ensures an efficient catalytic cycle, a slower secondary reaction occurs, the reaction of the allyl radical with one of the iron-porphyrin meso positions. In the free radical produced by this process, the meso methine bridge opposite to the methylene bridge has the highest spin density.[26] Reaction of this methine carbon with either allyl bromide or an allyl radical formed in steady-state concentration would lead to the observed iron(II) porphodimethene complex (Scheme II). This mechanism is in agreement with the results obtained with propargyl bromide, the nonsymmetrical radical formed in this case existing as either a propargyl or an allenyl radical. The fact that we never observed such porphodimethene formation upon reduction of halogenated compounds different from allyl or propargyl halides might be explained by the spin delocalization of the allyl and propargyl radicals which places one reactive carbon in good proximity of the meso carbons of the porphyrin ring.

(26) Fuhrhop, J. H. In "Porphyrins and Metalloporphyrins"; Smith, K. M., Ed.; Elsevier: New York, 1975; pp 594-623.

Conclusion

The aforementioned results indicate a new way of preparation of porphodimethenes in very mild conditions (temperature 20 °C, pH 7.4, mild reducing agent). In that regard it is noteworthy that previously described porphodimethenes have been prepared only in the OEP series and have involved hard conditions (reductive alkylation of metalloporphyrins with sodium anthracenide as reducing agent).[12,20b] A similar irreversible modification of the porphyrin ring could occur during the reductive metabolism of allyl and propargyl halides by cytochrome P-450.

Registry No. 1a, 91128-68-6; **1b'**, 91128-69-7; **1b''**, 91128-70-0; **1b'''**, 91158-26-8; **2a**, 91178-21-1; **2b'**, 91158-27-9; **2b''**, 91158-28-0; **2b'''**, 91158-29-1; allyl bromide, 106-95-6; propargyl bromide, 106-96-7; Fe(TPP)(Cl), 16456-81-8.

Tris(imidazole)-Containing Phosphine:M^{2+} Complexes as Biomimetic Catalysts. Importance of a L:M^{2+}–OH^- in the Catalyzed Bimolecular Hydrolysis of *p*-Nitrophenyl Picolinate

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Abstract: A series of tris(imidazole)-containing phosphines were prepared and their M^{2+} complexes studied as biomimetic catalysts for the hydrolysis of *p*-nitrophenyl picolinate. Triimidazol-2-ylphosphine (**3**) and tris[4(5)-(hydroxyethyl)-imidazol-2-yl]phosphine (**4**) as their Zn^{2+} complexes promote the hydrolysis of pNPP in aqueous solution, their catalytic activities increasing with pH. Because they have relatively low affinities for Zn^{2+}, they are incompletely complexed at concentrations of 5×10^{-4} M which complicates analysis of the kinetic data. Formation of precipitates occurs above pH 7.6. At a given pH, the second-order catalytic rate constants $k_{3:Zn^{2+}}^{cat.}$ and $k_{4:Zn^{2+}}^{cat.}$ are 2–10-fold larger than those for Zn^{2+} or the ligand alone which indicates a cooperative interaction between ligand and Zn^{2+} producing a more active catalyst. Bis(4,5-diisopropyl-imidazol-2-yl)imidazol-2-ylphosphine (**5**) and bis(4,5-diisopropylimidazol-2-yl)[4(5)-(hydroxyethyl)imidazol-2-yl]phosphine (**6**) bind both Zn^{2+} and Co^{2+} more strongly but require media consisting of 80% ethanol–H_2O for their study. As a function of pH, **5**:Zn^{2+} and **6**:Zn^{2+} become increasingly active but precipitation occurs above pH 7.2. However their Co^{2+} complexes are more soluble and can be studied up to pH 8.6. Below pH 7.4 their activities increase with a first-order dependence on [OH^-] and level off thereafter, indicating that a basic form of the complex (L:Co^{2+}–OH^-) with a pK of ~7.6–7.8 is the active species. Since no evidence of a preequilibrium formation of a L:Co^{2+}:pNPP ternary complex is observed, the basic form of the complex is acting as a bimolecular nucleophile toward pNPP.

Introduction

A large number of Zn^{2+}-containing metalloenzymes are known whose physiological role stems from the ability of the active site metal to promote hydrolysis or hydration reactions.[1] Among these are some well-studied hydrolases such as carboxypeptidase A (CPA), Thermolysin, angiotensin-converting enzyme and alkaline phosphatase, and the lyases, the most well-studied member being carbonic anhydrase.[2] Although the detailed mechanisms of action of these enzymes are presently not well understood, the great bulk of evidence points to the ability of the active-site Zn^{2+} to activate H_2O as a nucleophile at some point along the reaction profile. Thus by virtue of ligation to the electropositive M^{2+}, the pK_a of H_2O is said to be reduced from ~15.7 in solution to values approaching 7 in the active site such that at physiological pH, a Zn^{2+}–OH^- is produced that is sufficiently nucleophilic to attack (depending upon the enzyme) the X=O linkage of esters, amides CO_2, and phosphate monoesters.[3] Of course additional roles for the metal are also likely such as a Lewis acid and/or template upon which the reaction can occur. The protein matrix in which the M^{2+} is embedded will also influence the chemistry particularly in terms of substrate specificity and orientation as well as by modifying the activity of the reactants by solvation effects.

A large number of recent studies have shown that small molecules incorporating both a metal-binding site and covalently

(1) For compendia of leading references to Zn^{2+} enzymes see: (a) Galdes, A.; Vallee, B. L. *Met. Ions Biol. Syst.* **1983**, *15*, 1–55. (b) Prince, R. H. *Adv. Inorg. Chem. Radiochem.* **1979**, *22*, 349–440. (c) Galdes, A.; Hill, H. A. O. *Inorg. Biochem.* **1979**, *1*, 317–346. (d) Galdes, A. *Ibid.* **1982**, *3*, 268–313.

(2) For a compendia of references to carbonic anhydrase see: (a) Lindskog, S.; Ibrahim, S. A.; Jonsson, B.-H.; Simonsson, I. in "The Coordination Chemistry of Metalloenzymes"; Bertini, I.; Drago, R. S., Luchinat, C., Eds.; D. Reidel Publishing Co.: Boston, MA, 1983, pp 49–64. (b) Silverman, D. N.; Vincent, S. H. *CRC Crit. Rev. Biochem.* **1983**, *14*, 207–255.

(3) In the case of alkaline phosphates that hydrolyze a wide range of phosphate monoesters, the primary catalytic step is to produce a phosphorylserine intermediate that is subsequently hydrolyzed. This second step requires that H_2O in the active site be activated to the point that it nucleophilically cleaves a normally unreactive phosphate. For discussions of the sequence of events see: Coleman, J. E.; Chlebowski, J. F. *Adv. Inorg. Biochem.* **1979**, *1*, 2–66.

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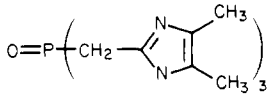
Table I. pK_a and $pK_{M^{2+}}$ Values for **3–6** Determined by Potentiometric Titration[a]

ligand	pK_{a_1}	pK_{a_2}	pK_{a_3}	$pK_{Zn^{2+}}$	$pK_{Co^{2+}}$
3[b]	5.26	6.59	7.44	3.40	
(**3**)[c]	(3.11)[c]	(6.00)[c]	(6.82)[c]	(4.57)[c]	
4[b]	5.75	6.84	7.70	3.73	
(**4**)[c]	(5.47)[c]	(6.45)[c]	(7.20)[c]	*d*	
5[c]	1.8	3.52	6.67	8.7	7.7
6[c]	0.5	3.55	6.27	6.5	5.7

[b] Purely aqueous medium, ionic strength = 0.18 M ($NaClO_4$), temp = 18 °C. [c] 80% ethanol–H_2O medium, ionic strength = 0.2 M ($NaClO_4$), temp = 25 °C.[8i] [d] Satisfactory value not obtained due to precipitate formation.

attached ester,[4] nitrile,[5] amide,[5b-g] or anhydride[6] exhibit strongly modified hydrolysis reactions of the latter groups. These "biomimetic" models offer important small-molecule demonstrations of a variety of catalytic roles for the metal such as nucleophilic M^{2+}–OH^-, Lewis acid promoted attack of H_2O, or M^{2+} stabilization of the leaving group. However, they are by design not true catalysts since once hydrolysis is complete, the catalytic function is destroyed. Indeed, with the exception of a limited number of cases,[7,8,10] few "biomimetic" hydrolytic catalysts having turnover possibilities have been presented.

