JOC Article

Calix[4]arene-Based Zn^{2+} Complexes as Shape- and Size-Selective Catalysts of Ester Cleavage

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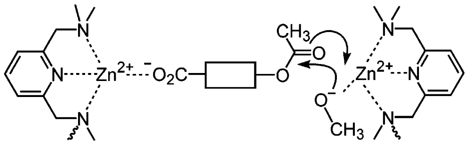
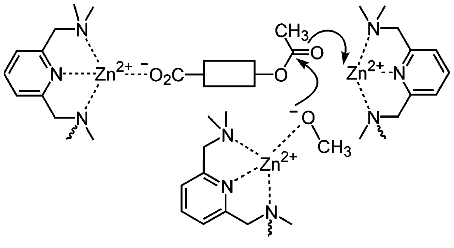


bimetallic catalysis



trimetallic catalysis

The kinetics of methanolysis of a number of esters endowed with a carboxylate anchoring group have been investigated in the presence of di- and trinuclear Zn^{2+} complexes of calix[4]arenes functionalized at the upper rim with nitrogen ligands. The results (i) emphasize the importance of a good match between ester size and intermetal distance, (ii) reveal a substrate independent superiority of the 1,2-vicinal dinuclear catalyst **1**−Zn_2 to its 1,3-distal regioisomer **2**−Zn_2, and (iii) provide further evidence for the concurrence of the three metal ions of **3**−Zn_3 in the catalytic mechanism.

The calix[4]arene scaffold blocked in the *cone* conformation is a convenient platform for the design of multifunctional catalysts, due to the possibility of introducing a large variety of functions at either rim of the calix by means of selective derivatization.[1,2] The high catalytic efficiency observed in many of the reported systems is believed to arise from a blend of preorganization of catalytic groups and flexibility of calix[4]arene frame (dynamic preorganization).[1c] As an extension of previous studies of calix[4]arene-based Zn^{2+} complexes as artificial

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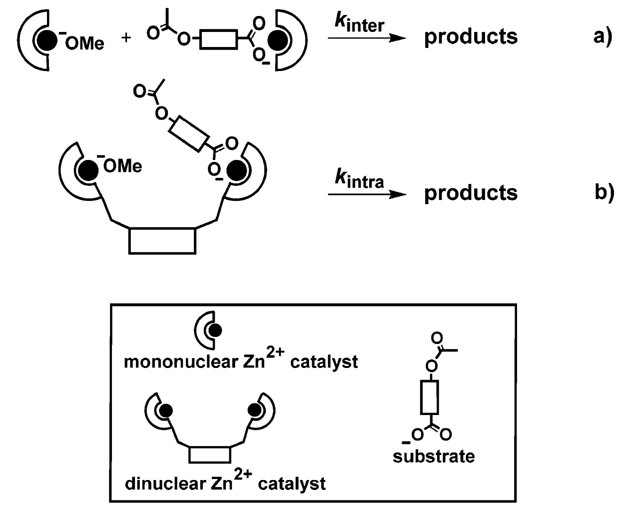
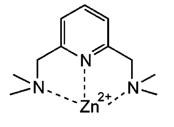
SCHEME 1

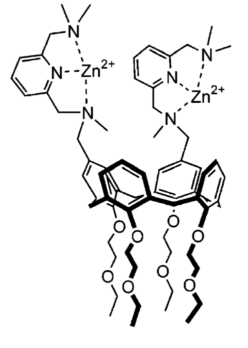


nucleases,[1c] we have recently reported on the methanolysis of ester **5**, catalyzed by dinuclear and trinuclear Zn^{2+} complexes of calixarenes **1**−**3**, functionalized at the upper rim with 2,6-bis[(dimethylamino)methyl]pyridine (BAMP) ligating units.[2a] We found a high degree of cooperation of the two metal ions in the dinuclear catalysts, with a marked superiority of the 1,2-vicinal complex **1**−Zn$_2$ over its distal regioisomer **2**−Zn$_2$. Furthermore, the higher efficiency of trinuclear compared with dinuclear catalysts provided a strong indication of the cooperation of the three Zn^{2+} ions of **3**−Zn$_3$ in the catalytic mechanism. The role played by the carboxylate group of **5** in the multiple catalysis is crucial.[3] It serves as an anchoring group, as schematically depicted in Scheme 1, thereby transforming an otherwise intermolecular reaction into an intramolecular (intracomplex) one. Given that substrate and catalyst must form a well-matched pair for the catalysis to be effective, carboxylate-functionalized esters of different shape and size are expected to experience marked variations in reactivity of catalyzed cleavage, as was actually observed to be the case in the reactions catalyzed by various dinuclear Ba^{2+} complexes.[2b,4]

