NH_3, and cyclohexylimine, since only the imine can be readily explained by radical attack on the parent amine.

$$2C_6H_{11}NH_2 + 2HN \longrightarrow C_6H_{11}NHNH_2 + C_6H_{10}NH + NH_3$$

The difference in chemical behavior between the two azide salts may be ascribed to the difference in structure and ease of diffusion through the crystal lattice of the two initially formed radicals, amino and cyclohexylamino, and the corresponding bases. The large and structurally complex cyclohexylamino radical results in stable products, such as imine and cyclohexyl-substituted hydrazines, while surfacing. Heterogeneous reaction depends upon the ability of survival or regeneration of reactive species, like the amino radical, within the solid azide such that they can finally diffuse to the surface and react.

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An Unusual Rate Enhancement in Metal Ion Catalysis of Phosphate Transfer

Sir:

Although divalent metal ions are required as cofactors in many enzyme-catalyzed phosphate transfer reactions,[1] the structural constraints necessary for catalytically active metal ion–substrate complexes remain largely undefined so that efforts to create suitable models have been unproductive. We wish to report a model reaction in which a dramatic rate acceleration has been observed.

The pH–rate profile for the hydrolysis of 2-(4(5)-imidazolyl)phenyl phosphate (I) in the presence and absence of Cu^{2+} is shown in Figure 1. At pH 6, Cu^{2+} at a $[Cu^{2+}]$:[substrate] ≅ 2 leads to an acceleration of $>10^4$ compared to the noncatalyzed reaction. This may be compared to the metal ion effects observed in the hydrolysis of salicyl phosphate[2] at a metal ion–ester ratio of unity, which finds Cu^{2+} increasing k_{obsd} sevenfold at pH 5.1, and VO^{4+} increasing k_{obsd} 28-fold at pH 4.5. A more analogous system, 2-pyridylmethyl phosphate,[3] finds Cu^{2+} leading to an 18-fold rate acceleration at pH 4.93 ($[Cu^{2+}]$:[substrate] = 1).

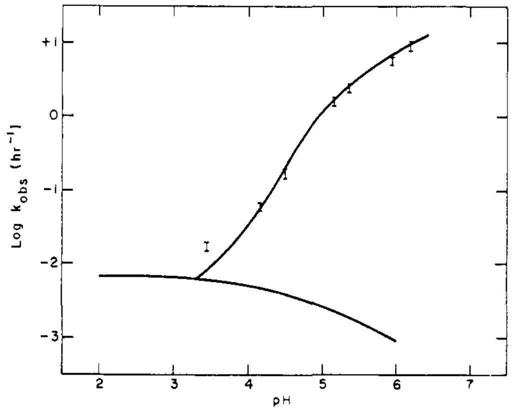

Figure 1. The pH–rate profiles for the spontaneous and Cu^{2+}-catalyzed (I) hydrolysis of 2-(4(5)-imidazolyl)phenyl phosphate; conditions: Cu_{total} (3.8×10^{-4} *M*), substrate (2.0×10^{-4} *M*), 55°, $\mu = 0.2$.

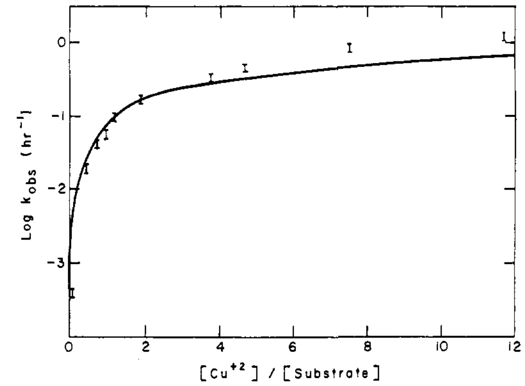

Figure 2. Log k_{obsd} *vs.* $[Cu^{2+}]$/[2-(4(5)-imidazolyl)phenyl phosphate] at 35°, pH 5.37, $\mu = 0.2$; substrate = 2.0×10^{-4} *M*.

The noncatalyzed reaction of I proceeds *via* pseudo-first-order kinetics, with concomitant formation of inorganic phosphate and 4-(2′-hydroxyphenyl)imidazole. This reaction, like those of most simple phosphate monoesters, is presumed to proceed through expulsion of a highly reactive monomeric metaphosphate species, which is quickly solvated.[4] The observed rate of hydrolysis of the monoanionic form of I is identical with that predicted by a structure–reactivity correlation for a series of phosphate monoester monoanions (based on a $pK_a = 8.62$ for a phenolic leaving group ortho to an imidazolium ion[5]). Thus, the noncatalyzed hydrolysis appears to be "normal," and not subject to any unusual steric or electronic effects.

