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Bifunctional catalysis of ester hydrolysis: novel hydrolytic enzyme models based on xanthene framework

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Abstract

Xanthene framework has been derivatized to carry adjacent hydrolytically active units. A comparison was made between the hydrolytic activities of the Zn(II) complexes of xanthene derivatives with two cyclen (**5**), one cyclen and one imidazole (**7**), and one cyclen and one hydroxymethyl (**12**) units. The cyclen-imidazole carrying derivative showed the largest rate acceleration (5700-fold), demonstrating the efficiency of multifunctional catalysis.

Keywords: Biomimetic catalysts; Artificial enzymes; Enzyme mimics; Enzyme models; Supramolecular chemistry

1. Introduction

Artificial enzyme design is an active field of supramolecular chemistry [1]. Metalloenzymes are attractive targets in such studies, because in these enzymes active sites feature metal ions, and the hydrolytic activity of these complexed ions can be relatively easily approximated in model systems. Many hydrolytic enzymes carry one or more metal centers, and in most cases there is a cooperativity between the metal centers [2]. However, in enzymes, there are always additional interactions; in fact, enzymatic catalysis is essentially a 'multifuctional' catalysis. Nucleophilic, general acid and general base catalysis are very common catalytic effects observed in hydrolytic enzymes. Combination of such hydrolytic functions, typically result in 'larger than additive' effects.

Xanthene derivatives, on the other hand, proved to be very useful rigid scaffolds in supramolecular chemistry [3–7]. As part of our work in biomimetic enzyme models [8–13] and in order to demonstrate the utility of multifunctional catalysis over simple metal catalysis, we designed and synthesized novel xanthene derivatives **5**, **7** and **12**. The Zn(II) complex of compound **12** is a mononuclear complex to serve as a reference point for assessing the effectiveness of multi-nuclear and bifunctional models. The binuclear Zn(II) complex of compound **5**, is the biomimetic model for a binuclear metalloenzyme and the mononuclear Zn(II) complex of compound **7** is expected to behave as a bifunctional catalyst. Imidazole group has pK_a near 7, and near neutrality, it is known to act as a general acid or general base catalyst [14]. Ribonuclease is an example of an enzyme with predominant general acid–base catalysis, where active site features two histidine imidazole moieties acting in cooperation. Thus, this set of xanthene derivatives would allow us to assess relative contributions of different catalytic modes.

2. Experimental

2.1. Materials and methods

All chemicals and solvents were purchased from Aldrich used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DPX-400 in $CDCl_3$ or DMSO-d_6 with TMS as internal standard. Absorption spectrometry was performed using Shimadzu-1600PC spectrophotometer. Kinetics of the reactions were studied in aqueous buffer solutions, following the increase in the absorption at 400 nm due to the release of the

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p-nitrophenolate ion. Column chromatography of all products were performed using Merck Silica Gel 60 (particle size: 0.040–0.063 mm, 230–400 mesh ASTM) pretreated with eluant. Reactions were monitored by thin layer chromatography using fluorescent coated aluminum sheets (20 cm × 20 cm).

