from the same excited state of the *s*-cis conformer.

Although nonsynchronous pathways of this type, which might be expected to occur around this conical intersection of surfaces, have been suggested for cyclobutene formation,[30,49] these studies have not taken the next step of combining the closure with double bond isomerization.[50] According to a potential surface of the type suggested, the relative yields of double bond isomerization and cyclobutene formation would be determined by the dynamics of the surface at the point where the two pathways diverge rather than by the presence of a barrier. Note also that the barrierless nonsynchronous closure pathway may be preferred even if there is no barrier to the synchronous closure, because again presumably the surface dynamics will determine the route along the surface that an excited molecule would take. Most importantly, this combined surface also suggests that the cyclobutene formation–double bond isomerization partitioning of an *s*-cis acyclic 1,3-diene would be strongly influenced by the stability of the zwitterionic excited state produced from the *s*-cis conformer. Further work on low-temperature photochemistry of 1,3-dienes is being carried out to investigate this supposition.

Summary

We have shown that the thermal chemistry of double bond rotation of 2,3-dimethyl-1,3-butadiene is similar to that of 1,3-butadiene in that two mechanisms exist: a cyclobutene closure and reopening mechanism with a barrier of 48 kcal/mol and a pathway via an allylmethylene biradical with a barrier of 55 kcal/mol. Both of these barriers are slightly higher than those of the parent compound, 1,3-butadiene.[35]

We have shown that several acyclic 1,3-dienes photochemically close at low temperatures despite a predicted barrier to the synchronous disrotatory closure on the excited-state surface. A dideuterio derivative of 2,3-dimethyl-1,3-butadiene was used to show that the *s*-cis conformer undergoes both major photochemical events, double bond isomerization and electrocyclic closure in roughly a 3:1 ratio. An excited-state potential surface was described that combines these two processes and allows a nonsynchronous disrotatory closure pathway. This surface suggests that the electrocyclic closure–double bond isomerization ratio from the *s*-cis conformer of an acyclic diene may depend greatly upon the energy of the allylmethylene excited state.

Divalent Metal Ion Catalyzed Reactions of Acyl Phosphates

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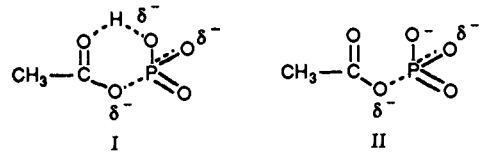
Abstract: The hydrolysis of the acyl phosphate, 1,10-phenanthroline-2-carbonyl phosphate, proceeds with a hydroxide ion catalyzed reaction of the dianionic species at high pH, a pH-independent reaction of that species in the pH range 7–10, and a reaction of the zwitterionic species (protonated phenanthroline nitrogen) at pH < 6 (pK_{app} = 5.6). The divalent metal ions Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} have a large effect on the rate of hydrolysis. At saturating concentrations of Ni^{2+}, Co^{2+}, and Zn^{2+} (0.003 M, 50-fold excess over the acyl phosphate), hydroxide ion catalyzed reactions occur that are $>10^7$-fold more favorable at 30 °C than in the absence of the metal ions. Likewise, Mg^{2+} exerts a sizable catalytic effect ($>10^4$), although binding is considerably weaker than with the other metal ions (saturation only occurs at Mg^{2+} concentrations greater than 0.1 M). The cupric ion promoted OH^--catalyzed reaction at 30 °C (0.002 M Cu^{2+}) is (5×10^{10})-fold more favorable than OH^- catalysis in the absence of the metal ion. At pH < 4 a Cu(II)-promoted pH-independent reaction takes place that has a ΔS^* of −34.3 eu. Incorporation of ^{18}O into the carboxylic acid product when the hydrolytic reactions were carried out in ^{18}O-enriched water showed conclusively that C–O bond breaking occurs in the metal ion promoted hydroxide ion and pH-independent processes. Both imidazole and pyridine are catalysts in the hydrolysis of the acyl phosphate, and the imidazole-catalyzed reaction is markedly enhanced by a saturating concentration of Ni^{2+}. The effect of the metal ion is much smaller in the reaction with pyridine; the second-order rate constant for the pyridine reaction is only increased 3-fold by the presence of a saturating concentration of Ni^{2+}. Thus, the strongly chelated metal ions greatly facilitate nucleophilic reactions that occur at the carbonyl carbon of the acyl phosphate rather than metaphosphate elimination or nucleophilic attack at phosphorus.

Acyl phosphates are phosphoric acid derivatives of considerable biological importance.[2] The hydrolysis reactions of acetyl phosphate have been extensively investigated.[3-6] Evidence was presented by Di Sabato and Jencks[6] in support of an elimination mechanism in both monoanion (I) and dianion (II) hydrolysis in



I

II

which P–O bond breaking gives a hypothetical metaphosphate intermediate. Such an intermediate had been previously suggested in the hydrolysis of alkyl and aryl phosphomonoesters,[3,7,8] but there is no evidence that free metaphosphate is formed in aqueous solution.[9-11] At high pH, an OH^--catalyzed reaction occurs with C–O bond breaking in the hydrolysis of acetyl phosphate.[4,5]

Metal ions (Mg^{2+}, Ca^{2+}, and Li^+)[3,4,12] were found to have only a small effect in the reactions of acetyl phosphate, as might be expected in the absence of an additional liganding group. The small effects at high metal ion concentrations have precluded