The influence of Cu^{2+} on the observed hydrolytic rate of I increases with conversion of both the imidazolyl and phosphoryl moieties to their free base forms ($pK_{IM} = 5.8$; pK_{a_2} phosphate = 6.6) but decreases with the dissociation of $Cu(H_2O)_6{}^{2+}$ to $Cu(H_2O)_5OH^+$ ($pK_a \cong 5.0$). The theoretical curve of Figure 1 is generated from eq 1 where

$$v = k'[Cu(H_2O)_6{}^{2+}][I^{2-}] \tag{1}$$

with $k' = 1.4 \pm 1.0 \times 10^6\ M^{-1}\ hr^{-1}$. A plot of log k_{obsd} *vs.* $[Cu^{2+}]$:[substrate] is shown in Figure 2. The theoretical curve is calculated from eq 2 based on a scheme assuming preequilibrium formation of a reactive 1:1 ester–metal ion complex. Given the scheme

$$Cu^{2+} + I \overset{K}{\rightleftharpoons} Cu\text{-}I \xrightarrow{k_r} \text{products}$$

it can be shown that

$$k_{obsd} = \frac{Kk_rCu_T}{(Cu_TK + 1) + E_TK(1 - k_{obsd}/k_r)} \tag{2}$$

where Cu_T and E_T are the initial stoichiometric quantities and the terms K and k_r are valued at $4.2 \pm 0.4 \times 10^2\ M^{-1}$ and $1.25 \pm 0.25\ hr^{-1}$, respectively. Deviation at higher metal ion:substrate ratios is attributed to the

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[1] T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. II, W. A. Benjamin, New York, N. Y., 1966, Chapter 5.

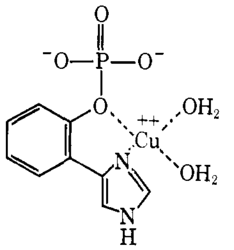
[2] R. Hofstetter, Y. Murakami, G. Mont, and A. E. Martell, *J. Amer. Chem. Soc.*, **84**, 3041 (1962).

[3] Y. Murakami and M. Takagi, *ibid.*, **91**, 5130 (1969).

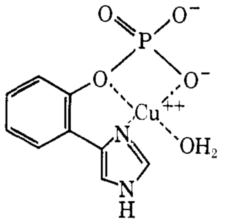
[4] A. J. Kirby and A. G. Varvoglis, *ibid.*, **89**, 415 (1967).

[5] S. J. Benkovic and L. K. Dunikoski, Jr., *Biochemistry*, **9**, 1390 (1970).

formation of additional higher order complexes in Cu^{2+}. These facts suggest that the transition state in the Cu(II)-promoted hydrolysis of I may be formulated as either **1** or **2**.



1



2

In **1**, the metal ion acts as a more effective acid catalyst than a proton, lowering the pK_a of the leaving group so that facile hydrolysis of the dianion—generally encountered only with leaving groups of $pK_a < 7$—may be observed. In **2** the Cu^{2+} may also serve to induce strain in the P–O bond and/or partially neutralize charge on the phosphate, leading to a nucleophilic displacement by solvent on phosphorus. It also is noted that hydrolysis of **2** *via* nucleophilic attack by water is kinetically indistinguishable from hydroxide attack on the monoanion of I. These second possibilities recall the rate accelerations of 10^5–10^7 encountered in strained five-membered cyclic phosphates and the 3200-fold enhancement in Cu^{2+}-catalyzed glycine ethyl ester hydrolysis, presumably owing to an increased susceptibility to nucleophilic attack as a result of chelation.

Solvolysis of I in mixed methanol–water solvents in the presence of Cu^{2+} displayed an identical methyl phosphate–inorganic phosphate product ratio with that observed in the uncatalyzed reaction, indicating no change of metaphosphate activity. This finding also rules against a possible phosphoramidate intermediate. If **2** or its kinetic equivalent represents the reaction pathway then one might have predicted a greater amount of methyl phosphate product owing to the more favorable susceptibility of **2** to nucleophilic attack on phosphorus. Further it might be expected that hydrolysis *via* **2** may proceed through preequilibrium formation of a pentacovalent phosphorus structure which would result in exchange between solvent and phosphoryl oxygens. When the hydrolysis of I in the presence of Cu^{2+} was conducted in $H_2{}^{18}O$-enriched water, no evidence of ^{18}O incorporation was observed. Thus it appears reasonable to argue that the Cu^{2+} ion in this reaction is acting simply as an acid catalyst. Analysis of the structure–reactivity relationship for phosphate esters[4] indicates that in order to account for the rate acceleration observed in this reaction, Cu^{2+} would have to lower the pK_a of the leaving group to $pK_a \approx 2$, a change of 6 pK_a units.