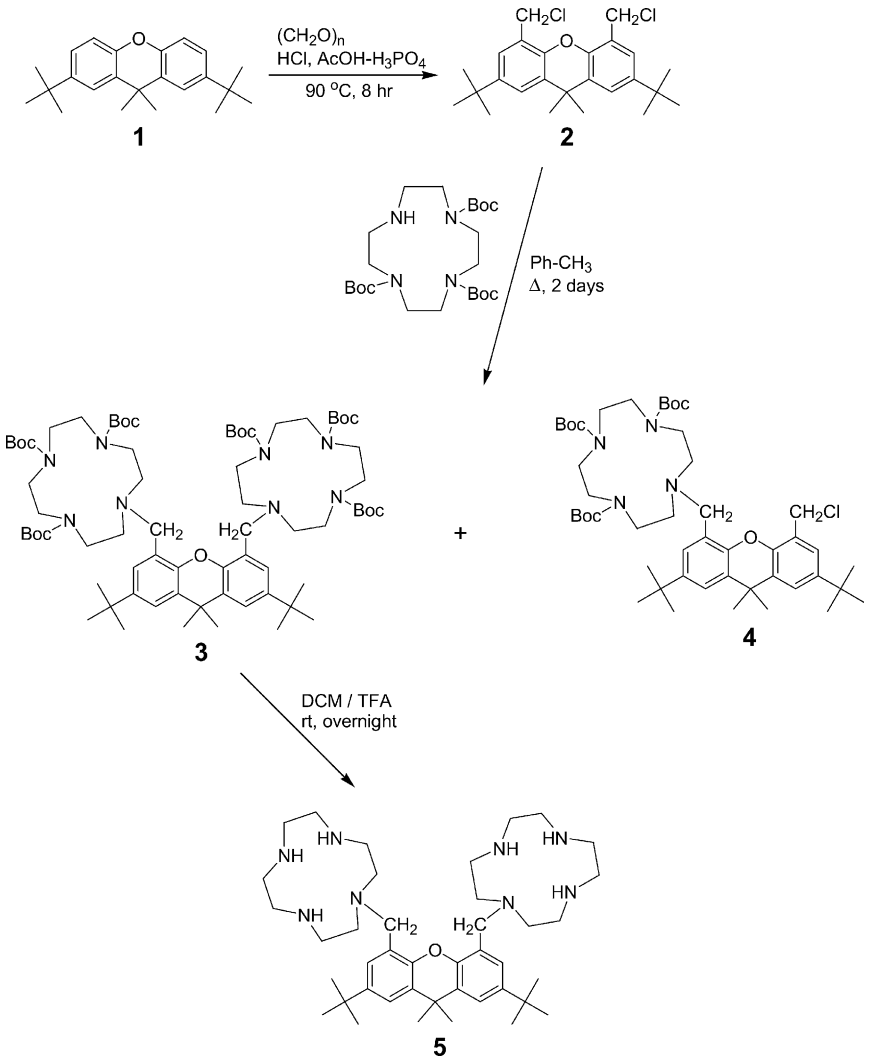
Elemental analyses and mass spectra were obtained at the TUBITAK instrumental analysis laboratory.

2.2. Synthesis of model compounds

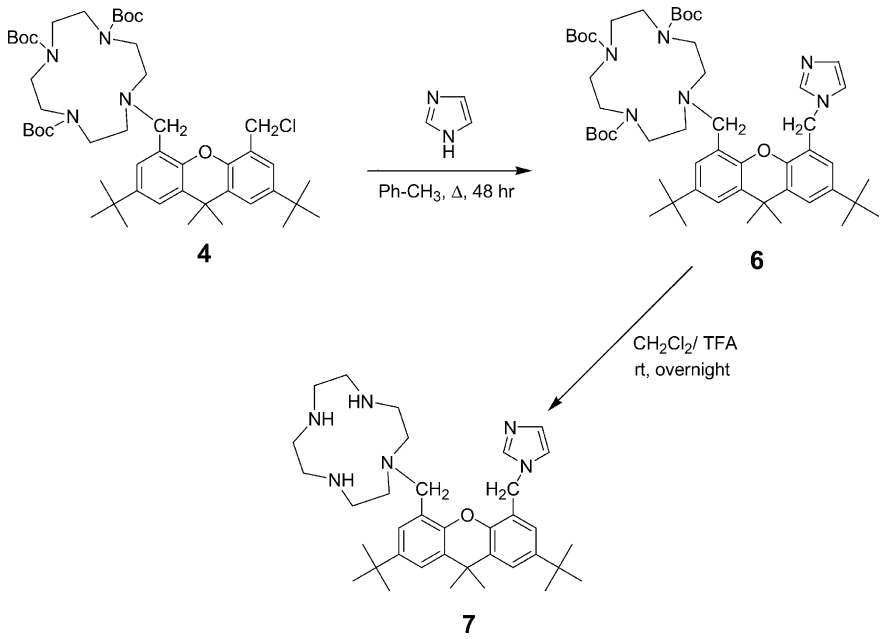
The synthesis of compounds **5** and **7** starts with the chloromethylation of xanthene **1**. The reaction proceeds smoothly to yield the 4,5-bis(chloromethyl) compound in near quantitative yield. The reaction of this compound with tri-(protected)-cyclen yields two compounds, **3** and **4**. These compounds were purified by silica gel chromatography, and obtained in analytically pure state. Compound **4** was then further reacted with imidazole in DMF to yield the protected derivative of the bifunctional model compound **7**. Deprotection yields the desired compounds **5** and **7**. Compound **12** was obtained starting from the dicarboxylic acid **8**, via $LiAlH_4$ reduction; conversion to monochloro compound **10**, and the reaction with tris-boc-protected cyclen, followed by deprotection (Schemes 1–3).