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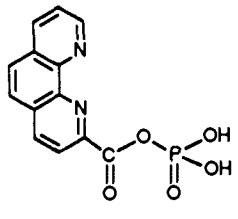
detailed mechanistic studies, but there appears to be a contribution from a metal ion promoted OH^--catalyzed pathway at high pH.[12] The exchange inert $[Co(NH_3)_5OPO_3COMe^+]$ has been prepared,[13] and ^{18}O studies established that the apparent OH^--catalyzed reaction proceeds with C–O bond cleavage. However, the second-order rate constant for that reaction is surprisingly small (k_{OH} = 0.53 M^{-1} s^{-1} at 25 °C, μ = 1.0 M). Divalent metal ions, especially Cu^{2+}, provide large rate enhancements in the hydrolysis of other types of phosphomonoester dianions when there are also chelating functional groups in the molecule.[14-17] Divalent metal ions will also effectively catalyze the hydrolysis of carboxylate esters[18-24] and anhydrides[25] via metal ion promoted OH^-- and water-catalyzed pathways. However, there have been no previous studies of the hydrolysis of acyl phosphates having chelating functional groups that would permit assessment of the effects of strongly bound metal ions. A number of phosphokinase and phosphatase enzymes are metalloenzymes or metal ion activated enzymes.[26] Acyl phosphates have been shown to be efficient substrates for alkaline phosphatase,[27] an enzyme which has an essential zinc ion in its active site.[28] Consequently, it is important to determine the manner and extent of the effect of strongly bound metal ions on the hydrolysis of acyl phosphates. We have therefore studied the hydrolysis reactions of the acyl phosphate 1,10-phenanthroline-2-carbonyl phosphate (PCOP) in the presence of divalent metal ions (Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+}, Mg^{2+}, and Ca^{2+}).



PCOP

Experimental Section

Materials. 1,10-Phenanthroline-2-carbonyl Phosphate Hydrochloride. 1,10-Phenanthroline-2-carboxylic acid, mp 209 °C (lit.[29] mp 209–210 °C), was prepared by the method of Corey et al.[29] Its acid chloride hydrochloride was prepared by the method of Sigman et al.[30] The acid chloride was dissolved in excess orthophosphoric acid (85%). This solution was stirred at room temperature and then heated at 100 °C in the dark under nitrogen. The solution was then concentrated under reduced pressure, and the residue was taken up in hot benzene. Crystallization occurred when the mixture was allowed to stand. The material melted at 239–240 °C. Anal. Calcd for $C_{13}H_{10}N_2O_5ClP$: C, 45.82; H, 2.96; N, 8.22. Found: C, 45.94; H, 3.12; N, 8.17. ^{31}P NMR spectra were obtained at 81 MHz by use of a Varian VXR-200 spectrometer equipped with a broad-band probe. D_2O was employed as both the solvent and the internal lock. A single sharp peak was observed due to phosphorus. The chemical shift in reference to external 85% H_3PO_4 is −8.1 ppm.

The acyl phosphate hydrochloride salt was analyzed for the phosphate content with an automated phosphate analyzer,[31] which dry ashes phosphate-containing compounds and determines the inorganic phosphate as the molybdenum blue product. The results were recorded on a Shimadzu CR3A integrating recorder. KH_2PO_4 was used as the external standard. Samples containing 25 μmol of the acyl phosphate or the standard were injected into the instrument, and the integrated peak areas were obtained. Inorganic phosphate (1 equiv) was produced from the acyl phosphate (1 equiv).

All buffer components were reagent grade. Amine buffer components were either recrystallized or freshly distilled prior to use. Reagent grade perchlorate salts of Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} from Alpha Products and reagent grade nitrate and chloride salts of Mg^{2+} and Ca^{2+} were employed in the kinetic studies.

Kinetic Methods. The rates of hydrolysis of 1,10-phenanthroline-2-carbonyl phosphate in H_2O were measured spectrophotometrically with a Pye-Unicam SP8-100 recording spectrophotometer by following the absorbance increase at 320 nm due to the appearance of the product (1,10-phenanthroline-2-carboxylic acid or its metal ion complex). The product spectra were quantitatively identical with those of equivalent concentrations of 1,10-phenanthroline-2-carboxylic acid under the same conditions. To initiate a kinetic run 20 μL of an absolute ethanol substrate stock solution containing 9 × 10^{-3} M PCOP was injected into 3 mL of the reaction solution maintained at the desired temperature. A Durrum D-110 stopped-flow spectrophotometer was employed to monitor the Cu(II)-promoted reactions at pH > 5. The reactions followed good pseudo-first-order kinetics for at least 4 half-lives. The values of k_{obsd}, the pseudo-first-order rate constant, were calculated by using a least-squares computer program. The rate constants had an average reproducibility of within 2–3%. Reaction mixture pH values were measured with a Beckman Model 3500 pH meter at the temperature of the kinetic measurements.

The ionic strength was 0.6 M, maintained with KCl, and the solutions used for the studies in the absence of metal ions contained 2 × 10^{-4} M EDTA as a precaution against trace metal ions in the buffer or salt. No corrections were made for buffer–metal ion complexation. In the pH range 1–3, HCl solutions were employed. The buffers employed in kinetic studies were formate (pH 3.2–4.5), acetate (pH 4.2–5.3), pyridine (pH 4.0–5.5), cacodylate (pH 5.5–6.5), 2,6-lutidine (pH 5.2–6.5), *N*-ethylmorpholine (pH 6.6–8.4), morpholine (pH 8.0–9.0), and carbonate (pH > 9). The values of k_{obsd} were obtained by extrapolation to zero buffer concentration or in 0.02 M buffer in cases in which the buffer does not have an experimentally significant catalytic effect. In calculating the second-order rate constants for hydroxide ion catalysis, k_{OH}, the K_w values were taken to be 1.47 × 10^{-14} at 30 °C and 3.02 × 10^{-13} at 85 °C.