The results of this work indicate two important factors which should be considered in the design of future model systems: the requirement for a rigid structural geometry, and the binding of the metal ion to the alcohol leaving group. Compounds such as phenyl phosphate, which have no metal ion binding site other than the phosphate moiety, may show a retarded hydrolytic rate in the presence of metal ions; this is presumably due to binding of the phosphoryl oxygen, making metaphosphate expulsion less likely.

In compound I the juxtaposition of an excellent second binding site (imidazolyl nitrogen) promotes Cu^{2+} interaction with the ether rather than phosphoryl oxygens. The planar relationship between the chelating ligands, furthermore, favors formation of a typical Cu^{2+} square planar complex. The overall result is to confer hydrolytic ability on the normally nonreactive phosphate monoester dianion.

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Photolysis of Diazomethane in Tetrachloromethane. An Abstraction Reaction of Singlet Methylene

Sir:

In this communication we present evidence based on nuclear polarization studies that the singlet state of methylene is involved in *insertion* reactions into, and *abstraction* reactions from, tetrachloromethane.

Urry and Eiszner discovered the remarkable photoreaction of diazomethane in tetrachloromethane, which affords pentaerythrityl tetrachloride (**4**).[1a] This product arises from the reaction of one molecule of tetrachloromethane with four molecules of diazomethane, despite the large excess of tetrachloromethane. The high percentage yield of **4**, the high quantum yield of the consumption of diazomethane,[1b] and analogous reactions of diazomethane with other polyhalomethanes[1c,d] were accommodated in the free-radical chain mechanism outlined in Scheme I.[1b] The important features of this mechanism are (a) that photochemically generated methylene[2] abstracts a chlorine atom from the solvent to start the chain, (b) that intermediate α-chloro radicals, *i.e.*, A′, B′, and C′, are stable to the extent that they do not readily abstract chlorine atoms from the solvent, but still readily induce the decomposition of diazomethane (Scheme I, diagonal arrows), (c) that the intramolecular chlorine migration in β,γ-chloro radical intermediates A, B, and C (Scheme I, horizontal arrows) is considerably faster than any intermolecular reaction of these radicals, and (d) that D, an unstable primary radical without a chlorine atom in the β position, abstracts a chlorine atom from the abundant solvent. A more detailed insight into this reaction can be expected from utilizing the recent observation[5,6] that radical reactions may afford products with polarized nuclear spins (CIDNP effect), whose nmr spectra exhibit signals in emission (E) or enhanced absorption (A). This technique may allow one to detect products

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(1) (a) W. H. Urry and J. R. Eiszner, *J. Amer. Chem. Soc.*, **73**, 2977 (1951); (b) W. H. Urry, J. R. Eiszner, and J. W. Wilt, *ibid.*, **79**, 918 (1957); (c) W. H. Urry and N. Bilow, *ibid.*, **86**, 1815 (1964); (d) N. Bilow, Ph.D. Dissertation, University of Chicago, 1956.

(2) Following a suggestion in the literature[3] the term "methylene" is employed to indicate that the divalent carbon intermediate, $:CH_2$, has a triplet ground state.[4]

(3) (a) R. M. Etter, H. S. Skovronek, and P. S. Skell, *J. Amer. Chem. Soc.*, **81**, 1008 (1959); (b) A. M. Trozzolo, R. W. Murray, and E. Wasserman, *ibid.*, **84**, 4990 (1962).

(4) *Cf.* (a) R. A. Bernheim, W. H. Bernhard, P. S. Wang, L. S. Wood, and P. S. Skell, *J. Chem. Phys.*, **53**, 1280 (1970); (b) E. Wasserman, W. A. Yager, and V. J. Kuck, *Chem. Phys. Lett.*, **7**, 409 (1970).

(5) (a) J. Bargon, H. Fischer, and U. Johnson, *Z. Naturforsch. A*, **22**, 1551 (1967); (b) J. Bargon and H. Fischer, *ibid.*, *A*, **22**, 1556 (1967).

(6) (a) H. R. Ward and R. G. Lawler, *J. Amer. Chem. Soc.*, **89**, 5518 (1967); (b) R. G. Lawler, *ibid.*, **89**, 5519 (1967).