2.3. Preparation of the 4,5-bis(chloromethyl)xanthene derivative *2*

2,7-Di-*tert*-butyl-9,9-dimethyl-xanthene (**1**, 1.55 mmol, 500 mg), paraformaldehyde (200 mg), acetic acid (0.6 ml), phosphoric acid (0.13 ml), and concentrated hydrochloric acid (0.6 ml) were placed in a sealed tube and stirred at 90 °C for overnight. Then, water (10 ml) was added into the reaction mixture and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was collected, dried with Na_2SO_4 and the solvent was removed under reduced pressure. Yield: 585 mg (90%).



Scheme 1. Synthesis of binucleating ligand **5** and the precursor **4**.



Scheme 2. Synthesis of the bifunctional enzyme model **7**.

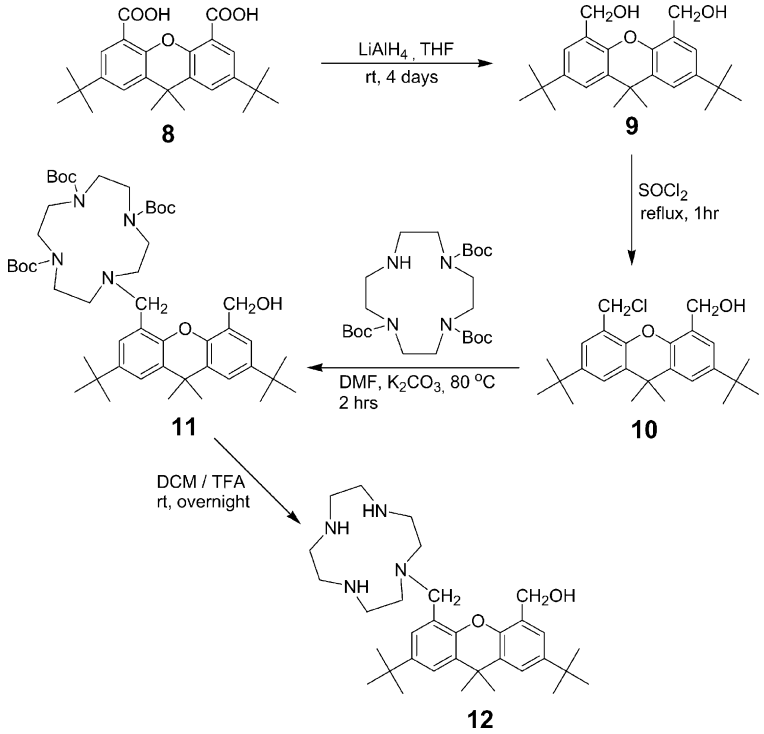
^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 1.27 (18 H, s, $C(CH_3)_3$), 1.57 (6H, s, CH_3), 4.75 (4H, s, CH_2), 7.17 (2H, s, Ar–H), 7.28 (2H, s, Ar–H).

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 31.9, 32.0, 32.8, 34.9, 42.5, 123.9, 124.4, 125.9, 130.0, 146.1, 146.4.

Elemental analysis: Found: C, 70.51; H, 7.74; Cl, 16.85. $C_{25}H_{32}Cl_2O$ requires C, 71.59; H, 7.69; Cl, 16.91. M^+(FAB): 418.2.

*2.4. Preparation and isolation of the dicyclen derivative 3 and the monosubstitution product **4***

2,7-Di-*tert*-butyl-4,5-bis-chloromethyl-9,9-dimethyl-9H-xanthene (**2**) (1.2 mmol, 500 mg) and tris(boc)-cyclen (4.8 mmol, 2.26 g) in toluene (6 ml) were refluxed for 2 days. The reaction mixture was then concentrated under reduced pressure. The products were separated and purified by



Scheme 3. Synthesis of the compound **12**.

column chromatography (silica gel, $CHCl_3$/MeOH 100:7, eluent). Yield for **3** 725 mg (47%) and for **4** 450 mg (42%).