Hydrolysis reactions were also run in 1.83% ^{18}O-enriched water, from M.S.D. Isotopes Ltd., both in the presence of saturating concentrations of Cu^{2+} or Ni^{2+} at 30 °C and in the absence of metal ions. At the completion of the reaction the metal ion was precipitated as the sulfide by employing H_2S, and the mixture was filtered. The filtrate was then warmed for 30 min to expel excess H_2S. A calculated amount of barium chloride was then added to precipitate $Ba_3(PO_4)_2$. This mixture was filtered, and the filtrate was evaporated. The residue was dissolved in

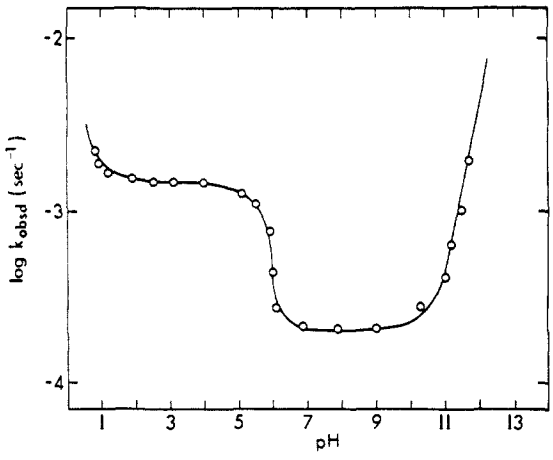


Figure 1. Plot of log k_{obsd} vs pH for hydrolysis of 1,10-phenanthroline-2-carbonyl phosphate at 85 °C (μ = 0.6 M with KCl) in H_2O.

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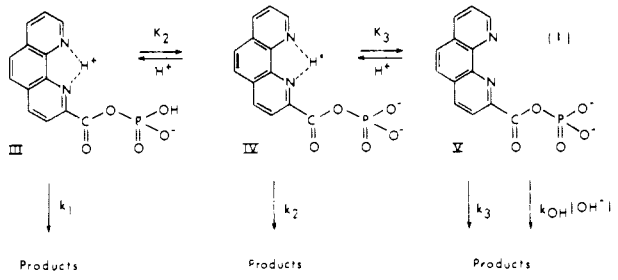
water and acidified. The 1,10-phenanthroline-2-carboxylic acid was isolated by the reported procedure[29] and recrystallized twice from ethanol. Mass spectral analyses were carried out. The extent of ^{18}O incorporation into 1,10-phenanthroline-2-carboxylic acid was determined by calculating the relative intensities of the molecular ion peaks.

Results

In Figure 1 is shown a plot of log k_{obsd} vs pH for the hydrolysis of 1,10-phenanthroline-2-carbonyl phosphate in H_2O at 85 °C. The plot at pH > 10 has a slope of +1.0, which indicates that an OH^--catalyzed reaction of the dianionic species is occurring. At pH 7–10 the reaction of the dianion is pH independent. Addition of a proton to the molecule produces a rate enhancement so that an apparent hydronium ion catalyzed reaction is observed at pH < 6. There is an apparent pK_a at pH 5.6, which is in reasonable agreement with the pK_a of 5.75 determined spectrophotometrically at 30 °C. At lower pH the reaction is again pH independent, and at pH < 2 a further apparent hydronium ion catalyzed reaction is observed. The reactions are shown in eq 1.



(1)

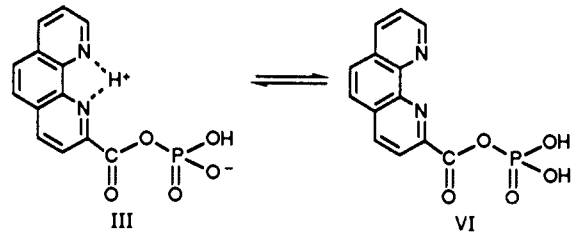
The equation for k_{obsd} (at zero buffer concentration) derived from the scheme of eq 1 is given in eq 2, where K_1 is the dissociation

$$k_{obsd} = \frac{k_1K_1a_H^2 + k_2K_1K_2a_H + k_3K_1K_2K_3 + k_{OH}K_1K_2K_3(OH^-)}{a_H^3 + K_1a_H^2 + K_1K_2a_H + K_1K_2K_3} \quad (2)$$

constant of the protonated species (not shown in eq 1). It is clear from the plot of Figure 1 that pK_1 is less than 1. Therefore, eq 2 will simplify to eq 3 in the pH range investigated, where $K_1 >$

$$k_{obsd} = \frac{k_1a_H^2 + k_2K_2a_H + k_3K_2K_3 + k_{OH}K_2K_3(OH^-)}{a_H^2 + K_2a_H + K_2K_3} \quad (3)$$

a_H. The experimental data give a good fit to eq 3, with $k_1/K_2 = 0.01\ M^{-1}\ s^{-1}$, $k_2 = 1.5 \times 10^{-3}\ s^{-1}$, $k_3 = 2 \times 10^{-4}\ s^{-1}$, $k_{OH} = 0.013\ M^{-1}\ s^{-1}$, $pK_3 = 5.6$, and pK_2 is less than 2. There is no observable inflection in the profile of Figure 1 that can be attributed to pK_2. The pK_2 could be greater than 2, e.g., in the range 2–3, if k_1 and k_2 are similar; the apparent hydronium ion catalyzed reaction at pH < 2 would then reflect hydrolysis of the protonated species. There are, of course, two kinetically equivalent neutral species (shown in eq 4), and also two equivalent monoanions (IV and VII in eq 5) that could be important.



