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Cooperativity of binuclear Zn(II) complexes of bisimidazolyl ligands in the hydrolysis of bis(2,4-dinitrophenyl) phosphate in aqueous solution

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Hydrolysis of bis(2,4-dinitrophenyl) phosphate (BDNPP) by Zn(II) with ligands bearing plural bis(imidazol-2-yl) groups was kinetically studied in aqueous solution. The binuclear Zn(II) complex of 1,3-bis(diimidazol-2-ylhydroxymethyl)benzene (**2a**) was found to be most effective for hydrolysis of BDNPP (1.2 × 10^3-fold). ESI-MS study revealed formation of **2a**·Zn(II)$_2$ in MeOH–H_2O, suggesting that the rate acceleration is due to so called double Lewis acid activation. The pH–rate profile showed that the pK_a of the active species is around 7.5. The rate accelerations by the complexes of **2a** with other metal ions were 4.3-fold for Ni(II), 7.1-fold for Co(II), and 1.9 × 10^2-fold for La(III).

Introduction

Phosphodiester bonds are known to be cleaved by nucleases possessing two (or more) divalent metal ions located in 3–5 Å in the active site.[1] Binuclear metal complexes have attracted considerable attention from the viewpoint of two-metal ion catalysis,[1a,2] and the activities for hydrolytic cleavage of phosphodiester bonds have been extensively investigated.[3] The metal ions are considered to activate the P–O bond and water bound to the metal ion, and to stabilize the transition state and the leaving group by acting as a Lewis acid. However, the hydrolytic activities are dependent on the kind of metal ions and the ligand structure. Recently, Reinhoudt *et al.* have reported that calix[4]arene functionalized with two bisimidazolyl groups shows a large rate enhancement for transesterification of 2-hydroxypropyl-*p*-nitrophenyl phosphate with Cu(II), but not with Zn(II).[3a,c] On the other hand, calix[4]arene functionalized with 2,6-bis(aminomethyl)pyridyl groups exhibits a much larger activity with Zn(II) than with Cu(II).[3b] These results indicate that combination of a ligand and a metal ion is important for the design of binuclear metal complexes for hydrolysis of phosphodiesters. More importantly, Reinhoudt *et al.* have mentioned that flexibility of the ligands is responsible for the catalytic activity.

Although there are imidazolyl ligands of histidines in the active sites of many native nucleases,[1] binuclear Zn(II) complexes of imidazolyl ligands have been scarcely studied in model systems.[4] For example, Trögler *et al.* have reported that Zn(II) complexes of tetrakis(1-methylimidazol-2-yl) derivatives show no cooperative rate enhancements for hydrolysis of bis(4-nitrophenyl) phosphate, probably due to the ligand structure being either too rigid or too flexible.[4b] This prompted us to design ligands bearing bisimidazolyl moieties as shown in Chart 1. In particular, we focused our attention on the substituent effect on N(1) of the imidazolyl groups of the ligands, since 1-methylimidazole is usually used. We report herein that a binuclear Zn(II) complex of 1,3-bis(diimidazol-2-ylhydroxymethyl)benzene (**2a**) shows a remarkable rate acceleration (1.2 × 10^3-fold) for hydrolysis of BDNPP in aqueous buffer solution.

Results and discussion

Synthesis of the ligands

The ligands were synthesized from 2-lithio-1-methylimidazole or 2-lithio-1-(methoxymethyl)imidazole with the corresponding carboxylic acid esters in THF according to literature procedures.[4b,5] Diethyl anthracene-1,8-dicarboxylate was prepared from 1,8-dichloroanthraquinone according to the literature.[6]