Some time ago as part of an ongoing study of carbonic anhydrase models[8f-i] we reported that the Co(II) complex of the tris(2-imidazolylmethyl)phosphine oxide (**1**)[8h] showed good cat-



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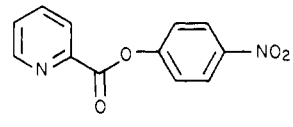
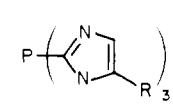


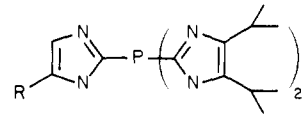
2

alytic activity in promoting the hydrolysis of *p*-nitrophenylpicolinate (pNPP, **2**). From this study it was noted that between pH 7.5 and 8.7 a saturation phenomenon occurred indicative of formation of a ternary **1**:Co(II):**2** complex that subsequently suffered rate-limiting expulsion of *p*-nitrophenol with an observed $k_{cat.}$ of 3×10^{-2} s^{-1} at pH 8.7. Thus the catalyst afforded an acceleration of 50-fold over the spontaneous hydrolysis of pNPP at pH 8.7.[9] However the kinetic data were not sufficient to delineate the actual mechanism of hydrolysis that could have involved a rate-limiting attack of Co(II)–OH^- on the bound **2** or a Lewis acid promotion of the attack of external OH^- and/or H_2O.

To further investigate the mechanism of action of similar chelates toward pNPP hydrolysis, we have expanded the study to include the Zn^{2+} and Co^{2+} complexes of phosphines **3–6**. Since

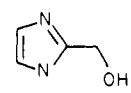


3, R = H
4, R = CH_2CH_2OH

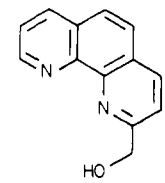


5, R = H
6, R = CH_2CH_2OH

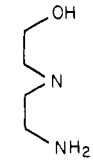
it has been reported that the hydroxyl group in the Zn^{2+} complexes **7–9**[10-12] show pronounced catalytic activity toward such substrates



7[t0]



8[t1]



9[t2]

as pNPP[10,12] or ATP,[11] the phosphine pairs (**3**,**4**; **5**,**6**) were chosen to investigate whether the covalently attached hydroxyethyl group in the phosphines was of any catalytic benefit. At least one of the Zn^{2+} hydrolases, alkaline phosphatase[3] contains at its active site, a serine OH which is activated toward nucleophilic attack on a phosphate monoester. The following represents our findings during the course of this study.

Experimental Section

Materials. *p*-Nitrophenyl picolinate (**2**) was prepared according to published procedure as were ligands **3**,[13] **5**,[8i] and **6**.[8i]

Tris[4(5)-(hydroxyethyl)imidazol-2-yl]phosphine (4). To 150 mL of dry THF cooled to −40 °C containing 12.6 g (0.075 mol) of freshly distilled ethoxyamide acetal of 4(5)-(hydroxyethyl)imidazole[14] under an atmosphere of N_2 was added 47 mL of 1.6 N *n*-Bu-Li (0.075 mol) at such a rate that the temperature did not exceed −40 °C. The red solution was stirred an additional 30 min, and then 3.43 g of freshly distilled PCl_3 (0.025 mol) was added via syringe (exothermic and yields thick ppte). The mixture was allowed to stir and come to room temperature overnight, ultimately yielding a red solution. Workup consisted of evaporating the solvent under reduced pressure, adding 100 mL of $CHCl_3$ to the residue, and treating the resultant suspension with 50 mL of 50% NH_4OH to dissolve the salts. The $CHCl_3$ layer was separated, washed quickly with H_2O, and dried over anhydrous Na_2SO_4. After the mixture was filtered and the $CHCl_3$ was removed, an oil was obtained that contained the protected triimidazolylphosphine. Deprotection was effected by dissolving the oil in 50% aqueous acetone and heating at reflux for 30 min. Removal of the volatiles under reduced pressure yielded ~10 g of a yellow semisolid that was twice recrystallized (~30 cm^3 ethanol containing ether to turbidity) to give 3.3 g of white crystals: mp 150–153 °C (36%); ^1H NMR (MeOH-d_4) δ 7.06 (s, 1 H), 3.80 (t, 2 H, J = 6 Hz), 2.84 (t, 2 H, J = 6 Hz); IR (KBr disk), 3600–2300 (br), 1564, 1397, 1363, 1278, 1196, 1174, 1111, 1079, 1016 cm^{-1}. Anal. Calcd for $C_{15}H_{21}N_6PO_3 \cdot {}^1/_2H_2O$: C, 48.26; H, 5.90; N, 22.52. Found: C, 48.32; H, 5.74; N, 22.51. The material proves to be very involatile and electron impact mass spectrometry yields only (hydroxyethyl)imidazole fragments (m/z 111, 112, 113) and peaks at m/e 140, 141, and 142 corresponding to a mono(hydroxyethyl)imidazole – P fragment. No M^+ is seen. However a fast atom bombardment technique whereby **4** in glycerol is

(4) (a) For a recent review of models for Zn^{2+} hydrolases see: Brown, R. S.; Huguet, J.; Curtis, N. J. *Met. Ions Biol. Syst.* **1983**, *15*, 55–99. (b) Wells, M. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 5341–5356. (c) Breslow, R.; McAllister, C. *Ibid.* **1971**, *93*, 7096–7097. (d) Fife, T. H.; Squillacote, V. L. *Ibid.* **1978**, *100*, 4787–4793. (e) *Ibid.* **1979**, *101*, 3017–3026. (f) Fife, T. H.; Przystas, T. J. *Ibid.* **1980**, *102*, 7297–7300. (g) *Ibid.* **1982**, *104*, 2251–2257. (h) Hay, R. W.; Clark, C. R. *J. Chem. Soc., Dalton Trans.* **1977**, 1866–1974, 1993–1998. (i) Suh, J.; Cheong, M.; Suh, M. P. *J. Am. Chem. Soc.* **1982**, *104*, 1654–1657

(5) (a) Breslow, R.; Fairweather, R.; Keana, J. *J. Am. Chem. Soc.* **1967**, *89*, 2135–2138. (b) Buckingham, D. A.; Davis, G. E.; Foster, D. M.; Sargeson, A. M. *Ibid.* **1970**, *92*, 5571–5579. (c) Buckingham, D. A.; Foster, D. M.; Sargeson, A. M. *Ibid.* **1974**, *96*, 1726–1729. (d) *Ibid.* **1970**, *92*, 6151–6158. (e) Buckingham, D. A.; Keene, F. R.; Sargeson, A. M. *Ibid.* **1974**, *96*, 4981–4983. (f) Groves, J. T.; Dias, R. M. *Ibid.* **1979**, *101*, 1033–1035. (g) Fife, T. H.; Squillacote, V. L. *Ibid.* **1977**, *99*, 3762–3769. (h) Groves, J. T.; Chambers, R. R., Jr. *Ibid.* **1984**, *106*, 631–638.

(6) (a) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1983**, *105*, 1638–1642. (b) Breslow, R.; McClure, D. E.; Brown, R. S.; Eisenach, J. *Ibid.* **1975**, *97*, 194–195. (c) Buckingham, D. A.; Englehardt, L. M. *Ibid.* **1975**, *97*, 5915–5917.

