aqueous methanol and the isolation of the aqua model complexes **1–3** and their hydroxide derivatives **4–6**, we proposed a mechanism for the hydrolysis of NA. At the first step: the coordinated water molecule in **1–3** can deprotonat at $pk_a = 8.5 - 9.0$ to produce the metal(II)-bound hydroxo species.^[11,18] Second: the metal center delivers the coordinated hydroxide that can nucleophically attack the NA molecule, while the metal ion simultaneously withdraw electron density away from the carbon atom by interacting with the carbonyl oxygen, forming pentaccordinated intermediate. Finally, the *p*-nitrophenolate is released and the metal(II)-bound acetate intermediate is replaced by water to form again the starting catalyst aqua metal(II) complexes, which are ready to start another catalytic cycle.

CONCLUSION

A series of aqua metal(II) complexes 1-3 and their hydroxide derivatives 4-6, containing different transition metal ions $(Co^{2+}, Cu^{2+}, and Zn^{2+})$ have been synthesized and fully characterized as structural models of the active sites of hydrolytic enzymes. Solid state studies of these aqua/hydroxo complexes 1-6 were investigated using FT-IR spectroscopy, elemental analysis, and thermogravimetric analysis. Solution studies of the metalligand interactions for determining the stoichiometry and the pK_a value of the coordinated water molecule using ¹H NMR and UV-visible spectroscopies. The reactivity of these aqua model complexes as potential bioinorganic catalysts, especially the nature of metal ions on the hydrolysis of both *p*-nitrophenyl acetates (NA), has been investigated. The results showed that cobalt(II) complex 3 is the most effective hydrolytic catalyst among complexes 1-3. This phenomenon may be due to the fact that cobalt(II) ion is likely to be the most effective electronwithdrawing ion and has the greatest electrophilicity. Therefore, it can activate the nucleophile OH⁻ most effectively. Zinc(II) is the opposite and has the lowest activity.

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