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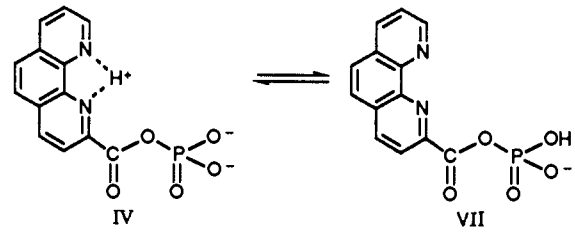

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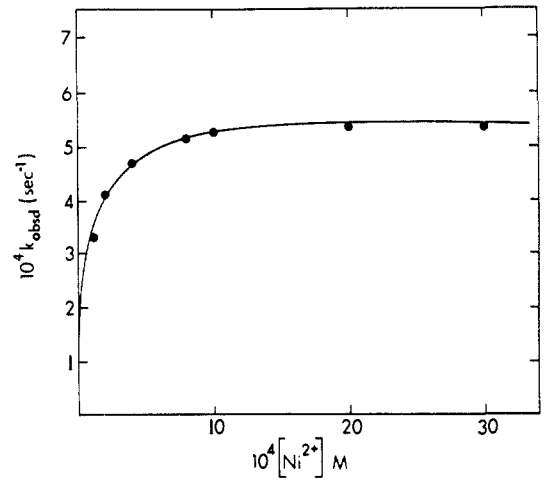

Figure 2. Plot of k_{obsd} for hydrolysis of 6×10^{-5} M 1,10-phenanthroline-2-carbonyl phosphate at 30 °C and pH 5.81 (μ = 0.6 M) vs the concentration of Ni^{2+}.

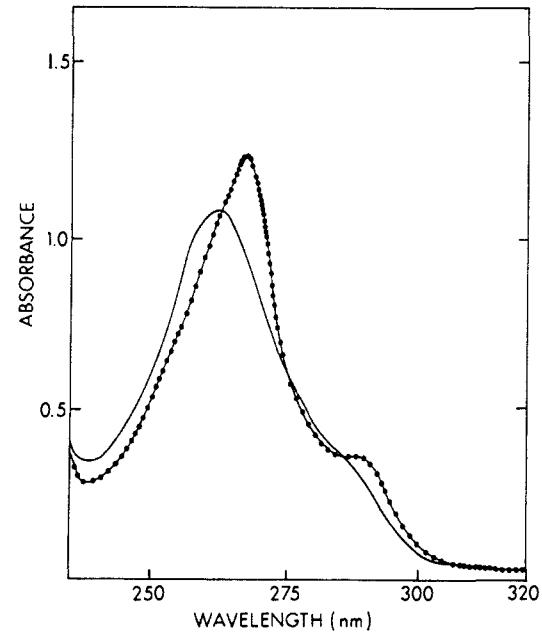

Figure 3. Absorbance spectra of 5×10^{-5} M 1,10-phenanthroline-2-carbonyl phosphate in the presence of 0.002 M Ni^{2+} (--) and in the absence of metal ion (—) at 30 °C and pH 5.03 in H_2O.

The spectrophotometrically determined pK_a of 5.8 is that of the monoanion and very likely reflects ionization of the phenanthroline nitrogen conjugate acid. The pK_a values of the phosphate oxygen conjugate acids will be lowered by the positive charge of species III and IV. The neutral species pK_a of 2-(1,10-phenanthrolyl) phosphate is 2.9, and the protonated species pK_a is less than 2.0 at 30 °C.[17]

The divalent metal ions Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} bind very strongly to 1,10-phenanthroline-2-carbonyl phosphate and have a large effect on the rate of hydrolysis. Saturation occurs at low metal ion concentration (<0.002 M). In Figure 2 a plot is shown of k_{obsd} vs the concentration of Ni^{2+} at 30 °C and pH 5.81. At constant pH the reactions follow eq 6, where k_M is the limiting

$$k_{obsd} = \frac{k_MK_M[M^{2+}]}{1 + K_M[M^{2+}]} \quad (6)$$

rate constant in the metal ion promoted reaction, and K_M is the metal ion association constant. From the plot of Figure 2, the limiting rate constant k_{Ni} is $5.5 \times 10^{-4}\ s^{-1}$, and K_{Ni} is $1.7 \times 10^4\ M^{-1}$. Similar plots were obtained with the other metal ions in the series. The values of the association constants are $K_{Cu} = 2 \times 10^4$

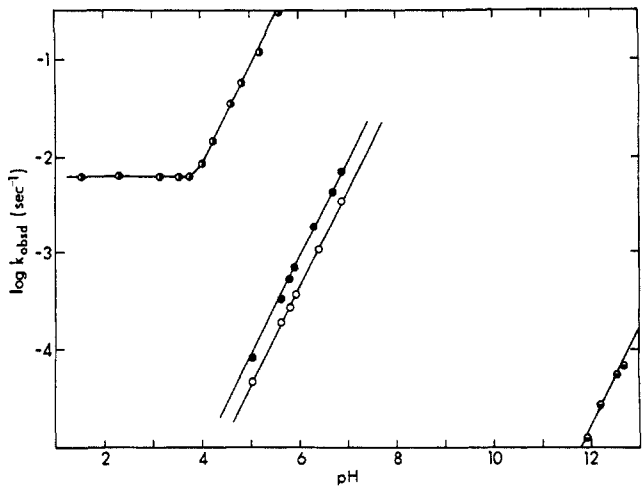

Figure 4. Plot of log k_{obsd} vs pH for the hydrolysis of 6×10^{-5} M 1,10-phenanthroline-2-carbonyl phosphate in the presence of Cu^{2+} (◑), Ni^{2+} (●), and Zn^{2+} (○) at saturating concentrations (0.002–0.003 M) and in the absence of metal ions (⊖) at 30 °C (μ = 0.6 M) in H_2O.