(7) (a) Lloyd, G. J.; Cooperman, B. S. *J. Am. Chem. Soc.* **1971**, *93*, 4883–4889. (b) Chipman, D.; Breslow, R. *Ibid.* **1965**, *87*, 4195–4196. (c) Hsu, C.-H.; Cooperman, B. S. *Ibid.* **1976**, *98*, 5652–5657. (d) *Ibid.* **1976**, *98*, 5657–5663.

(8) Catalysts modelled after carbonic anhydrase are more prevalent. (a) Chaffe, E.; Dasgupta, T. P.; Harris, G. M. *J. Am. Chem. Soc.* **1973**, *95*, 4169–4173. (b) Harrowfield, J. MacB.; Norris, V. A.; Sargeson, A. M. *Ibid.* **1976**, *98*, 7282–7289. (c) Wooley, P. *J. Chem. Soc., Perkin Trans. 2* **1977**, 318–324. (d) Wooley, P. *Nature (London)* **1975**, *258*, 677–682. (e) Tabushi, I.; Kuroda, Y.; Mochizuki, A. *J. Am. Chem. Soc.* **1980**, *102*, 1152–1153. (f) Huguet, J.; Brown, R. S. *Ibid.* **1980**, *102*, 7571–7572. (g) Curtis, N. J.; Huguet, J.; Brown, R. S. *Ibid.* **1981**, *103*, 6953–6959. (h) Brown, R. S.; Salmon, D.; Curtis, N. J.; Kusuma, S. *Ibid.* **1982**, *104*, 3188–3194. (i) Brown, R. S.; Slebocka-Tilk, H.; Cocho, J. L. *Ibid.* **1984**, *106*, 2421–2431.

(9) This acceleration is based upon data derived from an Eadie plot[8h] consistent with a mechanism of **1**:Co(II) + **2** $\rightleftharpoons$ **1**:Co(II):**2** $\xrightarrow{k_{cat.}}$ products where $k_{cat.} = 3 \times 10^{-2}$ s^{-1}.

(10) (a) Eiki, T.; Kawada, S.; Matsushima, K.; Mori, M.; Tagaki, W. *Chem. Lett.* **1980**, 997–1000. (b) Ogino, K.; Shindo, K.; Minami, T.; Tagaki, W.; Eiki, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1101–1106.

(11) Sigman, D. S.; Wahl, G. M.; Creighton, *Biochemistry* **1972**, *11*, 2236–2242.

(12) Sigman, D. S.; Jorgensen, C. T. *J. Am. Chem. Soc.* **1972**, *94*, 1724–1730.

(13) Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038–4040.

(14) Brown, R. S.; Ulan, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 2382–2388.

bombarded with Xe^+ yields a M + H^+ = 365 peak.

pK_a and p$K_{M^{2+}}$ values for ligands **3**–**6** were determined by potentiometric titration techniques and equipment previously described.[15] For reasons of solubility **5** and **6** required a medium of 80% ethanol–H_2O.[8i] The values reported in Table I are the averages of at least two separate determinations and have an error of <0.1 unit. Stock metal solutions were made from the perchlorate salts and were standardized by EDTA titration.[16]

Kinetic Studies. Rates of hydrolysis of pNPP were monitored at 25.0 ± 0.2 °C (**3** and **4**) or 26.0 ± 0.2 °C (**5** and **6**) with a Cary 210 UV–visible spectrophotometer (adapted as previously described[14]) by monitoring either the rate of appearance of *p*-nitrophenol (320 nm) or *p*-nitrophenoxide (400 nm) depending upon pH. In selected cases the rate of disappearance of pNPP was monitored at 280 nm, the k_{obsd} values being identical with those observed for the appearance of product. Buffers employed were MES (pH 5.6–6.0), MOPS (pH 6.4–7.6), and tricine or CHES (pH 7.6–8.84) and were used as supplied (Sigma). The purely aqueous solutions used for the study of **3** and **4** contained 0.3 M buffer, ionic strength 0.3 M ($NaClO_4$). Solubility requirements of **5** and **6** necessitated media consisting of 80% ethanol–H_2O (v/v) and 0.048 M buffer with an ionic strength of 0.048 M ($NaClO_4$). These solutions were prepared from the 0.3 M aqueous buffers by dilution with the appropriate amount of 95% ethanol and readjustment of the pH with aliquots of concentrated $HClO_4$ or NaOH. pH values are those read from a Radiometer GK2322C combination electrode (standardized with Fisher pH 4.00 and 7.00 buffers) immersed directly in the solution and are uncorrected for the relatively high organic content. Such corrections are small and amount to a reduction from the obseved readings by ~0.2 units.[17]

The rate of hydrolysis of pNPP in the above solutions was monitored as a function of varying concentrations of M^{2+}, ligand, and equimolar ligand and M^{2+}. Stock aqueous metal solutions of $Zn(ClO_4)_2$ and $CoCl_2$ were standardized by EDTA titration.[16] Observed pseudo-first-order rate constants were obtained in triplicate by fitting the data with a standard nonlinear least-squares treatment and have a precision of ±5%. ^1H NMR experiments (Bruker 200-MHz FT spectrometer) were conducted using 0.02 M solutions of **5** and **6** and the spectra monitored as a function of added 0.25 M $ZnCl_2$ in D_2O.

Results and Discussion

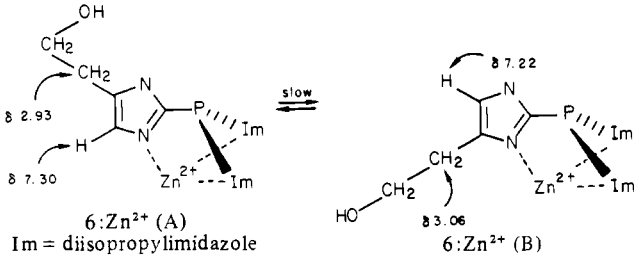
Presented in Table I are the pK_a and p$K_{M^{2+}}$ values determined for ligands **3**–**6**. For **3** and **4**, values were determined in H_2O and 80% ethanol–H_2O, while for **5** and **6**, solubility required 80% ethanol–H_2O. In H_2O, the three pK_a's for each of **3** and **4** differ by only ~2 units, while those reported for the carbon analogue tri-2-imidazolecarbinol[18] differ by at least 5 units. This is consistent with the idea that charge repulsion between the three protonated imidazoles is reduced in the phosphine series as a consequence of the extended P–C bond length. Disappointingly however, the ability of **3** or **4** to bind Zn^{2+} is substantially lower than that reported for tri-2-imidazolylcarbinol.[18] The low binding constants for **3** and **4** indicate that at the concentrations employed for the subsequent catalytic studies (vide infra) not all the ligand will be complexed.

However, apparently **5** and **6** bind Zn^{2+} and Co^{2+} quite strongly, a likely consequence of the reduced solvation of the divalent ion in 80% ethanol–H_2O that tends to favor complexation. Such might be supported by the observation that **3** binds Zn^{2+} more strongly in 80% ethanol–H_2O that it does in H_2O. This in turn facilitates analysis of the kinetic data since the great bulk of ligand in solution will exist as complex even at relatively low concentrations.[19]

Titration of an 80% EtOH–H_2O solution containing equimolar $CoCl_2$ and **5** or **6** shows ionization of some group associated with the complex having a pK_a of ~7.7. This is similar to the situation observed with **1**:Co(II) (pK_a = 7.8[8h]) and is attributed to the ionization of a metal bound H_2O. However, unlike **1**:Co(II) neither **5**:Co(II) nor **6**:Co(II) show an intense blue color accompanying this ionization that would be evidence for the formation of a 4- or 5-coordinate complex.[8i] In both cases, a faint blue color is observed when 8.3 × 10^{-3} M **L**:Co(II) is titrated, but judging from the extinction coefficients (ϵ_{640nm}^{max} = 10–15 M^{-1} cm^{-1} at pH 8.0), the great bulk of the complex present in solution at that pH must be octahedral.