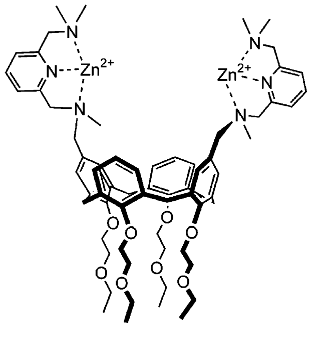
In view of the wide current interest in dinuclear and trinuclear metal complexes endowed with biomimetic hydrolytic activity[1c,2a−c,5] and of the important question of the influence of the intermetal distance on catalytic efficiency, we report here the results of a study of the catalytic activity of complexes BAMP−Zn, **1**−Zn$_2$, **2**−Zn$_2$, and **3**−Zn$_3$ in the basic methanolysis of esters **4**, **6**, and **7**, under the same conditions used for the methanolysis of **5**.[2a] Substrates **4**−**7** form a series in which the distance between the carboxylate and the ester carbonyl, taken as a gross measure of substrate size, increases in the given order.[6]



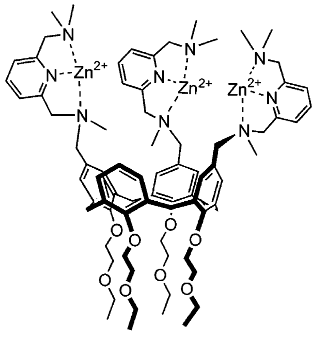
BAMP-Zn



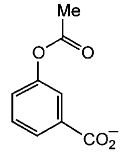
1-Zn$_2$



2-Zn$_2$



3-Zn$_3$



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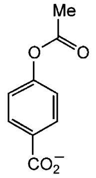

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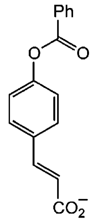

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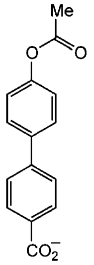

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Results and Discussion

Methanolysis of esters **4**, **6**, and **7** in the presence of Zn^{2+} complexes of nitrogen ligands BAMP and **1**−**3** were carried out as before in anhydrous methanol, at pH 10.4.[7] Typically, 0.10 mM (time-course experiments) or 0.50 mM (initial rate technique) substrate solution was reacted in the presence of 1.00 mM metal catalyst. Excess catalyst minimizes product inhibition and complication arising from multiple binding of the carboxylate substrate to

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(3) In the reaction of the parent phenyl acetate only moderate rate enhancements and small differences between the various metal catalysts were observed (see ref 2a).

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(6) The values of the distance between carboxylate and ester carbonyl, taken between *C*-atoms, are given in nm in parentheses: **4** (0.54); **5** (0.60); **6** (0.84); **7** (1.07). The calculation is straightforward for **5** and **7**, whereas for **4** and **6** average values are given.

(7) According to the molar autoprotolysis constant of CH$_3$OH, K_{ap} = $10^{-16.77}$ (Bosch, E.; Bou, P.; Allemann, H.; Rosés, M. *Anal. Chem.* **1996**, *68*, 3651−3657), the pH value corresponding to neutrality is 8.39 in this solvent. At pH 10.4 the concentration (activity) of methoxide ion is 2 log units higher than under neutral conditions.

TABLE 1. Basic Methanolysis of Esters 4−7 Catalyzed by the Zn^{2+} Complexes of Nitrogen Ligands BAMP and 1−3 (MeOH, pH 10.4, 25 °C)[a]