3: ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 1.35 (18 H, s, $C(CH_3)_3$), 1.51 (54 H, s, $C(CH_3)_3$), 1.62 (6H, s, CH_3), 2.66–2.85 (8H, m, N–CH_2), 3.20–3.65 (24H, m, N–CH_2), 4.0 (4H, s, Ar–CH_2–), 7.24 (2H, s, Ar–H), 7.37 (2H, s, Ar–H).

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 28.8, 31.9, 34.8, 35.4, 48.9, 50.0, 52.7, 55.9, 57.5, 79.8, 121.7, 123.7, 130.9, 145.4, 147.9, 156.0, 156.5.Elemental analysis: Found: C, 65.94; H, 9.18; N, 8.61. $C_{71}H_{118}N_8O_{13}$ requires C, 66.02; H, 9.21; N, 8.67. M^+ (FAB): 1290.9.

4: ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 1.19 (9H, s, $C(CH_3)_3$), 1.24 (9H, s, $C(CH_3)_3$), 1.33 (27H, s, $C(CH_3)_3$), 1.51 (6H, s, CH_3), 2.60–2.80 (4H, m, N–CH_2), 3.12–3.49 (12H, m, N–CH_2), 3.95 (2H, s, N–CH_2), 4.65 (2H, s, Ar–CH_2–), 7.06 (1H, s, Ar–H), 7.11 (1H, s, Ar–H), 7.20 (2H, s, Ar–H), 7.26 (1H, s, Ar–H).

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 28.9, 31.9, 34.7, 34.9, 35.3, 42.6, 48.8, 50.2, 54.9, 56.9, 79.8, 121.8, 123.5, 124.0, 126.0, 127.6, 130.6, 131.0, 145.6, 146.0, 147.3, 147.7, 155.9, 156.6.Elemental analysis: Found: C, 67.21; H, 8.81; Cl, 4.11; N, 6.49. $C_{48}H_{75}ClN_4O_7$ requires C, 67.38; H, 8.84; Cl, 4.14; N, 6.55. M^+(FAB): 854.5.

2.5. Deprotection of *3*

Disubstitution product **3** (0.19 mmol, 250 mg) was dissolved in TFA–CH_2Cl_2 mixture (4 mL 50:50) and stirred at room temperature for overnight. Then the reaction mixture neutralized and washed with 10% NaOH (3 × 10 mL) and organic phase was dried with $NaSO_4$ and removed under reduced pressure. Yield: 90 mg (68%).

^{13}C NMR (400 MHz, $CDCl_3$) δ(ppm) 1.08 (18 H, s, $C(CH_3)_3$), 1.34 (6H, s, CH_3), 2.25–2.35 (8H, m, CH_2), 2.36–2.62 (24H, m, CH_2), 3.57 (4H, s, CH_2), 7.02 (2H, s, Ar–H), 7.18 (2H, s, Ar–H).

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 32.0, 34.9, 35.2, 46.0, 47.1, 47.8, 52.1, 52.8, 125.6, 125.8, 130.1, 145.2, 147.4.Elemental analysis: Found: C, 71.30; H, 10.24; N, 16.31. $C_{41}H_{70}N_8O$ requires C, 71.26; H, 10.21; N, 16.22. M^+(FAB): 690.6.

2.6. The reaction of compound *4* with imidazole to yield compound *6*

Monocyclen substituted xanthene derivative (**4**) (0.23 mmol, 200 mg) and imidazole (0.23 mmol, 16 mg) were refluxed in 2 ml toluene for 2 days. The reaction mixture was then concentrated under reduced pressure. The product was purified by column chromatography (silica gel, $CHCl_3$/MeOH 100:7, eluent). Yield: 143 mg (69.5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 1.29 (9H, s, $C(CH_3)_3$), 1.32 (9H, s, $C(CH_3)_3$), 1.48 (27H, s, $C(CH_3)_3$), 1.68 (6H, s, CH_3), 2.06 (2H, s, CH_2), 2.60–3.65 (16H, m, CH_2), 3.80 (2H, s, CH_2), 5.34 (2H, s, CH_2), 6.80 (1H, s, Ar–H), 6.95 (1H, s, Ar–H), 7.10 (1H, s, Ar–H), 7.15 (1H, s, Ar–H), 7.33 (1H, s, Ar–H), 7.40 (1H, s, Ar–H), 7.55 (1H, s, Ar–H).