NMR Spectra of 5 and 6:Zn^{2+} in Methanol-d_4 (0.02 M). In the absence of Zn^{2+}, the ^1H resonances for **5** appear as a pair of doublets at δ 1.25 and 1.27, respectively (isopropyl CH_3's; J = 7 Hz), an unresolved pair of septets at δ 3.04 (isopropyl methine, J = 7 Hz) and a singlet at δ 7.18 (imidazole C–H). After the addition of 1 equiv of $ZnCl_2$ (in D_2O), the peaks attributable to **5** have been replaced by a set of broadened resonances centered at δ 1.25 (isopropyl CH_3's), δ 3.22 (isopropylmethine), and two discreet but somewhat broadened peaks at δ 7.45 and 7.50 corresponding to the simple imidazole 4- and 5-hydrogens. Since further additions of Zn^{2+} do not alter the appearance of this spectrum, it arises from a 1:1 complex of **5**:Zn^{2+} in which the isopropylimidazoles are undergoing a dynamic intracomplex exchange process likely due to a debinding, rotation, and rebinding of a given diisopropylimidazole through the opposite nitrogen. Such a dynamic process is substantiated by temperature studies that show two distinct but somewhat broadened isopropyl resonances at 0 °C but a single isopropyl doublet at 50 °C. However, the simple imidazole is less prone to dynamic exchange since the 4- and 5-H's have discreet chemical shifts, indicating they reside at different distances from the bound Zn^{2+}, the nearest H appearing at lowest field.[15]

Ligand **6** behaves similarly. In the absence of $ZnCl_2$ the free ligand exhibits a pair of doublets at δ 1.12 and 1.14, respectively (isopropyl CH_3's, J = 7 Hz), as well as a septet at δ 3.02 (isopropylmethines, J = 7 Hz). Additional resonances corresponding to the (hydroxyethyl)imidazole are seen at δ 2.88 (CH_2CH_2OH, t, J = 8 Hz), 3.74 (CH_2CH_2OH, t, J = 8 Hz), and 6.97 (s, imidazole 4(5)-H). In the presence of equimolar Zn^{2+}, the spectrum now shows broadened isopropyl signals centered at δ 1.25 (CH_3's) and 3.2 (C–H) similar to those observed in the case of **5**:Zn^{2+}, the broadening being suggestive of a dynamic intracomplex process. Interestingly, there are now two sets of resonances attributable to the (hydroxyethyl)imidazole since discreet signals appear at δ 2.93 (t, J = 7 Hz) and 3.06 (t, J = 8 Hz), these corresponding to the $HOCH_2CH_2$ resonances of hydroxyethyl groups that reside at different distances from the bound Zn^{2+}. As well, the $HOCH_2CH_2$ signal appears as two overlapping triplets centered at δ 3.78 while the imidazole 4(5) hydrogen appears as two separate signals at δ 7.22 and 7.30, respectively. Careful integration reveals that imidazole H and $HOCH_2CH_2$ signals at δ 7.30 and 2.93, respectively, arise from one form of the complex, while those at δ 7.12 and 3.06 arise from another as is shown in eq 1. In a given form of the complex (**6**:Zn^{2+} A or B), those



6:Zn^{2+} (A) 6:Zn^{2+} (B)

Im = diisopropylimidazole (1)

imidazole hydrogens residing closest to the bound Zn^{2+} will as expected[15] have the highest downfield chemical shift. From the sharpness of these peaks it is clear that the (hydroxyethyl)-imidazole is not undergoing a rapid dynamic process. The important aspect for our purposes is that these NMR data provide evidence that the hydroxyethyl group can occupy the position adjacent to the metal which is a minimum prerequisite if it is to be activated as a nucleophile in the kinetic processes.

^1H NMR spectra of **4** (0.09 M, CH_3OH-d_4) as a function of added $Zn^{2+}(Br^-)_2$ showed a considerable broadening of the res-

(15) Brown, R. S.; Huguet, J. *Can. J. Chem.* **1980**, *58*, 889–901.
(16) Flaschka, H. A. In "EDTA Titrations", 2nd ed.; Pergamon Press: New York, 1964.
(17) Bates, R. G.; Paabo, M.; Robinson, R. A. *J. Phys. Chem.* **1963**, *67*, 1833–1838.
(18) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918–3922 report a p$K_{Zn^{2+}}$ for triimidazol-2-ylcarbinol of 6.77.
(19) For the weakest binding case, that of **6** and Co^{2+}, if both are present in initial concentrations of 5 × 10^{-4} M, the [**6**:Co^{2+}] present will be 4.69 × 10^{-4} M. For **5**:Zn^{2+}, if each component is present in initial concentrations of 5 × 10^{-4} M, the [**5**:Zn^{2+}] is 4.99 × 10^{-4} M.

Table II. Pseudo-First-Order Rate Constants for Hydrolysis of pNPP[a] (k_{obsd}, s^{-1}, H_2O)

pH	blank	$[ZnClO_4]^b$	[3][b]	[4][b]	[3:Zn^{2+}][b]	[4:Zn^{2+}][b]
5.6	5.33×10^{-6} (−5.27)	1.42×10^{-5} (−4.85)	2.38×10^{-5} (−4.6)	1.82×10^{-5} (−4.74)	3.06×10^{-5}	1.81×10^{-5}
6.0	7.24×10^{-6} (−5.14)	2.33×10^{-5} (−4.63)	4.31×10^{-5} (−4.36)	3.63×10^{-5} (−4.44)	6.78×10^{-5}	7.01×10^{-5}
6.4	2.21×10^{-5} (−4.65)	5.12×10^{-5} (−4.3)	1.07×10^{-4} (−3.97)	6.28×10^{-5} (−4.2)	1.57×10^{-4}	1.73×10^{-4}
6.8	3.12×10^{-5} (−4.50)	1.10×10^{-4} (−3.96)	2.19×10^{-4} (−3.66)	1.59×10^{-4} (−3.79)	4.06×10^{-4}	3.37×10^{-4}
7.2	6.49×10^{-5} (−4.18)	2.70×10^{-4} (−3.57)		3.19×10^{-4} (−3.49)	7.18×10^{-4}	1.05×10^{-3}
7.6	1.22×10^{-4} (−3.91)	5.76×10^{-4} (−3.24)	6.14×10^{-4} (−3.21)	5.16×10^{-4} (−3.29)	1.18×10^{-3}	2.30×10^{-3}
8.05	3.96×10^{-4} (−3.40)	*c*	4.55×10^{-3} (−3.34)	4.61×10^{-3} (−2.33)	*c*	*c*
8.4	9.56×10^{-4} (−3.02)	*c*			*c*	*c*
8.84	1.28×10^{-3} (−2.89)					

[a] T = 25.0 °C; ionic strength = 0.3 M ($NaClO_4$), [buffer] = 0.3 M, 5×10^{-5} M pNPP; k_{obsd} (precision ±5%) uncorrected for buffer catalysis. Error in k_{obsd} is ±5%. log k_{obsd} values in parentheses. [b] 4.82×10^{-4} M. [c] Precipitation observed.