M^{-1} (pH 3.52). $K_{Co} = 3 \times 10^4$ M^{-1} (pH 6.88), and $K_{Zn} = 2 \times 10^4$ M^{-1} (pH 6.39). These constants were obtained at the indicated pH by employing eq 6 and are not corrected for protonation of the phenanthroline nitrogens. The binding of the metal ions to 1,10-phenanthroline gives rise to a characteristic absorbance change at 270 nm.[32] As seen in Figure 3, that is also the case with PCOP. Thus, the metal ions are chelated by the phenanthroline nitrogens of PCOP. The binding of Mg^{2+} to PCOP is considerably weaker than with Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+}, but nevertheless saturation occurs at concentrations less than 0.2 M. The association constant K_{Mg} has the value 1.1×10^2 M^{-1} at pH 7.12. Binding of Ca^{2+} to PCOP is still weaker, and saturation effects were not observed at concentrations less than 0.2 M. The plot of k_{obsd} for the hydrolysis reaction vs the concentration of Ca^{2+} at pH 7.12 has some apparent curvature, but k_{obsd} is still dependent on metal ion concentration at 0.2 M.

Figure 4 is a plot of log k_{obsd} for hydrolysis of PCOP vs pH at 30 °C and μ = 0.6 M in the presence of saturating concentrations of Cu^{2+}, Ni^{2+}, and Zn^{2+}. The ratio of metal ion to substrate in the reactions is more than 33 with Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+}, and 3300 with Mg^{2+}. The points for the Co(II)-promoted reaction lie between those of the Ni(II)- and Zn(II)-promoted reactions and have been omitted from the plot of Figure 4 for increased clarity. The slopes of the plots are in each case 1.0, which indicates that the reactions are hydroxide ion catalyzed. Rate measurements could not be carried out at pH values greater than 7 with Cu^{2+}, Ni^{2+}, Co^{2+}, or Zn^{2+} because of precipitation of the metal ions. However, with Mg^{2+} the rate constants could be determined at pH values as high as 8. In addition to the metal ion promoted OH^--catalyzed reaction, the Cu(II)-catalyzed hydrolysis reaction at pH < 4 is pH independent as shown in Figure 4. These rate constants were also determined at 20, 40, and 50 °C. The ΔH^* for the pH-independent reaction is 10.4 ± 1 kcal/mol and ΔS^* is −34.3 ± 3 eu at 30 °C. The rate constants for these reactions are given in Table I.

The hydrolysis of the Cu(II) complex of PCOP was carried out at pH 3 and 6 in ^{18}O-enriched water at 30 °C, and the Ni(II) complex was hydrolyzed in ^{18}O-enriched water at pH 6.2. Mass spectral analysis of the products revealed that there was incorporation of ^{18}O into the carboxylic acid, 1,10-phenanthroline-2-carboxylic acid (95–98%). That was also the case when PCOP was hydrolyzed in the absence of metal ion at pH 11 (97% incorporation of ^{18}O). There was no significant exchange of ^{18}O into 1,10-phenanthroline-2-carboxylic acid under identical conditions. Thus, C–O bond breaking is occurring in the hydrolytic reactions.

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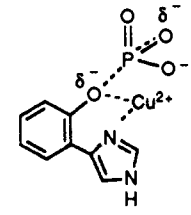
Amines catalyze the hydrolysis of PCOP as seen in Figure 5, which is a plot of k_{obsd} vs the total concentration of imidazole (B + BH^+) at 30 °C (μ = 0.6 M) in the presence of 0.003 M Ni^{2+} and in the absence of metal ion at 85 °C. The slopes of the lines increase as the pH is increased, which shows that the base species of the buffer is catalytically active. The intercepts at zero imidazole concentration are slightly less than those obtained with cacodylate or *N*-ethylmorpholine buffers at the same pH when Ni^{2+} is present. The second-order rate constant k_{Im}, in the presence of Ni^{2+} at 30 °C is 0.04 M^{-1} s^{-1}. In contrast, k_{Im} in the absence of metal ion and at 85 °C is 4×10^{-4} M^{-1} s^{-1}. Thus, Ni^{2+} greatly facilitates this reaction. Pyridine catalysis is also enhanced in the presence of 0.003 M Ni^{2+}; k_{Py} is 2.2×10^{-3} M^{-1} s^{-1} at 30 °C as contrasted with $k_{Py} = 6.8 \times 10^{-4}$ M^{-1} s^{-1} in the absence of metal ion at 30 °C.

Discussion

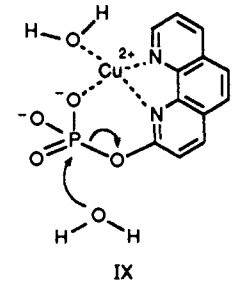
The plot of log k_{obsd} vs pH for hydrolysis of 1,10-phenanthroline-2-carbonyl phosphate (Figure 1) shows that OH^--catalyzed and pH-independent reactions of the dianion species occur in the pH range greater than 6. These reactions are governed by k_{OH} and k_3, respectively, in eq 1. Similar reactions have been observed previously in the hydrolysis of acyl phosphates.[6,33] At pH less than 6 an apparent hydronium ion catalyzed reaction occurs that very likely is due to an accelerating effect of protonation of the phenanthroline nitrogens. Protonation of nitrogen will lower the pK_a of the carboxyl leaving group and will thereby increase the ease of P–O bond breaking in metaphosphate elimination.