substrate	entry	catalyst	k (s^{-1})	k/k_{bg}[b]	$k_{dinuclear}/k_{mononuclear}$	EM (M)
4	1[c]	BAMP−Zn	2.6×10^{-5}	120		
	2	**1**−Zn_2	3.3×10^{-3}	15000	130	6.3×10^{-2}
	3[c]	**2**−Zn_2	2.2×10^{-4}	1000	8.5	4.2×10^{-3}
	4	**3**−Zn_3	2.9×10^{-3}	13000		
5[d]	5	BAMP−Zn	2.1×10^{-5}	38		
	6	**1**−Zn_2	3.4×10^{-3}	6200	160	8.1×10^{-2}
	7	**2**−Zn_2	1.3×10^{-4}	240	6.2	3.1×10^{-3}
	8	**3**−Zn_3	1.3×10^{-2}	24000		
6	9	BAMP−Zn	1.3×10^{-5}	81		
	10	**1**−Zn_2	2.2×10^{-4}	1400	17	1.6×10^{-2}
	11	**2**−Zn_2	1.6×10^{-5}	100	1.2	$\ll 1.1 \times 10^{-3}$
	12	**3**−Zn_3	5.5×10^{-4}	3400		
7	13	BAMP−Zn	3.6×10^{-5}	40		
	14	**1**−Zn_2	1.0×10^{-4}	110	2.8	2.5×10^{-3}
	15	**2**−Zn_2	3.7×10^{-5}	42	1.0	$\ll 0.9 \times 10^{-3}$
	16	**3**−Zn_3	1.6×10^{-4}	180		

[a] Runs carried out in the presence of 1.00 mM catalyst. Substrate concentration was 0.10 mM (time-course experiments), unless otherwise stated. [b] Rate constants for background methanolysis k_{bg} were calculated at pH 10.4 from second-order rate constants k_2 obtained in experiments carried out with 5.00 mM tetramethylammonium methoxide. Second-order rate constant k_2 ($M^{-1}\ s^{-1}$) and k_{bg} (s^{-1}) values are listed in the given order for the different substrates (in parentheses): 0.51, 2.2×10^{-7} (**4**); 0.38, 1.6×10^{-7} (**6**); 2.1, 8.9×10^{-7} (**7**). [c] Initial rate measurements, 0.50 mM substrate. [d] Rate constants k and k_{bg} from ref 2a.

dinuclear and trinuclear metal complexes. Consistently, good adherence to first-order time dependence was found in all time-course experiments. The results of catalytic experiments are expressed as pseudo-first-order rate constants k. As shown in our previous paper,[2a] under the conditions of the kinetic experiments run in the presence of **1**−Zn_2 and **2**−Zn_2, the concentration of the productive complex (Scheme 1b) amounts to no less than 3/4 of the total substrate concentration, and similar considerations apply to the reaction catalyzed by **3**−Zn_3. Hence, the catalytic rate constants k provide a reasonable estimate for the k_{intra} values (Scheme 1b).

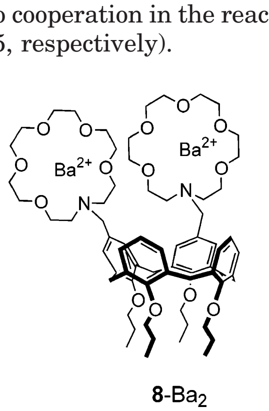
Since reactions of given esters in the absence of catalyst at the pH of the experiments were inconveniently slow for rate measurements, pseudo-first-order rate constants for background methanolysis (k_{bg}) were calculated from the second-order rate constants (k_2) measured in experiments carried out at 5.00 mM tetramethylammonium methoxide by means of eq 1, where pOMe = 16.77−10.4. Catalytic rate constants k and k/k_{bg} ratios are listed in Table 1, where the corresponding data related to the methanolysis of **5** are also reported. Inspection of the k/k_{bg} ratios

$$k_{bg} = k_2 \times 10^{-pOMe} \tag{1}$$

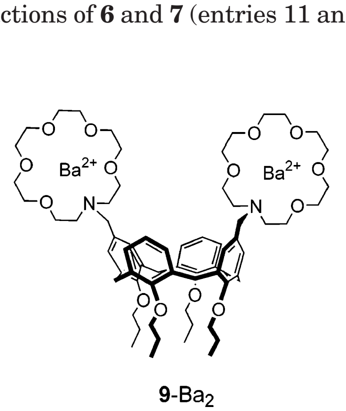
shows that metal complexes promote in all cases enhanced rates compared with background methanolysis. As previously noted,[2a] the moderate electron-releasing (rate-retarding) carboxylate substituent is converted into a strong electron-withdrawing (rate-enhancing) substituent upon binding to Zn^{2+} ion. This explains why rate enhancements caused by the mononuclear complex BAMP−Zn (entries 1, 5, 9, and 13) are much higher than the modest 5.6-fold rate increase measured under the same conditions in the methanolysis of phenyl acetate.[2a]