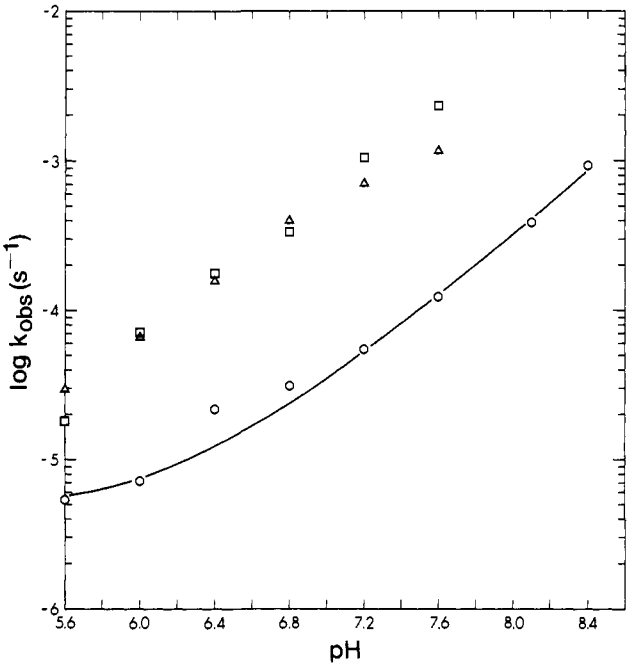


Figure 1. A plot of log k_{obsd} for the hydrolysis of pNPP (5×10^{-5} M) as a function of pH: ○, uncatalyzed; △, (5×10^{-4} M **3** and 5×10^{-4} M $ZnClO_4$); □, (5×10^{-4} M 4 and 5×10^{-4} M $ZnClO_4$).

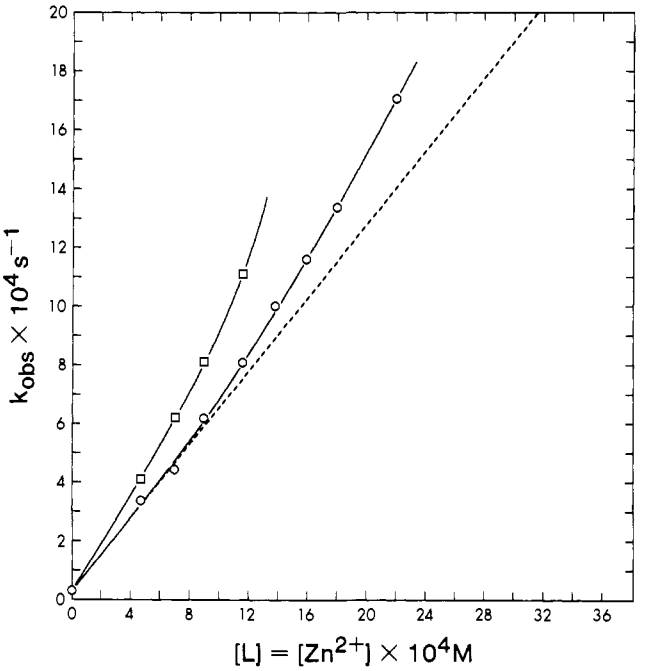
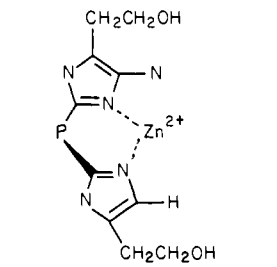


Figure 2. A plot of k_{obsd} for the catalyzed hydrolysis of pNPP (pH 6.8) as a function of equimolar [L] and [Zn^{2+}] ○, **3** × Zn^{2+}; □, **4** + Zn^{2+}. Dashed line indicates an arbitrary linear dependence for purposes of reference.

onances attributable to free ligand when [Zn^{2+}] < [**4**]. At equimolar [Zn^{2+}] and above, a sharp symmetrical spectrum is observed: δ 3.00 (t, J = 6 Hz, CH_2CH_2OH), 3.83 (t, J = 6 Hz, CH_2CH_2OH), 7.25 (s, imidazole 4(5)-H. The symmetry of the spectrum indicates either a dynamic intracomplex exchange that averages all three imidazoles, or preferential binding to form one complex in which the three hydroxyethyl groups reside at similar distances from the Zn^{2+}. For the latter possibility, given the



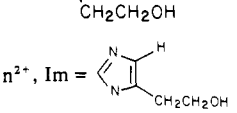
4:Zn^{2+}, Im = 

Table III. Second-Order Catalytic Rate Constants of pNPP Hydrolysis Afforded by **3**, **4**, and Zn^{2+} in H_2O[a,b]

pH	$k_{Zn^{2+}}^{cat.}$, M^{-1} s^{-1}	$k_3^{cat.}$, M^{-1} s^{-1}	$k_4^{cat.}$, M^{-1} s^{-1}
5.6	1.84×10^{-2}	3.8×10^{-2}	2.6×10^{-2}
6.0	3.3×10^{-2}	7.4×10^{-2}	6.0×10^{-2}
6.4	6.0×10^{-2}	1.76×10^{-1}	8.4×10^{-2}
6.8	1.6×10^{-1}	3.9×10^{-1}	2.6×10^{-1}
7.2	4.25×10^{-1}		5.27×10^{-1}
7.6	9.41×10^{-1}	9.9×10^{-1}	8.2×10^{-1}

[a] T = 25.0 °C; 0.3 M buffer; 0.3 M ionic strength; 5×10^{-5} M pNPP. [b] Evaluated as $k_x^{cat.} = [k_{obsd}(\text{with x}) - k_{obsd}(\text{without x})]/[x]$.

downfield shift of the imidazole 4(5)-H and relatively small perturbations of the hydroxyethyl resonances (relative to the uncomplexed ligand), the spectrum likely arises from a complex (**4**:Zn^{2+}) in which the hydroxyethyl groups are located distal to the bound imidazole nitrogens and hence do not interact with the Zn^{2+} to aid in its chelation. This is also substantiated by the similar values for Zn^{2+} binding ability of **4** and **3** (Table I).

Kinetic Studies. (a) 3 and 4. Given in Table II are the k_{obsd} values for pNPP hydrolysis as a function of pH in the absence

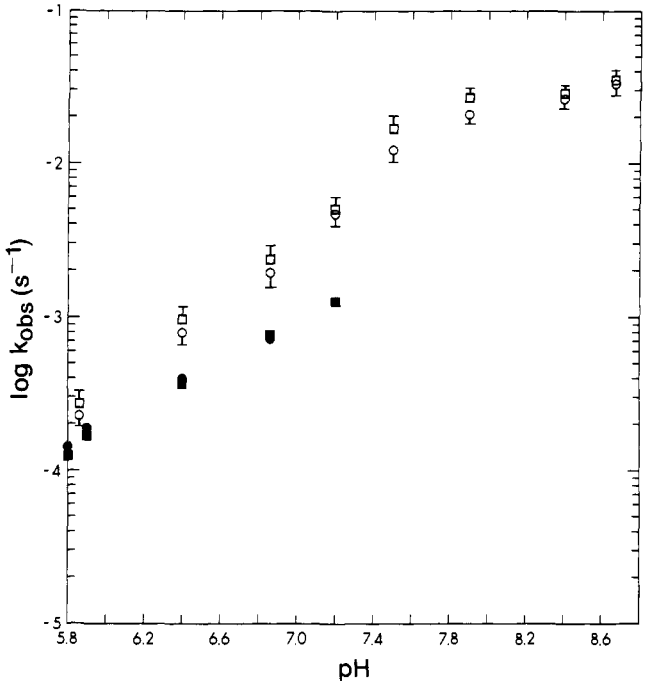


Figure 3. A plot of log k_{obsd} for the hydrolysis of pNPP as a function of pH in the presence of 4.83×10^{-4} M L:M^{2+}: ●:Zn^{2+}; ■, **6**:Zn^{2+}; ○, **5**:Co^{2+}; □, **6**:Co^{2+} (80% ethanol–H_2O).

and presence of Zn^{2+}, **3**, **4**, and equimolar Zn^{2+} and ligand, the latter two sets of data being illustrated in Figure 1. The values have precisions of <5% and are uncorrected for buffer effects that account for some of the scatter as in the lower curve of Figure 1. Each of the ligands, as well as Zn^{2+} alone catalyzes the hydrolysis to an extent that increases as a function of pH. Second-order catalytic rate constants constants for **3**, **4**, and Zn^{2+} alone at each pH are given in Table III. From these data it is clear that the hydrolysis of pNPP at a given pH in the absence of complex can be described by a multitermed rate law as in eq 2, where L = **3** or **4**.

$$\frac{-d[pNPP]}{dt} = k_{obsd}[pNPP] = (k_{blank} + k_{Zn^{2+}}^{cat.}[Zn^{2+}] + k_{L}^{cat.}[L])[pNPP] \quad (2)$$

For Zn^{2+} alone, the increase in activity with pH could involve a Zn^{2+}–OH^- nucleophilic attack or simple Lewis acid coordination of the metal ion to pNPP followed by attack of external OH^-, both processes having ample precedent.[4-7] For this case the data are insufficient to distinguish between the two processes since precipitation of $Zn^{2+}(OH^-)_x$ occurs above pH 7.6. Since they are protonated below pK_{a_3}, the most likely explanation for the pH-dependent catalysis exhibited by **3** and **4** is that the free base is the active species acting either as a general base or nucleophile to promote the hydrolysis of pNPP.