The effects of added metal ions in the hydrolysis of acetyl phosphate are quite small.[3,4,12] Likewise, sizable metal ion catalysis is not observed in the hydrolysis of other types of phosphomonoesters in the absence of metal ion chelating functional groups. However, large rate enhancements are achieved in the hydrolysis of phosphomonoester dianions when there is a metal ion chelating functional group located in the molecule.[14-17] In the cases where the metal ion can bind to the leaving group oxygen,[15,16] these reactions possibly involve metal ion enhancement of metaphosphate elimination, as in the Cu(II)-promoted hydrolysis of *o*-(4-imidazolyl)phenyl phosphate (VIII).[15] On the other hand, in the



VIII

case of 2-(1,10-phenanthrolyl) phosphate, metal ion chelation by the leaving group oxygen cannot be favorable in a 1:1 complex because a 4-membered chelate ring would be required; the cupric ion promoted reaction then proceeds via attack of a water molecule on the metal ion complex (IX).[17] Metal ion promoted OH^-



IX

catalyzed reactions such as those occurring in the hydrolysis of 1,10-phenanthroline-2-carbonyl phosphate have been found in the

(33) Phillips, D. R.; Fife, T. H. *J. Org. Chem.* **1969**, *34*, 2710.

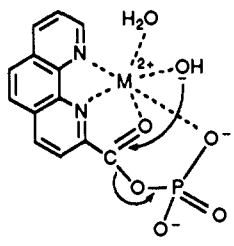
Table I. Rate Constants for Hydrolysis of 1,10-Phenanthroline-2-carbonyl Phosphate in H_2O at 30 °C and μ = 0.6 M (with KCl) in the Presence and Absence of Saturating Concentrations of Divalent Metal Ions

metal ion[a]	k_{OH}, M^{-1} s^{-1}	k_0, s^{-1}
none	1.1×10^{-3}	
Cu^{2+}	5.4×10^{7}	6.5×10^{-3}
Ni^{2+}	6.0×10^{4}	
Co^{2+}	3.7×10^{4}	
Zn^{2+}	3.1×10^{4}	
Mg^{2+}	7.6×10^{2} [b]	

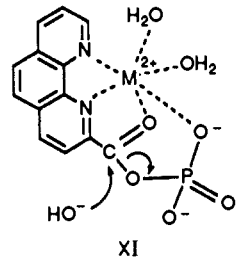
[a] The metal ion concentration was 0.002 M with Cu^{2+}, 0.003 M with Ni^{2+}, Co^{2+}, and Zn^{2+}, and 0.2 M with Mg^{2+}. [b] At 85 °C.

hydrolysis reactions of carboxylate esters,[18-24] anhydrides,[25] and amides,[34,35] but comparable catalytic effects have not been observed previously in the hydrolysis of phosphomonoesters.[36] The presence of the carbonyl group and the reasonably good leaving group (PO_4^{3-}) must make such a reaction favorable with acyl phosphate dianions when the metal ion is strongly chelated.

The highly favorable metal ion promoted hydrolysis reactions of 1,10-phenanthroline-2-carbonyl phosphate, very likely involve either an internal attack of metal ion bound OH^- (X) at the carbonyl group or metal ion enhancement of the attack of external OH^- (XI).[37]



X



XI

The experiments employing ^{18}O-enriched water show conclusively that C–O bond breaking is occurring in the apparent OH^--catalyzed reactions of the metal ion complexes. The metal ions bind to the phenanthroline nitrogens of PCOP as shown by the spectral data of Figure 3. Therefore, complexation of the carbonyl oxygen should also be sterically favorable in a 1:1 complex (five-membered ring), and further chelation by the phosphate oxygens would require an additional six-membered ring.[38,39] Chelation by the oxygen linking carbon and phosphorus would be sterically possible, but that oxygen would be of relatively low basicity. The reactions are surely proceeding via a 1:1 complex in view of the large ratio of metal ion to substrate.[40]

Table II. Rate Enhancements in Cu(II)-Promoted Hydroxide Ion Catalyzed Hydrolysis Reactions at Saturating Concentrations of Metal Ion in Comparison with the Corresponding Reactions in the Absence of Metal Ion

compound	k_{OH},[a] M^{-1} s^{-1}	enhancement in k_{OH}[b]	ref
PCOP[c]	5.4×10^{7}	5×10^{10}	
N-(6-carboxypicolinyl)benzimidazole[c]	5.4×10^{11}	10^{9}	35
8-acetoxyquinoline-2-carboxylic acid[d]	1.4×10^{8}	2×10^{8}	20
8-(2-carboxyquinolyl) hydrogen glutarate[c]	8.2×10^{7}	4×10^{7}	22
2-(6-carboxypyridyl)methyl hydrogen succinate[e]	5.5×10^{5}	10^{6}	23
2-(6-carboxypyridyl)methyl acetate[e]	6.8×10^{5}	4×10^{5}	23
salicyl phenanthroline-2-carboxylate[e]	7.9×10^{6}	10^{5}	22
ethyl 6-carboxypicolinate[e]	4.6×10^{5}	10^{5}	24
cinnamic 6-carboxypicolinic anhydride[f]		$>10^{7}$	25

[a] The second-order rate constant for hydroxide ion catalyzed hydrolysis in the presence of the metal ion, i.e., $k_{Cu}/[OH^-]$. [b] Enhancements were calculated as the ratio of k_{OH} values in the presence and absence of a saturating concentration of Cu(II) at the same temperature. [c] At 30 °C in H_2O. [d] At 25 °C in H_2O. [e] At 50 °C in H_2O. [f] At 30 °C in 50% dioxane–H_2O.