Rate enhancements caused by dinuclear and trinuclear metal complexes are strongly dependent on the substrate/catalyst combination and amount to 4 orders of magnitude in the most favorable cases. We first note the catalytic superiority of the 1,2-vicinal dinuclear complex **1**−Zn_2 compared with its 1,3-distal regioisomer **2**−Zn_2 for all the investigated substrates (compare entries 2, 6, 10, and 14 with entries 3, 7, 11, and 15, respectively). A similar picture was already observed in the basic methanolysis of a series of carboxylate-functionalized esters, catalyzed by the bis-barium complexes **8**−Ba_2 and **9**−Ba_2.[2b] Thus, the order of catalytic efficiency 1,2-vicinal ≫ 1,3-distal turns out to be a remarkable feature of upper rim bimetallic catalysts of acyl transfer reactions, which appears to be independent of the shape and size of the ester substrate, the nature of the metal ion and of the corresponding ligating unit.

The $k_{dinuclear}/k_{mononuclear}$ ratios listed in Table 1 are a measure of the cooperation of the metal ions in the bimetallic complexes. In the reaction catalyzed by the 1,2-vicinal complex **1**−Zn_2, the extent of cooperation is high for esters **4** and **5** (entries 2 and 6, respectively), significantly lower for ester **6** (entry 10), and even lower for ester **7** (entry 14). The most reasonable explanation for the loss of catalytic efficiency observed in the reactions of the "longer" substrates is that catalyst **1**−Zn_2 experiences an increasing difficulty to fit the altered substrate in the transition state when the ester size exceeds that of **5**. A similar trend of reactivity is observed in the reactions catalyzed by the less effective catalyst **2**−Zn_2. There is still a certain degree of cooperation in the reactions of **4** and **5** (entries 3 and 7, respectively), but no cooperation in the reactions of **6** and **7** (entries 11 and 15, respectively).



8-Ba_2



9-Ba_2

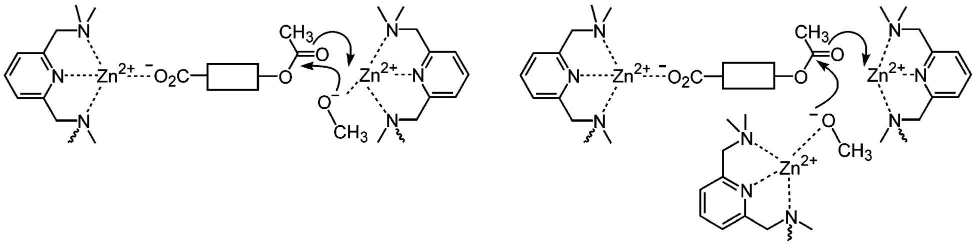


FIGURE 1. Schematic pictures of bimetallic (left) and trimetallic (right) catalysis.

The finding that the trimetallic complex **3**−Zn_3 exhibits the highest reactivity in the cleavage of **5** was taken as an indication of the simultaneous involvement of the three Zn^{2+} ions in the catalysis.[2a] The proposed mechanism is based on three different functions performed by the metal ions, namely, (i) binding to carboxylate, (ii) nucleophile delivery, and (iii) Lewis acid activation of the ester carbonyl. Consistent with the proposed mechanism for metal-catalyzed ester hydrolysis and alcoholysis,[8] both nucleophile delivery and carbonyl activation are important. In our system, the alternative between bi- and trimetallic catalysis depends on whether both functions are performed by the same Zn^{2+} ion or by two properly located Zn^{2+} ions (Figure 1). We now see that in the reactions of ester **6**, as in those of ester **5**, the trinuclear complex **3**−Zn_3 is the most effective catalyst, which argues in favor of the simultaneous involvement of three metal ions also in this case. Interestingly the order of catalytic efficiency **3**−Zn_3 > **1**−Zn_2 > **2**−Zn_2 ≈ BAMP−Zn is the same in the reaction of esters **6** and **7**, but rate enhancements in the reactions of **7** are too small to draw definite conclusions about the multiple involvement of metal ions in the catalysis.