Metal binding

The binding ability of the ligands **2a**, **2b**, and **2d** for Zn(II) was spectrophotometrically examined in aqueous solution. Plots of the absorption changes of **2** at 249.3 nm upon addition of Zn(II) are shown in Fig. 1. The absorption changes of **2a** and **2b** are saturated at [Zn(II)]/[**2**] = 2, indicating formation of binuclear Zn(II) complexes of **2a** and **2b**, whereas the absorption changes of **2d** are saturated at [Zn(II)]/[**2d**] = 1. Potentiometric pH titrations were performed as follows. An aqueous solution of **2** (2.0 × 10^{-4} mol dm^{-3}) in 0.1 mol dm^{-3} KNO_3 was acidified with HNO_3 (8.0 × 10^{-4} mol dm^{-3}) and titrated with KOH (2.0 × 10^{-2} mol dm^{-3}) under a stream of humidified N_2 at 25 °C in the absence (for determination of ligand protonation constants) and presence of Zn$(NO_3)_2$ (for determination of binding constant and deprotonation constants of Zn(II) bound water). pH values were recorded with a Fisher Scientific Accumet AC-15 pH meter. However, the protonation and binding constants were not obtained accurately because of too slow an equilibrium. Spectrophotometric titration of **3** and Zn(II) showed the 1 : 1 complex formation of **3**, which could be explained by involvement of the pyridine N of **3** as a fifth ligand. Meanwhile, the binding constants of **1** and diimidazol-2-ylmethane with Zn(II) are known to be 9 × 10^4 and 5.4 × 10^5 dm^3 mol^{-1}, respectively.[4a,5a]

The complex formation of **2** and Zn(II) was also examined in MeCN and 50% MeOH–H_2O by electron spray ionization mass spectroscopy (ESI-MS). In MeCN, molecular peaks corresponding to binuclear Zn(II) complexes were observed: *m*/*z* 761 ([**2a**·Zn(II)$_2$·$(NO_3^-)_3$·MeCN]$^+$), *m*/*z* 776 ([**2b**·Zn(II)$_2$·

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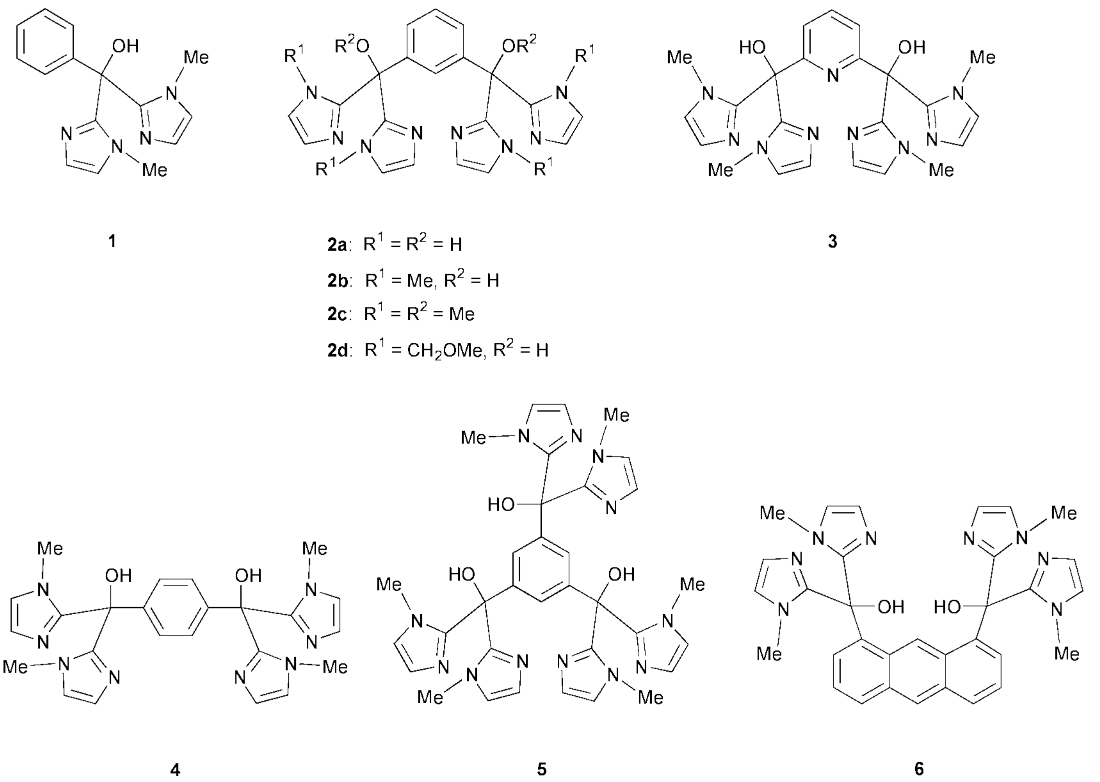