In the presence of equimolar ligand and Zn^{2+} the rate of hydrolysis is accelerated modestly over the situation where one of the components is absent (Table II). Such requires a cooperative interaction between ligand and Zn^{2+} that produces a more active catalyst. However due to the relatively low Zn^{2+} binding constants for these ligands, substantial amounts of uncomplexed materials exist at the concentrations employed. This is most clearly demonstrated by a representative plot of k_{obsd} against [L = Zn^{2+}] at pH 6.8 as shown in Figure 2 that exhibits an upward curvature as is required if increasingly larger proportions of a more active complex are produced at higher [L = Zn^{2+}]. Similar plots of k_{obsd} with [L] or [Zn^{2+}] alone yield straight lines, the slopes of which are the second-order catalytic rate constants for each component.

The weak affinity of the ligands for metal ion complicates the analysis of the data obtained for pNPP hydrolysis in the presence of equimolar ligand and Zn^{2+}, the rate law of which is given in eq 3. An attempted analysis to evaluate $k_{L:Zn^{2+}}^{cat.}$ can however be

Table IV. Values of $k_{L:Zn^{2+}}^{cat.}$ for the Catalyzed Hydrolysis of pNPP[a] in H_2O[b]

pH	$k_{3:Zn^{2+}}^{cat.}$, M^{-1} s^{-1}	$k_{4:Zn^{2+}}^{cat.}$, M^{-1} s^{-1}
6.0	0.287	0.180
6.4	0.343	0.427
6.8	0.753	1.097
7.2	1.27	3.18
7.6	2.58	7.06

[a] T = 25.0 °C, 0.3 M buffer, 0.3 M ionic strength ($NaClO_4$), 5×10^{-5} M pNPP. [b] Error limits expected to be ±30%.

Table V. Observed Pseudo-First-Order Rate Constants for the Hydrolysis of pNPP in 80% Ethanol–H_2O[a]

	k_{obsd}, s^{-1}		
pH	blank[b]	$[Zn^{2+}]$[c]	$[Co^{2+}]$[c]
5.8	4.26×10^{-6}	1.37×10^{-4}	1.89×10^{-4}
5.9	4.23×10^{-6}	2.25×10^{-4}	
6.4	7.27×10^{-6}	5.85×10^{-4}	6.32×10^{-4}
6.85	1.83×10^{-5}	1.26×10^{-3}	1.35×10^{-3}
7.2	1.06×10^{-5}	2.32×10^{-3}	3.50×10^{-3}
7.5	2.18×10^{-4}	*d*	8.82×10^{-3}
7.9	3.32×10^{-4}	*d*	1.13×10^{-2}

[a] 5×10^{-5} M pNPP, T = 26.0 °C; error in k_{obsd} ±5%. [b] Not corrected for buffer catalysis; MES, pH 5.8 and 5.9; MOPS, pH 6.4–7.2; CHES, pH 7.5–7.9 (latter values from ref 8 h). [c] 5×10^{-4} M added $ZnClO_4$ or $CoCl_2$. [d] Precipitates observed.

$$\frac{-d[pNPP]}{dt} = k_{obsd}[pNPP]$$

$$\frac{-d[pNPP]}{dt} = (k_{blank} + k_{L}^{cat.}[L] + k_{Zn^{2+}}^{cat.}[Zn^{2+}] + k_{L:Zn^{2+}}^{cat.}[L:Zn^{2+}])[pNPP] \quad (3)$$

made given the $pK_{Zn^{2+}}$ values for **3** and **4** (Table I) as well as the rate constant data given in Tables II and III. Since the [Zn^{2+}], [L], and [L:Zn^{2+}] can be approximated,[20] the second order catalytic rate constant for L:Zn^{2+} can be calculated as in eq 4 and are presented in Table IV.

$$k_{L:Zn^{2+}}^{cat.} = \frac{k_{obsd} - k_{L}^{cat.}[L] - k_{Zn^{2+}}^{cat.}[Zn^{2+}] - k_{blank}}{[L:Zn^{2+}]} \quad (4)$$

Given the uncertainties in the calculation of the concentrations of the species,[20] as well as the cumulative errors in the rate constants used to evaluate $k_{L}^{cat.}$ and $k_{Zn^{2+}}^{cat.}$, the errors in the values for $k_{L:Zn^{2+}}^{cat.}$ are likely to be substantial.[20b] However even considering the above, two things become apparent. First, the complexes are at a given pH between 2- and 10-fold larger than for Zn^{2+} or ligand alone and increase in a more or less first-order fashion with pH, suggesting that a basic form of the complex is active. The latter might be supported by the slight downward curvature in the plot of k_{obsd} in the presence of equimolar **3** and Zn^{2+} against pH given in Figure 1 which might suggest an ionization of some group associated with the complex. However since there is no substantial difference in the $k_{L:Zn^{2+}}^{cat.}$ values for **3**:Zn^{2+} or **4**:Zn^{2+}, it is clear that the presence of the hydroxyethyl group in the latter complex is of no catalytic advantage.

(b) 5 and 6. Given in Table V are the k_{obsd} values for pNPP

(20) (a) Although the $pK_{M^{2+}}$ values of Table I are conditional upon pH, they serve as a useful guide in assessing the amount of free **3** or **4** and Zn^{2+} as well as the [complex] in the kinetic experiments. Given a $pK_{Zn^{2+}}$ of 3.4 and an initial [**3**] = [Zn^{2+}] = 4.82×10^{-4} M, the [**3**:Zn^{2+}] = 2.01×10^{-4} M. (b) Since the calculation of $k_{L:Zn^{2+}}^{cat.}$ in eq 3 requires four experimentally derived rate constants, the precision of each being ±5%, we estimate that the cumulative errors in the values presented in Table IV should be at least ±30%. However this value may itself be too low, since evaluation of $k_{L:Zn^{2+}}^{cat.}$ requires an accurate assessment of [L], [Zn^{2+}], and [L:Zn^{2+}] under the experimental conditions. This is likely the most serious source of error.

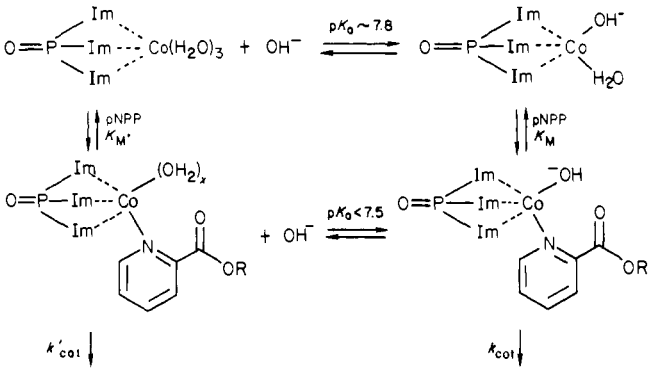
(21) In an attempt to compare the data for **3** and **4** with that for **5** and **6**, the hydrolysis of pNPP catalyzed by 4:Zn^{2+} was investigated in 80% ethanol–H_2O. Unfortunately at pH 6.4–7.2, the kinetic traces monitored at 315 or 288 nm were clearly biphasic. In all cases, precipitates of an undetermined nature were formed that precluded analysis of the kinetics.