Complexation of the carbonyl oxygen of acyl derivatives by a metal ion would facilitate the attack of a nucleophile at carbon and would lead to large rate enhancements if the leaving group is sufficiently good so that the attack step is rate limiting. Nucleophilic attack will be the rate-determining step if the reaction is concerted or if a tetrahedral intermediate breaks down to products more rapidly than it reverts to reactants. The intramolecular nature of X would also further enhance the reaction.[41] In the Cu(II)-promoted hydrolysis of *N*-(6-carboxypicolinyl)-benzimidazole, where nucleophilic attack by OH^- is rate determining, the reaction must involve metal ion bound OH^- because an alternative reaction of external hydroxide ion would require a second-order rate constant greater than that for a diffusion-controlled reaction.[35] The enhancement in the second-order rate constant for OH^- catalysis, k_{OH}, due to the presence of cupric ion in that reaction is 10^9 in comparison with the k_{OH} for OH^--catalyzed hydrolysis in the absence of a metal ion. The enhancements in k_{OH} at 30 °C in the metal ion promoted OH^--catalyzed reactions of the acyl phosphate PCOP are in fact larger than with the *N*-acylbenzimidazole, ranging from 5×10^{10} with Cu^{2+} to 3×10^7 with Zn^{2+} at 0.003 M metal ion. Even Mg^{2+}, which does not bind strongly to PCOP, gives an enhancement in k_{OH} of 6×10^4 (at 85 °C and a metal ion concentration of 0.2 M). These are the largest catalytic effects that have been found in metal ion promoted OH^- reactions of acyl derivatives, as illustrated by the examples in Table II for Cu^{2+}. Note the much smaller rate enhancements obtained with phenolic esters having leaving groups of reasonably low pK_a, e.g., salicyl phenanthroline-2-carboxylate. The magnitude of the rate enhancements in the reactions of PCOP must partly reflect the slow OH^--catalyzed reaction in the absence of metal ions, which is very likely the result of electrostatic repulsion of OH^- by the negatively charged phosphate oxygens. Consequently, the rapid metal ion promoted reactions strongly suggest a partial screening of negative charge by the metal ion.[42]

The values of k_{obsd} in the Cu(II)-promoted hydrolysis of PCOP are pH independent at pH < 4. The ΔS^* for that reaction is −34.3 eu at 30 °C. Such a highly negative ΔS^* is clearly not compatible with metaphosphate elimination; the ΔS^* values in the hydrolysis

(34) (a) Groves, J. T.; Dias, R. M. *J. Am. Chem. Soc.* **1979**, *101*, 1033. (b) Groves, J. T.; Chambers, R. R., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 630.

(35) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 4631.

(36) An attack of metal ion bound OH^- on phosphorus apparently takes place in reactions of the substitution inert ethylenediamine Co(III) complex of *p*-nitrophenyl phosphate. Jones, D. R.; Lindoy, L. F.; Sargeson, A. M. *J. Am. Chem. Soc.* **1983**, *105*, 7327. However, such a reaction was not observed in the metal ion catalyzed reactions of 2-(1,10-phenanthrolyl) phosphate.[17] Attack of a negatively charged nucleophile at phosphorus would not, of course, be expected to be competitive with attack at the carbonyl in reactions of acyl phosphates.

(37) A metal ion promoted OH^--catalyzed reaction will give a plot of log k_{obsd} vs pH with a slope of 1.0, as observed, until the pK_a of the metal ion bound water molecule. The pK_a values for ionization of the aquo complexes of the metal ions at 25 °C are as follows: Cu^{2+}, 6.8; Zn^{2+}, 8.8; Ni^{2+}, 10.6; Co^{2+}, 8.9. Basolo, F.; Pearson, R. G. *Mechanisms of Inorganic Reactions*, 2nd ed.; Wiley: New York, 1967; p 32.

(38) An octahedral configuration of the metal ion would accommodate binding of OH^- and the phosphate oxygens as in X. In addition to 4-coordinate complexes, tetragonally distorted octahedral complexes of Cu(II) are also possible. Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1972; p 912.

(39) Complexes of the protonated species could also occur. However, pK_1 and pK_2 must be less than 3 in the presence of a chelated metal ion. Therefore, the OH^--catalyzed reactions would proceed via pH-independent processes if such complexes were kinetically important. Only with Cu(II) is a pH-independent reaction observed.

(40) With 1,10-phenanthroline as the ligand (1:1) the $Cu_2(OH)_2L_2^{2+}$ species is formed in appreciable concentrations in the neutral pH range. Perrin, D. D.; Sharma, V. S. *J. Inorg. Nucl. Chem.* **1966**, *28*, 1271. The negatively charged phosphate group in the 2-position of PCOP would, of course, greatly reduce the likelihood of that type of dimer complex.

(41) Bruice, T. C. In *The Enzymes*; Boyer, P. D., Ed.; Academic Press: New York, 1970; Vol. 2, Chapter 4, p 217.

(42) Cooperman, B. S. *Metal Ions in Biological Systems*; Sigel, H., Ed.; Marcel Dekker: New York, 1976; Vol. 5, p 79.

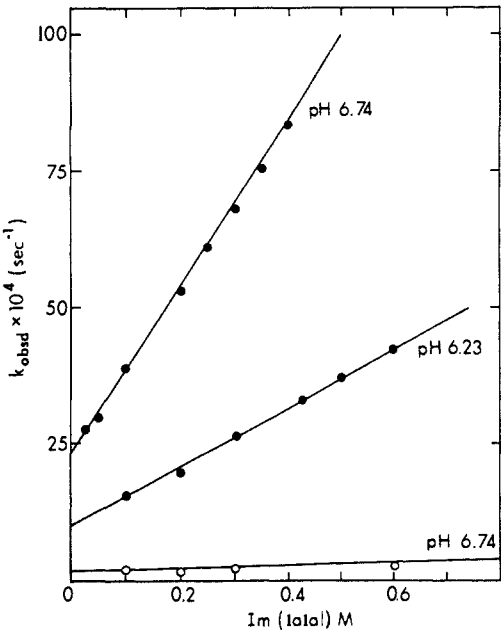
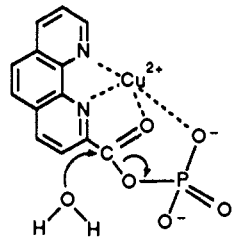