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 14.5, 21.4, 23.1, 28.9, 29.7, 31.8, 31.9, 34.9, 35.2, 46.9, 60.8, 79.9, 119.8, 122.0, 123.2, 129.7, 130.7, 137.6, 146.4.

Elemental analysis: Found: C, 68.92; H, 8.94; N, 9.53. $C_{51}H_{78}N_6O_7$ requires C, 69.04; H, 8.86; N, 9.47. M^+(FAB): 886.6.

2.7. Deprotection of *6*

Compound **6** was deprotected (0.24 mmol, 215 mg) in TFA-CH_2Cl_2 mixture (6 mL, 50:50). The solution was stirred at room temperature for overnight. Then the reaction mixture neutralized and washed with 10% NaOH (3 × 10 mL) and the organic phase was dried with $NaSO_4$. The solvent was removed under reduced pressure. Yield: 49 mg (35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 1.40 (9H, s, $C(CH_3)_3$), 1.46 (9H, s, $C(CH_3)_3$), 1.75 (6H, s, CH_3), 2.63–2.97 (16H, m, CH_2), 3.81 (2H, s, CH_2), 5.44 (2H, s, CH_2), 6.93 (1H, s, Ar–H), 7.04 (1H, s, Ar–H), 7.17 (1H, s, Ar–H), 7.40 (1H, s, Ar–H), 7.49 (1H, s, Ar–H), 7.54 (1H, s, Ar–H), 7.68 (1H, s, Ar–H).

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 30.1, 31.8, 32.5, 45.7, 46.8, 47.6, 52.2, 52.5, 119.7, 121.8, 122.7, 123.3, 124.3, 126.0, 129.4, 129.9, 130.6, 137.8, 146.0, 146.4, 146.5.

Elemental analysis: Found: C, 73.62; H, 9.33; N, 14.27. $C_{36}H_{54}N_6O$ requires C, 73.68; H, 9.27; N, 14.32. M^+(FAB): 586.4.

2.8. The reduction of 2,7-di-t-butyl-9,9-dimethyl-4,5-xanthenedicarboxylic acid (*8*)

$LiAlH_4$ (1.22 mmol, 500 mg) in 15 ml dry THF was cooled to 0 °C in an ice bath and then 2,7-di-*t*-butyl-9,9-dimethyl-4,5-xanthenedicarboxylic acid (**8**, 1.5 mmol, 600 mg) in 10 ml of THF solution was added in portions. The solution was stirred at RT for 4 days. The carboxylic acid proved to be highly resistant to complete reduction and even an aldehyde product was isolated from the reaction mixture. After 4 days the reaction mixture was first treated with H_2O until no bubbling observed and then extracted with ether. The solvent was removed under reduced pressure, and then purified by column chromatography (silica gel, $CHCl_3$/MeOH 100:3, eluent). The yield of the desired product **9** was 165 mg (35.2%).

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 1.26 (18H, s, $C(CH_3)_3$), 1.57 (6H, s, CH_3), 3.38 (2H, brs, OH), 4.64 (4H, s, CH_2), 7.07 (2H, s, Ar–H), 7.28 (2H, s, Ar–H).

^{13}C NMR ($CDCl_3$) δ(ppm) 30.1, 32.0, 32.5, 34.9, 62.5, 122.6, 125.3, 127.5, 129.9, 145.5, 147.3.

Elemental analysis: Found: C, 78.31; H, 9.07. $C_{25}H_{34}O_6$ requires C, 78.49; H, 8.96. M^+(FAB): 382.3.