Table VI. Observed Pseudo-First-Order Rate Constants for pNPP Hydrolysis in the Presence of 4.83×10^{-4} M L:M^{2+} [a]

	k_{obsd},[b] s^{-1}			
pH	**5**:Zn^{2+}	**5**:Co^{2+}	**6**:Zn^{2+}	**6**:Co^{2+}
5.8	1.40×10^{-4}	2.27×10^{-4}	1.26×10^{-4}	2.72×10^{-4}
5.9	1.90×10^{-4}		1.79×10^{-4}	
6.4	3.95×10^{-4}	8.04×10^{-4}	3.81×10^{-4}	9.92×10^{-4}
6.85	7.33×10^{-4}	1.92×10^{-3}	7.45×10^{-4}	2.34×10^{-3}
7.2		4.75×10^{-3}	1.27×10^{-3}	4.90×10^{-3}
7.5		1.28×10^{-2}		1.76×10^{-2}
7.9		2.07×10^{-2}		2.68×10^{-2}
8.4		2.67×10^{-2}		2.75×10^{-2}
8.63		3.34×10^{-2}		3.47×10^{-2}

[a] 5×10^{-5} M pNPP; T = 26.0 °C; 80% ethanol–H_2O. [b] Error in k_{obsd} ± 5%.

Scheme I[8h]



hydrolysis as a function of pH under various conditions. Since the medium of 80% ethanol–H_2O required for ligand solubility is different from that used for the study of **3** and **4**, comparison of the two sets of data is not possible.[21] Since we are primarily interested in rate differences afforded by the complexes, the values of k_{obsd} presented in Table V are not corrected for buffer catalysis.

Neither **5** nor **6** affords any enhancement in rate at concentrations of 5×10^{-4} M; however, Zn^{2+} or Co^{2+} at the same concentrations afford about 100-fold acceleration over the blank rates. Zn^{2+} is insoluble above pH 7.2, while Co^{2+} remains in solution to pH 7.9.

In Table VI are the k_{obsd} values in the presence of 5×10^{-4} M each of **5** or **6** and M^{2+}. Since in this medium both ligands have a high affinity for M^{2+}, the complexes are essentially completely formed.[19] Thus analysis of the data in Table VI is not complicated by the presence of signficant quantities of uncomplexed M^{2+} ion and the increase in k_{obsd} over that of the blank reactions can be attributed to the catalysis afforded by the complex. Due to the formation of precipitates, the L:Zn^{2+} complexes could only be studied at pHs <7.2. Apparently there is no difference in activity between **5**:Zn^{2+} and **6**:Zn^{2+}, and in fact both are slightly less active than Zn^{2+} alone. It appears that the activities of these complexes increase with [OH^-] although from the downward curvature not in a first-order way. Whether this is due to the formation of invisible Zn^{2+} aggregates that decrease the total [Zn^{2+}] or to an ionization of the complex to a basic form is uncertain due to the limited pH range available.

Because of increased solubility, the Co^{2+} complexes could be studied over a much wider range. Below pH 7.4, the catalyzed k_{obsd} values increase with a first-order dependence on [OH^-], but at higher values tend to level off, indicating the formation of a catalytically active basic form having a pK_a of ~7.6–7.8. This coincides nicely with the trimetric pK_a for **5**:Co^{2+} or **6**:Co^{2+} of ~7.7. The most likely candidate for the active form is a complexed Co^{2+}–OH^- as in eq 5 that at a given pH is only modestly

$$L{:}Co^{2+}(H_2O)_x + OH^- \rightleftharpoons L{:}Co^{2+}(H_2O)_yOH^- \quad (5)$$

more active than uncomplexed Co^{2+}, judging by comparison of the k_{obsd} values in Tables V and VI. The main virtue of the ligand therefore is to hold the metal ion in solution at higher pH values, probably by restricting the number of available Co^{2+} sites available to OH^-[22] which reduces the tendency to aggregate as $Co^{2+}(OH^-)_x$. A similar phenomenon is seen with the Co^{2+} complex of phosphine oxide **1** that remains in solution up to at least pH 9.[8h]

Earlier studies with **1**:Co^{2+} indicated that the process by which it facilitated the hydrolysis of pNPP involved preequilibrium formation of a ternary **1**:Co^{2+}:pNPP complex that then suffered rate limiting hydrolysis according to Scheme I.[8h] Analysis of that data showed that the maximal $k_{cat.}$ at pH 8.7 for the ternary complex ($k_{cat.}^{max} = k_{cat.} + k'_{cat.}$) = 3.0×10^{-2} s^{-1} while the Michaelis constant ($K_{M_{tot}} = K'_M + K_M$) = 1.0×10^{-3} M.[8h]

In order to ascertain whether a similar situation obtains with **5**:Co^{2+} and **6**:Co^{2+}, a series of experiments were conducted at pH 6.85 and 7.9 by varying the [L:Co^{2+}] from 2.5×10^{-4} to 33×10^{-4} M, the [pNPP] being 5×10^{-5} M. No evidence of a saturation phenomenon is seen at these concentrations of the complexes since a linear dependence of k_{obsd} vs. [L:Co^{2+}] is observed, the slope of which could be used to define $k_{L:Co^{2+}}^{cat.}$, the second-order catalytic rate constant for the complex. These values are given in Table VII and show clearly a first-order dependence on [OH^-] below pH 7.5 and a levelling off at higher pH. The lack of an observed saturation behavior for the complexes does not necessarily mean a ternary complex is not formed, but only that if it is formed, the K_M value must be ~10^{-2} M or greater. Alternatively, the data can be analyzed in terms of a basic form of the complex acting as a bimolecular nucleophile. Since there is no substantial difference in activity between **5**:Co^{2+} and **6**:Co^{2+}, it is clear that the hydroxyethyl group in the latter complex is of no catalytic benefit in the hydrolysis of pNPP.

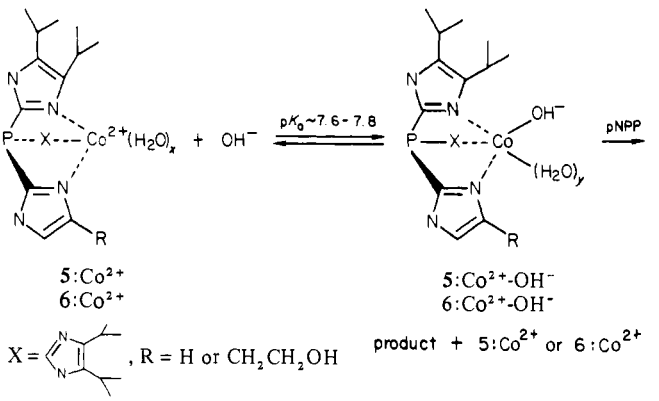
Throughout the above discussion we have contended that the complexes are true turnover catalysts. However since the k_{obsd} values have been determined under conditions where [L:M^{2+}] > 10[pNPP], the possibility that a given molecule of catalyst is being destroyed as it hydrolyses pNPP is not ruled out. Such was observed in the case of the Co^{2+} complex of the more weakly

Table VII. $k_{L:Co^{2+}}^{cat.}$ as a Function of pH for the Hydrolysis of pNPP[a]

	$k_{L:Co^{2+}}^{cat.}$,[b] M^{-1} s^{-1}	
pH	**5**:Co^{2+}	**6**:Co^{2+}
5.8	0.46	0.55
6.4	1.65	2.04
6.85	3.93	4.8
7.2	9.8	10.1
7.5	26.1	36.0
7.9	42.2	54.9
8.4	54	55.8
8.63	67.5	70.2

[a] T = 28.0 °C; 80% ethanol–H_2O; [pNPP] = 5×10^{-4} M; [complex] 4.83×10^{-4} M. [b] $k_2^{cat.} = (k_{obsd}(\text{with complex}) - k_{obsd}(\text{blank}))/[\text{complex}]$; values ±5%.