2a: $R^1 = R^2 = H$
2b: $R^1 = Me, R^2 = H$
2c: $R^1 = R^2 = Me$
2d: $R^1 = CH_2OMe, R^2 = H$

Chart 1

Table 1 Pseudo-first-order rate constants and relative rates for hydrolysis of BDNPP by imidazolyl ligands in the presence of Zn(II)

Ligands	k_{obs}/s^{-1}	Relative rates
None	1.7×10^{-7}	1.0
Zn(II)	1.0×10^{-6}	6.0
1 + Zn(II)	1.8×10^{-6}	11
2a + Zn(II)	2.0×10^{-4}	1200
2b + Zn(II)	3.5×10^{-5}	210
2c + Zn(II)	3.3×10^{-5}	200
2d + Zn(II)	6.8×10^{-6}	40
3 + Zn(II)	6.3×10^{-7}	3.7
4 + Zn(II)	1.1×10^{-5}	65
5 + Zn(II)	4.8×10^{-5}	280
6 + Zn(II)	6.8×10^{-7}	4.0

[BDNPP] = 5.0×10^{-5} mol dm^{-3}, [ligand] = 2.5×10^{-4} mol dm^{-3}, [$Zn(NO_3)_2 \cdot 6H_2O$] = 1.0×10^{-3} mol dm^{-3}, pH 7.0 (0.05 mol dm^{-3} HEPES, $I = 0.1$ with KNO_3), 25 °C.

$(NO_3^-)_3]^+$), and *m*/*z* 896 ([**2d**·Zn(II)$_2$·$(NO_3^-)_3]^+$), respectively. The isotope patterns were in good agreement with the theoretical ones. In 50% MeOH–H_2O, however, the peak for the binuclear Zn(II) complex was observed only for **2a**, whereas the peaks corresponding to mononuclear complexes, [**2b**·Zn(II)·$NO_3^-]^+$ and [**2d**·Zn(II)·$NO_3^-]^+$ were observed. These results suggest that the binding ability of **2a** to Zn(II) is stronger than that of **2b** or **2d** in aqueous solution in order of bulkiness of substituents.

Hydrolytic activity

Hydrolytic activities of the ligands in the presence of the metal ions were kinetically evaluated for hydrolysis of BDNPP in aqueous solution. Pseudo-first-order rate constants (k_{obs}) were determined spectrophotometrically by following absorption increases of 2,4-dinitrophenolate at 400 nm at 25 °C in aqueous solution.

The effects of the ligands on k_{obs} were firstly examined in the presence of Zn(II) at pH 7.0. The rate constants and relative rates are listed in Table 1. It should be noted that the rate constants were calculated within 10% reaction, although the following hydrolysis of 2,4-dinitrophenyl phosphate was confirmed to be about 10 times slower than that of BDNPP under the conditions of Table 1. As expected, the rate accelerations were dependent on the structure of the ligands. In a series of **2**, the rates are sensitive to the *N*(1)-substituent of the imidazole groups (**2a**, **2b**, and **2d**), but not to the *O*-substituents (**2b** and **2c**), suggesting that hydroxy groups of the ligands are not involved during the hydrolysis. The activity of the ligand **5** bearing three bis(1-methylimidazol-2-yl)hydroxy units is almost the same as that of **2b**, indicating no participation of the third bisimidazolyl unit. No effect of **3** can be explained by a 1 : 1 complexation, and no effect of **6** may be explained by unsuitable positioning of two Zn(II)'s. Since the *m*-phenylene spacer series (**2**) was effective, further kinetic study was undertaken by employing **2**.