2.9. Synthesis of the monochlorinated compound **10**

(2,7-Di-*tert*-butyl-9,9-dimethyl-4,5-bis(hydroxymethyl)-9H-xanthene (**9**, 0.13mmol, 50 mg) and $SOCl_2$ (8 ml) put into a flask and refluxed for 1 h. Then the solvent was removed under reduced pressure. Although, ordinarily the bis-chloromethyl compound (**2**) is the expected product, compound **10** was isolated in good yield from the reaction mixture. Yield 34 mg (65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 1.18 (9H, s, $C(CH_3)_3$), 1.27 (9H, s, $C(CH_3)_3$), 1.57 (6H, s, CH_3), 3.40 (1H, br s, OH), 4.77 (4H, d, CH_2), 7.18 (2H, s, Ar–H), 7.30 (2H, s, Ar–H)

^{13}C NMR ($CDCl_3$) δ(ppm) 23.1, 29.8, 32.3, 32.8, 34.9, 42.5, 124.6, 125.9, 127.0, 128.2, 128.6, 130.0, 132.6, 146.1, 146.4, 146.7.

Elemental analysis: Found: C, 74.80; H, 8.39; Cl, 8.71. $C_{25}H_{33}ClO_2$ requires C, 74.88; H, 8.30; Cl, 8.84. M^+(FAB): 400.2.

2.10. Synthesis of compound **11**

Tris(boc)-cyclen (0.46 mmol, 220 mg) was dissolved in DMF (4 ml) and then K_2CO_3 (200 mg) was added. The mixture was stirred at room temperature for 1 h. Then the monochloromethyl derivative (**10**, 0.3 mmol, 120 mg) in DMF (5 ml) was added dropwise to the tris(boc)cyclen solution. The reaction mixture was heated at 80 °C for 2 days. Then H_2O (15 mL) was added to the solution and the resulting white solid was collected by filtration. The product was purified by column chromatography {silica gel, EtOAc: Hexane (1:5), eluent). Yield 115 mg (45.7%) .

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 1.24 (9H, s, $C(CH_3)_3$), 1.27 (9H, s, $C(CH_3)_3$), 1.40 (27H, s, $C(CH_3)_3$), 1.54 (6H, s, CH_3), 2.65–2.80 (4H, m, CH_2), 3.18–3.60 (12H, m, CH_2), 3.99 (2H, s, CH_2), 4.69 (2H, s, CH_2), 7.07 (1H, s, Ar–H), 7.15 (1H, s, Ar–H), 7.24 (1H, s, Ar–H), 7.30 (1H, s, Ar–H).

Elemental analysis: Found: C, 68.11; H, 9.22; N, 6.76. $C_{48}H_{76}N_4O_8$ requires C, 68.87; H, 9.15; N, 6.69. M^+(FAB): 836.6.

2.11. Deprotection of compound **11**

The protected compound (**11**) (0.14 mmol, 120 mg) was dissolved in TFA:CH_2Cl_2 (2 ml:2 ml). The reaction mixture was stirred at room temperature for overnight. The reaction mixture was then washed with 10% NaOH (3 × 10 ml) and the organic phase was dried with $NaSO_4$. The solvent was removed under reduced pressure. Yield: 25 mg (33.2%).

^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 1.26 (18 H, s, $C(CH_3)_3$), 1.51 (6H, s, CH_3), 2.35–2.67 (16H, m, CH_2), 3.73 (2H, s, CH_2), 4.64 (2H, s, CH_2), 7.03 (2H, s, Ar–H), 7.23 (1H, s, Ar–H), 7.27 (1H, s, Ar–H).

^{13}C NMR ($CDCl_3$) δ(ppm) 30.0, 32.0, 34.8, 34.8, 35.7, 45.5, 46.2, 47.3, 52.3, 56.0, 57.0, 121.1, 121.3, 126.0, 126.6, 127.2, 129.3, 131.8, 132.2, 145.2, 146.0.

Elemental analysis: Found: C, 73.79; H, 9.85; N, 10.29. $C_{33}H_{52}N_4O_2$ requires C, 73.84; H, 9.76; N, 10.44. M^+(FAB): 536.4.

3. Results and discussion

The kinetics of the hydrolysis reactions were studied using *p*-nitrophenylacetate as a model substrate in buffered solutions at different pH values. The rate data is shown in Table 1.