Scheme II



(22) From the visible absorption spectra of **5**:Co^{2+} or **6**:Co^{2+} throughout the pH range studied, no evidence for the formation of low coordinate tetrahedral Co^{2+} is observed. Given one coordination position occupied by OH^- and two or three by the ligand, there must be two or three additional sites occupied by H_2O or some other species from the solution. For a more complete description of the Co^{2+} visible absorption spectra of **5** and **6** see ref 8i.

binding phosphine oxide **1**[8h] since picolinate, the product of hydrolysis, was observed to strongly chelate the metal. Experiments conducted with 4.82×10^{-4} M **5**:Co^{2+} or **6**:Co^{2+} as a function of increasing [pNPP] from 4.83×10^{-4} to 2.2×10^{-3} M at pH 6.85 showed no difference in the k_{obsd} values for hydrolysis. Thus it is clear that the complexes are indeed turnover catalysts and function as in Scheme II.

Conclusion

Tris(imidazole)-containing phosphines such as **3** or **4** when compared to Zn^{2+} provide modest catalysts for the hydrolysis of pNPP. They are from 2 to 10 times more active than either ligand alone or Zn^{2+} alone, and their catalytic activity increases as a function of pH. Because of the weak M^{2+} affinity neither ligand is completely complexed at the concentrations employed which complicates the kinetic analysis since free ligand and Zn^{2+} exist in the solution.

Ligands **5** and **6** bind M^{2+} more strongly and their complexes are nearly fully formed in 80% ethanol-H_2O at concentrations of $\sim 5 \times 10^{-4}$ M. While the Zn^{2+} complexes cannot be studied at pH's in excess of 7.2 due to precipitation, the Co^{2+} complexes remain in solution up to pH 8.6. Uncomplexed Co^{2+} precipitates above pH 7.9. **5**:Co^{2+} and **6**:Co^{2+} show evidence of a titration phenomenon having a pK_a of ~ 7.6-7.8, the basic form of the complex being catalytically active. Since the Co^{2+} complexes have about the same $k_2^{cat.}$ values as uncomplexed Co^{2+} (at pHs below that where uncomplexed Co^{2+} precipitates from solution), the major virtue of the complexes is to hold the metal ion in solution at higher pH. Apparently the complexes act as bimolecular nucleophiles with the Co^{2+}-OH^- nucleophilically attacking pNPP, but the hydroxyethyl group in **6**:Co^{2+} is not of any catalytic benefit in the hydrolysis of this ester.

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Registry No. 2, 24690-42-4; **3**, 74483-06-0; **4**, 91084-07-0; **5**, 89210-50-4; **6**, 89210-51-5; 4(5)-(hydroxyethyl)imidazole ethoxyamide acetal, 84802-87-9.

Photochemistry of Phenyl Azide: Chemical Properties of the Transient Intermediates

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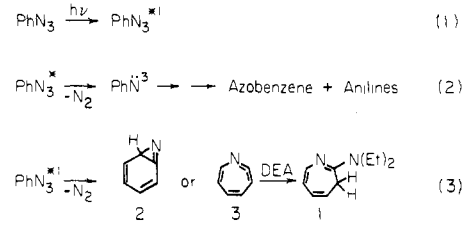
Abstract: The photochemistry of phenyl azide was examined by laser-flash photolysis in inert and reactive (nucleophilic) solvents. Direct irradiation and triplet sensitization give triplet phenylnitrene (PhN^3). The products of the reaction of PhN^3 depend dramatically on the concentration of the azide and on the power of the light source. In the direct irradiation, a relatively long-lived precursor to PhN^3 is formed. This singlet-state intermediate reacts with the nucleophilic solvents. The structure of this species and the rates of its reaction with secondary amines are discussed.

The photochemical and thermal reactions of aryl azides have been studied for over 60 years.[1] Despite this long history there are still many important details of these reactions that are incompletely understood. In this paper we report the results of our investigation of the photolysis of phenyl azide (PhN_3). The accompanying paper contains[2] a report on the investigation of some polynuclear aromatic azides.

The photochemistry of aromatic azides has gained considerable attention due to the utility of these compounds in photoimaging systems[3] and as photoaffinity labels.[4] Both applications take advantage of the unusually high reactivity of short-lived intermediates formed when these azides are irradiated with ultraviolet light. Our objective is to identify the structure of these intermediates and to characterize their chemical and physical properties.

Scheme I



Thermolysis or photolysis of phenyl azide in an inert solvent, such as benzene or acetonitrile, is reported by different investigators to give either intractable "tars" and a low yield (4%) of azobenzene[5] or, at sufficiently low conversion, exclusively azo-

(1) The subject has been reviewed periodically: (a) Abramovitch, R. A.; Davis, B. A. *Chem. Rev.* **1964**, *64*, 149. (b) Abramovitch, R. A.; Kyba, E. P. "The Chemistry of the Azido Group"; Patai, S., Ed.; Wiley: New York, 1971, p 256 (c) Iddon, B.; Meth-Cohn, O.; Scriven, E. F. V.; Suschitzky, H.; Gallagher, P. T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 900. (d) Boyer, J. H. In "Mechanisms of Molecular Migrations"; Thyagarajan, B. S., Ed.; Wiley: New York, 1969; Vol. 2, p 296. (e) Smith, P. A. S. In "Nitrenes"; Lwowski, W., Ed.; Wiley: New York, 1970. (f) Brown, R. F. C. "Pyrolytic Methods in Organic Chemistry"; Academic Press: New York, 1980. (g) Lwowski, W. In "Reactive Intermediates"; Jones, M, Jr., Moss, R. A., Eds.; Wiley: New York, 1981; Vol. 1 and 2. (h) Wentrup, C. *Adv. Heterocycl. Chem.* **1981**, *28*, 279. (i) Smith, P. A. S. "Open-Chain Organic Nitrogen Compounds: Derivatives of Hydrazine and Other Hydronitrogens Having N-N Bonds"; Benjamin-Cummings: New York, 1982. (j) Scriven, E. F. V. In "Reactive Intermediates"; Abramovitch, R. A., Ed.; Plenum Press: New York, 1982. (k) Reiser, A.; Wagner, H. M. In "The Chemistry of the Azido Group"; Patai, S., Ed.; Interscience: New York, 1971.

(2) Following paper in this issue.

(3) Suga, K.; Watanabe, S. *Isr. J. Chem.* **1969**, *6*, 521. Tsunoda, T.; Tamaoka, T.; Osabe, Y.; Hata, Y. *Photogr. Sci. Eng.* **1976**, *20*, 188.

(4) Bayley, H. In "Laboratory Techniques in Biochemistry and Molecular Biology"; Work and Burdon Eds.; Elsevier: Amsterdam 1983. Knowles, J. R. *Acc. Chem. Res.* **1972**, *5*, 155. Bayley, H.; Knowles, J. R. In "Advances in Enzymology" Jakoby, W. B., Ed.; Academic Press: New York, 1977; Vol. 46. Chowdhry, V.; Westheimer, F. H. Annu. *Rev. Biochem.* **1979**, *48*, 293.

(5) (a) Horner, L.; Christman, A. *Chem. Ber.* **1963**, *96*, 399. (b) Abramovitch, R. A.; Challand, S. R. *J. Chem. Soc., Chem. Commun.* **1972**, *964*. (c) DeGraff, B. A.; Gillespie, D. W.; Sundberg, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 7491.

0002-7863/84/1506-5228$01.50/0