The effects of the concentration of Zn(II) are shown in Fig. 2. The rate for **2a** increases abruptly at [Zn(II)] = 5.0×10^{-4} mol dm^{-3} (2 molar excess over [**2a**]) and reaches saturation, suggesting that the reactive species is binuclear complex **2a**·[Zn(II)]$_2$. A bulkier substituent on the N(1) of the imidazolyl groups decreases the rates (**2a** > **2b** = **2c** > **2d**). This order could be explained by steric hindrance of the *N*-substituents for the metal complexation and/or the subsequent coordination to the substrate BDNPP.

The effects of pH on the rates were examined by employing **2b**·[Zn(II)]$_2$ in buffer solutions containing MeCN (33.3% v/v) to prevent precipitation. As shown in Fig. 3,† the rate is first-order with respect to [OH^-] and reaches saturation at pH *ca.* 7.5. This implies that the hydrolysis proceeds *via* an attack of Zn(II) bound hydroxide ion, because the pK_a of **1**·Zn(II) bound water is reported to be 7.4.[4a]

The activities of other metal ions such as Ni(II), Co(II) and La(III) with **2a** for hydrolysis of BDNPP were briefly examined (Table 2), indicating Zn(II) to be the most effective. It should

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† Ten equivalents of $Zn(NO_3)_2 \cdot 6H_2O$ were used for complete formation of **2b**·[Zn(II)]$_2$. The pH–rate profile for **2a**·[Zn(II)]$_2$ was complicated, probably because proton dissociation of the imidazolyl groups is involved.

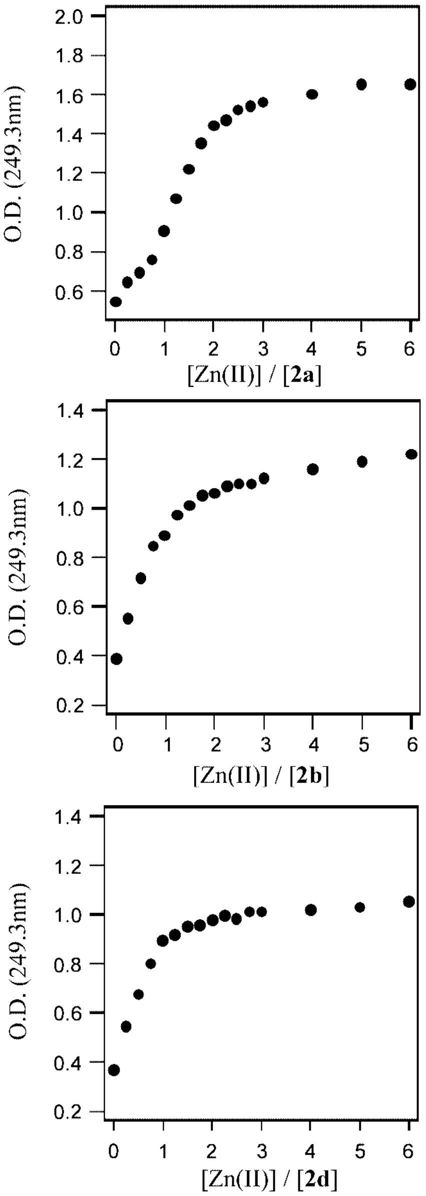

Fig. 1 Titration of **2** with Zn(II). [**2**] = 4.0 × 10^{-4} mol dm^{-3}, [$Zn(NO_3)_2 \cdot 6H_2O$] = 0–2.4 × 10^{-3} mol dm^{-3}, pH 7.0 (0.05 mol dm^{-3} HEPES, I = 0.1 with KNO_3), at 25 °C.