In the cleavage of ester **4**, at variance with the behavior of esters **5**, **6**, and possibly **7**, complexes **1**−Zn_2 and **3**−Zn_3 show very nearly the same catalytic efficiency (entries 2 and 4, respectively). This finding clearly indicates that in the reaction of **4** the trinuclear complex **3**−Zn_3 actually behaves as a bimetallic catalyst, most likely using two vicinal metal centers in the catalytic mechanism, with the third metal acting as a spectator. Isomeric esters **4** and **5** have quite similar distances between carboxylate and ester carbonyl,[6] but differ markedly in shape. Whereas the degree of cooperation of the two metals in the dinuclear catalysts does not appear to be affected to a significant extent by the shape of the ester, as shown by the corresponding $k_{\mathrm{dinuclear}}/k_{\mathrm{mononuclear}}$ ratios (compare entry 2 with 6 and entry 3 with 7), the trinuclear complex acts as a trimetallic catalyst in the reaction of the para isomer **5**, but not in that of the meta isomer **4**. It appears therefore that, not surprisingly, the simultaneous involvement of three metal ions in the catalytic mechanism is more geometrically demanding and, consequently, more sensitive to the shape of the substrate than the involvement of two metal ions only.

It is of interest to compare the efficiency of dinuclear catalysts **1**−Zn_2 and **2**−Zn_2 with that of the structurally related Ba^{2+} complexes[2b] **8**−Ba_2 and **9**−Ba_2. The two sets of measurements share esters **5**, **6**, and **7** as common substrates but were carried out under different reaction conditions (solvent, pH, and catalyst concentration). The above difficulty can be overcome by resorting to the effective molarity (EM) concept, defined as $k_{\mathrm{intra}}/k_{\mathrm{inter}}$ (Scheme 1).[9] When applied to supramolecular catalysis,[10] the EM is a measure of catalytic efficiency which is independent of the chemical activation provided by catalytic groups, but solely depends on the way the catalyst template organizes reactants in a geometry suitable for the reaction to occur.

The EM data listed in the last column of Table 1 were calculated on the assumption that $k_{\mathrm{intra}} \approx k$ (see above) and on a set of k_{inter} values calculated as shown in the Experimental Section using the catalytic rate constants k measured in the presence of BAMP−Zn. The above assumption strictly holds whenever the intramolecular process is much faster than the intermolecular one (entries 2, 6, and 10) and is still reasonably valid when the latter process is slower, but not negligible compared with the former (entries 3, 7, and 14). In the reactions of **6** and **7** catalyzed by **2**−Zn_2 (entries 11 and 15), which shows no sign of cooperation between metal ions, the catalytic mechanism is purely intermolecular. As a consequence, the pertinent EM values are of necessity much lower than the quantities calculated as k/k_{inter} (Table 1) that, as expected, turned out to be indistinguishable from the catalyst concentration (1 mM).[11]

EM data from the present work are plotted in Figure 2 as a function of the distance between carboxylate and ester carbonyl, together with available data related to the ethanolysis of **5**−**7** catalyzed by dinuclear Ba^{2+} complexes **8**−Ba_2 and **9**−Ba_2.[2b] The superiority of both 1,2-vicinal and 1,3-distal Ba^{2+} complexes to the structurally related Zn^{2+} complexes is evident. No doubt, there are more demanding directional constraints in the coordination to BAMP-ligated Zn^{2+} ions than to azacrown-ligated Ba^{2+} ions. According to this view, the lower EMs observed in the reactions catalyzed by the Zn^{2+} complexes are believed to reflect increased strain energies in the transition state complexes with dinuclear catalysts whose coordinative interactions have more stringent stereo-

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[8] For a review article, see: Chin, J. *Acc. Chem. Res.* **1991**, *24*, 145−152. For a recent example, see also: Cacciapaglia, R.; Di Stefano, S.; Fahrenkrug, F.; Lüning, U.; Mandolini, L. *J. Phys. Org. Chem.* **2004**, *17*, 350−355.

[9] (a) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183−278. (b) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1−111.

[10] For a discussion of EM in supramolecular catalysis, see: Cacciapaglia, R.; Di Stefano, S.; Mandolini, L. *Acc. Chem. Res.* **2004**, *37*, 113−122.

[11] By definition, the EM represents the catalyst concentration needed for the intermolecular reaction to proceed with a pseudo-first-order rate constant equal to that of the intramolecular reaction. This implies that the intramolecularly catalyzed reactions whose EM is lower than the catalyst concentration are obscured by the competing intermolecular reactions.