Cyclen-complexed Zn(II) carries a water molecule as an additional ligand in aqueous solutions [15]. The pK_a of the metal-bound water drops to 6–8. Thus, metal-bound hydroxide is an effective nucleophile near neutral pH's. In many examples of metallo-enzyme mimics, the metal-bound hydroxide appears as the critical nucleophile at pH 7. There are examples of binuclear mimics, where there is a full cooperative action between the metal centers. In such examples, it is believed that one of the metal ions, is the source for metal bound hydroxide (M–OH), but the other one, by coordinating to the carbonyl (or phosphoryl) group activates the ester/amide group (or phosphate) for a nucleophilic attack. In certain model systems, this cooperative action has been demonstrated. With that in mind, we synthesized and studied the binuclear complex **5**. On the other hand, in a bifunctional model, two different functional groups are expected to functionally complement each other. Considering the transition-state complementary nature of the enzyme active site, it is obvious that there must an array of stabilizing, and activating interactions which ease the substrate over the activation energy barrier. So, artificial catalytic systems mimicking enzymatic multifunctional catalysis are likely to yield satisfactory catalysts.

The binuclear complex **5** features two cyclen-complexed Zn(II) ions. While catalysis due the this binuclear metal

Table 1
Apparent pseudo-first order hydrolysis rate constants (s^{-1}) for the hydrolysis of *p*-nitrophenylacetate[a,b,c]

pH	Uncatalyzed	Compound **5**	Compound **7**	Compound **12**
7.0	7.1×10^{-5} (2.1×10^{-6})[d]	9.0×10^{-4}	1.2×10^{-2}	1.5×10^{-3}
7.5	2.3×10^{-4}	1.6×10^{-3}	2.5×10^{-3}	1.6×10^{-3}
8.0	6.1×10^{-4}	4.5×10^{-3}	4.8×10^{-3}	3.6×10^{-3}
8.5	1.6×10^{-3}	1.2×10^{-2}	7.5×10^{-3}	5.1×10^{-3}

[a] The reactions were carried out in 0.15 M buffer solutions at the indicated pH, in the presence of 2 mM catalyst and $Zn(ClO_4)_2$ (2 mM for compounds **7** and **12** and 4 mM for compound **5**). For pH 7.0 and 7.5 MOPS and for pH 8.0 and 8.5 tris was used as buffering material.

[b] The substrate (*p*-nitrophenylacetate) concentration was 50 μM. The reactions were followed for more than eight half-lives.

[c] The reactions were carried out at 298 K.

[d] Extrapolated to 0 buffer concentration.

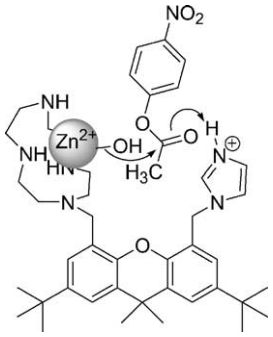


Fig. 1. Bifunctional catalysis of *p*-nitrophenylacetate hydrolysis with the enzyme model **7**.

complex is also significant, the bifunctional model **7** seems to be the most active catalyst. This compound shows the maximum rate acceleration at pH 7, and at this pH, the rate acceleration is approximately 5700-fold compared to the reported reaction rate for the uncatalyzed hydrolysis of *p*-nitrophenylacetate [16]. Using the bifunctional model compound **7**, the reaction rate decreases on going to more alkaline pH's. This is an interesting finding, proving the catalytic role of the imidazole unit as a general acid. In solutions with higher pH, imidazole is deprotonated, and cannot act as a general acid catalyst. As expected in the pH range of 7.0–8.5 uncatalyzed reaction rate increases as the pH increases. A mechanistic interpretation of the hydrolysis is depicted in Fig. 1.

While the difference between the reaction rate in the presence of **7** and the other catalysts (**5** and **12**) differ only by an order of magnitude, the difference is significant; the reported values are the averages of five different runs.

The large rate acceleration obtained with compound **7** clearly demonstrates the potential of such multifunctional enzyme models. Well-designed models of enzyme active sites with critically located multiple functionalities are promising candidates for biomimetic catalysts.

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