Table 2 Effect of metal ions on hydrolysis of BDNPP with **2a**

Metal ion	k_{obs}/s^{-1}	Relative rates
Zn(II)	2.0 × 10^{-4}	1200
Ni(II)	7.3 × 10^{-7}	4.3
Co(II)	1.2 × 10^{-6}	7.1
La(III)	3.3 × 10^{-5}	190

[BDNPP] = 5.0 × 10^{-5} mol dm^{-3}, [**2a**] = 2.5 × 10^{-4} mol dm^{-3}, [metal ion] = 1.0 × 10^{-3} mol dm^{-3}, pH 7.0 (0.05 mol dm^{-3} HEPES, I = 0.1 with KNO_3), 25 °C.

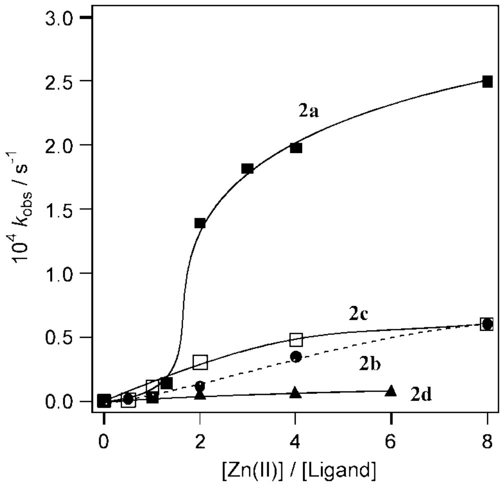

Fig. 2 Plots of k_{obs} *vs.* [Zn(II)]. [BDNPP] = 5.0 × 10^{-5} mol dm^{-3}, [ligand] = 2.5 × 10^{-4} mol dm^{-3}, [$Zn(NO_3)_2 \cdot 6H_2O$] = 0–2.0 × 10^{-3} mol dm^{-3}, pH 7.0 (0.05 mol dm^{-3} HEPES, I = 0.1 with KNO_3), at 25 °C.

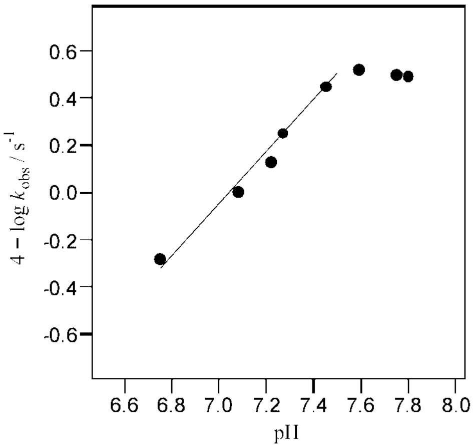

Fig. 3 Plots of k_{obs} *vs.* pH. [BDNPP] = 5.0 × 10^{-5} mol dm^{-3}, [**2b**] = 2.5 × 10^{-4} mol dm^{-3}, [$Zn(NO_3)_2 \cdot 6H_2O$] = 2.5 × 10^{-3} mol dm^{-3}, 0.05 mol dm^{-3} HEPES, I = 0.1 with KNO_3 with MeCN (33.3%, v/v), at 25 °C.

be emphasized that the combination of Zn(II) and the bis-imidazolyl ligand shows a cooperative rate acceleration for hydrolysis of phosphate diesters.

The data obtained indicate cooperativity of two metal ions in the presence of ligands. Namely, one Zn(II) bound to the ligand is associated with a negative charge of BDNPP to form a complex, and the second Zn(II) provides a ligated hydroxide ion which acts as a nucleophile within the complex, wherein either of the Zn(II)'s assists the nucleophilic attack by acting as a Lewis acid. Of particular interest in this work is that the largest rate acceleration is observed for the binuclear Zn(II) complex of 1-unsubstituted imidazolyl ligand **2a**. A CPK model study of **2a**·[Zn(II)]$_2$ suggests that there is some flexibility compared with **2b**·Zn(II)$_2$ and **2d**·Zn(II)$_2$, the **2a** complex being able to adopt a position suitable for the two metal ion mechanism.