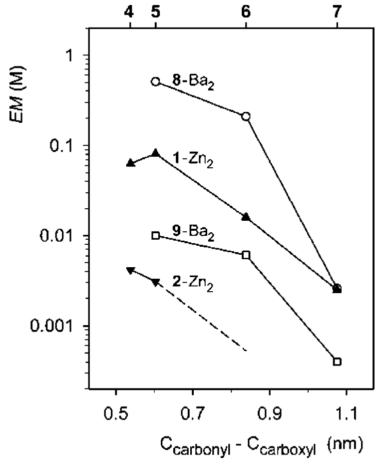

FIGURE 2. EM profiles for alcoholysis of esters endowed with a carboxylate anchoring group in the presence of dinuclear metallo complexes of calix[4]arene ligands. Data for metal complexes **8**−Ba$_2$ and **9**−Ba$_2$ from ref 2b.

chemical requirements and, consequently, are less adaptable than the Ba^{2+} complexes.

In conclusion, the results of the present work fully confirm both the marked superiority of 1,2-vicinal dinuclear catalysts to their 1,3-distal regioisomers, and the crucial influence of the size of the ester substrate on reactivity, which is ruled by the prerequisite of a good match between substrate size and intermetal distance. Furthermore, at least one additional example has been provided of the rarely observed concurrence of three metal ions in a catalytic mechanism of ester cleavage. More in general, combination of the present data with analogous data from previous investigations,[2a,b] illustrates once more the remarkable versatility of the upper rim of calix[4]arenes as convenient platforms in the construction of multifunctional metallocatalysts.

Experimental Section

Materials. Acids[2b] **6**·H$^+$ and **7**·H$^+$ and nitrogen ligands[2a] BAMP and **1**−**3** were available from previous investigations. Acid **4**·H$^+$ was prepared as described in the literature[12] [mp 130.5−132 °C (lit.[12] mp 128.7−131.3 °C)].

Kinetic Measurements. Catalytic experiments were carried out as previously reported[2a] in anhydrous methanol buffered at pH 10.4 by means of a 10 mM 1:1 mixture of *N*,*N*-diisopropyl-*N*-(2-methoxyethyl)amine and its perchlorate salt.[2a] Substrates **4**, **6**, and **7** were generated in situ by addition of the parent phenolic compound to the buffered reaction medium. Metal catalysts were freshly prepared (1.00 mM) in the reaction vessel by mixing equivalent amounts of free ligand and Zn(ClO$_4$)$_2$.

Spectrophotometric measurements (kinetic runs involving substrates **6** and **7** and methanolysis of 0.10 mM **4** with 5.00 mM tetramethylammonium methoxide) were carried out on either a double beam or on a diode-array spectrophotometer. HPLC analyses (methanolysis of ester **4** carried out in the presence of metal complexes) were performed on a liquid chromatograph fitted with a UV−vis detector operating at 220 nm. Kinetic runs monitored by HPLC were carried out in the presence of 1,4-dimethoxybenzene as an internal standard. Samples were analyzed on a Supelcosil LC-18 DB column (25 cm × 4.6 mm i.d., particle size 5 μm). At convenient time intervals 0.1 mL of the reaction mixture were quenched with 0.1 mL of 10 mM aqueous solution of HBr and subjected to HPLC analysis with CH$_3$CN/MeOH/H$_2$O-0.03% trifluoroacetic acid 10/45/45 (*v*/*v*) as eluent, at a flow rate of 0.6 mL/min.

Error limits of rate constants are in the order of ±5% (time-course kinetics) and ±10% (initial rate technique). Nonlinear least-squares calculations of kinetic data were carried out using the program SigmaPlot 2002 for Windows, Version 8.0 (SPSS, Inc.).

The second-order rate constant of the intermolecular process (k_{inter}) has been calculated as the ratio between the first-order rate constant obtained in the presence of the mononuclear complex BAMP−Zn and the concentration of the reactant BAMP−Zn(OMe) ([BAMP−Zn(OMe)] = c_{BAMP} − [BAMP−Zn(substrate)] = $c_{\text{BAMP}} - c_{\text{substrate}}$). Calculated values of k_{inter} (M^{-1} s^{-1}) are listed below for the reaction of the different substrates (in parentheses): 5.2×10^{-2} (**4**); 4.2×10^{-2} (**5**); 1.4×10^{-2} (**6**); 4.0×10^{-2} (**7**).

Other materials and procedures were as previously described.[2a]

Warning! Care was taken when handling *N*,*N*-diisopropyl-*N*-(2-methoxyethyl)ammonium perchlorate because it is potentially explosive.[13] No accident occurred in the course of the present work.

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