Conclusion

In summary, we have demonstrated that a binuclear Zn(II) complex of **2a** shows a considerable rate acceleration for hydrolysis of activated phosphate diester in aqueous solution. To our knowledge, it is the first example of a combination of Zn(II) and imidazolyl ligands which shows cooperative rate accelerations in the hydrolysis of phosphate diesters. We believe that the present results would be useful for the design of ligands using imidazole groups.

Experimental

THF was purified by distillation from Na–benzophenone. MeCN was dried and distilled over calcium hydride. Other reagents were of analytical or special grade. $M(NO_3)_2 \cdot 6H_2O$ (M: Zn, Co, Ni) and $La(NO_3)_3 \cdot 6H_2O$ were used. Buffer solutions were prepared in deionized and distilled water by employing 0.05 mol dm^{-3} 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid (HEPES) with I = 0.1 (KNO_3). UV–vis spectra were recorded on Shimadzu UV-2200A and JASCO

Ubest-560 spectrometers with a thermal regulator (±0.5 °C). ^{1}H NMR spectra were measured on a Varian Gemini-200 spectrometer. Electron spray ionization mass spectra (ESI-MS) were recorded on a Perkin-Elmer Sciex API-100 spectrometer. Column chromatography was performed by using Wakogel C-200 (silica gel, 70–250 μm, Wako Chemical Co. Ltd). Melting points are uncorrected. Elemental analyses were performed at the Center of Instrumental Analysis of Gunma University.

Synthesis

Pyridinium bis(2,4-dinitrophenyl) phosphate (BDNPP) was prepared according to the literature, mp 157–158 °C (lit.,[7] 159–160 °C).

The ligands were synthesized from the corresponding carboxylic acid esters and 2-lithio-1-methylimidazole or 2-lithio-1-(methoxymethyl)imidazole in THF under N_2.[5] Ligands **1** and **4** were known from the literature.[5b] Ligands **2b** and **3** were supplied from our previous work.[5c]

1,3-Bis{bis[1-(methoxymethyl)imidazol-2-yl]hydroxymethyl}-benzene (2d). To a stirred solution of 1-(methoxymethyl)imidazole (2.25 g, 20 mmol) in THF (50 ml) at −78 °C was added *n*-butyllithium (1.64 mol dm^{-3} in hexane, 13 ml, 21.3 mmol) over 10 min under N_2. After stirring for 30 min at −78 °C, diethyl isophthalate (0.6 ml, 3 mmol) in THF (10 ml) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C and 4 h at rt. After addition of water, the reaction mixture was extracted with EtOAc (100 ml × 3). After drying over Na_2SO_4, the solvent was evaporated *in vacuo*. The oily product was purified by column chromatography (CH_2Cl_2–MeOH = 10 : 1), and recrystallization from EtOAc. Yield 1.29 g (45%), mp 107–108 °C; δ_H (200 MHz, $CDCl_3$) 3.07 (12 H, s), 5.11 (8 H, q, *J* 10.3), 6.1 (2 H, br s), 6.96 (4 H, d, *J* 1.2), 7.10 (4 H, d, *J* 1.2), 7.2–7.4 (3 H, m) and 7.42 (1 H, t, *J* 1.6).

1,3-Bis(diimidazol-2-ylhydroxymethyl)benzene (2a). A solution containing **2d** (0.5 g, 0.86 mmol) and conc. HCl (6 ml) in 50% EtOH–H_2O (30 ml) was refluxed overnight. The reaction mixture was evaporated *in vacuo*, and the residue was recrystallized from MeOH–diethyl ether. Yield 0.37 g (78%), mp 183–186 °C (Found: C, 42.88; H, 4.57; N, 19.36. $C_{20}H_{22}Cl_4N_8O_2\cdot H_2O$ requires C, 42.42; H, 4.27; N, 19.79%); δ_H (200 MHz, CD_3OD) 7.6–7.7 (10 H, br), 7.9 (3 H, m) and 8.21 (1 H, d, *J* 1.2).

1,3-Bis[bis(1-methylimidazol-2-yl)methoxymethyl]benzene (2c). To a stirred solution of NaH (66 mg, 2.8 mmol) in THF (20 ml) was injected **2b** (0.63 g, 1.4 mmol) with a syringe under N_2 at rt. After 1 h stirring, MeI (0.3 ml, 4.8 mmol) was added with a syringe and the mixture was stirred overnight. After addition of brine (30 ml), the mixture was extracted with hot $CHCl_3$ (50 ml × 2). The $CHCl_3$ layer was dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was recrystallized from EtOAc–hexane. Yield 0.49 g (72%), mp 180–181 °C; δ_H (200 MHz, $CDCl_3$) 3.13 (6 H, s), 3.46 (12 H, s), 6.83 (4 H, d, *J* 1.2), 6.94 (4 H, d, *J* 1.2) and 7.3–7.6 (4 H, m).

1,3,5-Tris[bis(1-methylimidazol-2-yl)hydroxymethyl]benzene (5). To a stirred solution of 1-methylimidazole (1.97 g, 24 mmol) in THF (50 ml) at −78 °C was added *n*-butyllithium (1.64 mol dm^{-3} in hexane, 16 ml, 26 mmol) under N_2. After stirring for 30 min at −78 °C, triethyl benzene-1,3,5-tricarboxylate (0.79 g, 2.7 mmol) in THF (20 ml) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C and 8 h at rt. Work-up and purification of the product were the same as described for **2d**. Yield 0.66 g (37%), mp 178–179 °C; δ_H (200 MHz, $CDCl_3$) 3.28 (18 H, s), 6.1 (3 H, br s), 6.81 (6 H, d, *J* 1.2), 6.88 (6H, d, *J* 1.2) and 6.90 (3 H, s).

1,8-Bis[bis(1-methylimidazol-2-yl)hydroxymethyl]anthracene (6). To a stirred solution of 1-methylimidazole (2.05 g, 18 mmol) in THF (15 ml) at −78 °C was added *n*-butyllithium (1.64 mol dm^{-3} in hexane, 17 ml, 28 mmol) under N_2. After stirring for 30 min at −78 °C, diethyl anthracene-1,8-dicarboxylate[6] (2.03 g, 6.3 mmol) in THF (20 ml) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C and 8 h at rt. After addition of brine (20 ml), the mixture was extracted with EtOAc (50 ml × 3). The organic layer was dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH. Yield 2.46 g (70%), mp 208–209 °C (Found: C, 68.10; H, 5.54; N, 19.42. $C_{32}H_{30}N_8O_2\cdot\frac{1}{4}H_2O$ requires C, 68.25; H, 5.46; N, 19.90%); δ_H (200 MHz, $CDCl_3$) 3.35 (s, 12H), 6.1 (br s, 2H), 6.55 (d, 2H, *J* 7.0), 6.81 (s, 4H), 7.07 (s, 4H), 7.2 (m, 2H), 7.94 (2 H, d, *J* 8.4), 8.42 (1 H, s) and 9.27 (1 H, s).

Kinetic measurements

In a cuvette containing 3 ml of buffer solution, suitable amounts of the ligand (5.0×10^{-2} mol dm^{-3} in MeOH or DMF) and a metal ion (2.5×10^{-1} mol dm^{-3} in H_2O) were placed. After temperature equilibration for 30 min, the reaction was initiated by injection of 15 μl of BDNPP (1.0×10^{-2} mol dm^{-3} in MeCN). The absorption increases of 2,4-dinitrophenolate at 400 nm were followed. The rate constants were calculated within 10% reaction.

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