Figure 5. Plot of k_{obsd} vs total imidazole concentration for the hydrolysis of 6×10^{-5} M 1,10-phenanthroline-2-carbonyl phosphate in the presence of 0.003 M Ni^{2+} (●) at 30 °C and in the absence of metal ion (○) at 85 °C in H_2O (μ = 0.6 M).

of the acetyl phosphate monoanion and dianion are −3.6 and +3.7 eu, respectively,[6] as would be expected in unimolecular reactions. That C–O bond breaking is occurring in the Cu(II)-promoted pH-independent hydrolysis of PCOP is shown by the incorporation of ^{18}O from ^{18}O-enriched water into the carboxylic acid product at pH 3. The reaction very likely involves attack of a water molecule on the metal ion complex (XII). Restriction of one or



XII

more water molecules in the transition state would account for the negative ΔS^* value. The kinetically equivalent attack of OH^- on the protonated phosphate species would require a second-order rate constant of 1.5×10^{10} M^{-1} s^{-1} (assuming that the pK_a is less than 1.5) and is therefore unlikely. Water attack on the protonated species would be pH independent at pH values less than the pK_a. The cupric ion promoted water reaction of PCOP is very likely brought about by an electron-deficient acyl group and the reasonably good leaving group so that attack by water is favored over elimination.

Acyl phosphates, e.g., acetyl phosphate, are susceptible to nucleophilic attack by amine bases.[6,33] Imidazole attacks exclusively at the carbonyl group,[6,33] while pyridine has been found to attack at phosphorus.[6] The presence of a chelated metal ion markedly enhances the catalysis by imidazole in the hydrolysis of PCOP.[43] In view of the large metal ion enhancement of the water and OH^- reactions, which are nucleophilic processes, it is reasonable that the metal ion is also promoting the nucleophilic reactions of the imidazole base in the same manner. The second-order rate constant for imidazole catalysis in the presence of 0.003 M Ni^{2+} is 100-fold larger at 30 °C than in the absence of metal ion at 85 °C. The rate enhancement provided by Ni^{2+} in the pyridine-catalyzed reaction is, however, close to a factor of 3. This large difference in catalytic effectiveness must reflect the differences in basicity and the different preferred positions of nucleophilic attack by the two amine bases. Pyridine might also attack the carbonyl group. Consequently, the enhanced catalysis by pyridine represents an upper limit for the effect of the metal ion on attack at phosphorus. Thus, the strongly chelated metal ions in the complexes of PCOP are greatly facilitating reactions that proceed with nucleophilic attack at the carbonyl group of acyl phosphates,[3-6] whereas attack of pyridine at phosphorus can only be enhanced moderately.[44]

Imidazole does not catalyze the hydrolysis of acyl phosphate dianions derived from aliphatic carboxylic acids,[33] and it will be noted that imidazole catalysis of the hydrolysis of the dianion of PCOP in the absence of metal ions is quite weak even at 85 °C. This is very likely due to the large difference in the pK_a values of the conjugate acids of imidazole and the PO_4^{3-} leaving group. Therefore, the significant imidazole catalysis in the hydrolysis of PCOP in the presence of Ni^{2+} (pH > 6) again suggests partial neutralization of the negative charge on oxygen, which will thereby aid expulsion of the phosphate group. The second-order rate constant for the imidazole-catalyzed reaction, k_{Im}, in the presence of Ni^{2+} is 19-fold larger than k_{Py} in the pyridine-catalyzed reaction. This ratio of k_{Im} to k_{Py} is nearly the same as the ratio of 15 in the *monoanion* reactions of isobutyryl phosphate.[33] Thus, the chelated metal ion is greatly increasing the hydrolytic reactivity of the dianion species of PCOP but is maintaining the relative reactivity of typical acyl phosphate monoanions, with which there is a proton in the transition state, toward amine nucleophiles.

Enzyme-Catalyzed Acyl Phosphate Reactions. There has been considerable discussion in the literature as to whether enzyme-catalyzed reactions of phosphate esters involve associative processes, i.e., nucleophilic reactions, or whether they proceed via metaphosphate elimination followed by capture of the metaphosphate by the appropriate acceptor.[26,45a] The very weak metal ion effects that had previously been observed in the hydrolysis of acyl phosphates had precluded any general conclusions based on the chemistry of these compounds. However, it is now clear that when a metal ion is strongly bound to an acyl phosphate and a chelating functional group in the molecule, an extremely large rate enhancement will result in the nucleophilic reactions of OH^-, and smaller but substantial rate enhancements will occur in the reactions of amine bases. A metal ion promoted OH^--catalyzed reaction is greatly favored over metaphosphate elimination in acyl phosphate reactions. Binding of the metal ion to the carbonyl oxygen would enhance both the attack of OH^- and the metaphosphate elimination, but binding to the phosphate oxygens would retard elimination. As a consequence, if there is a direct complexation of an acyl phosphate with a metal ion in the active site of a metalloenzyme or metal ion activated enzyme, then it is probable that the ensuing reaction will involve chemistry similar to that of the complexes of PCOP, i.e., nucleophilic processes that result in direct hydrolysis or acylation of the enzyme.

Kinase enzymes catalyze phosphoryl-group transfer to ADP.[2] In the reactions of a kinase enzyme that utilizes an acyl phosphate substrate, e.g., 3-phosphoglycerate kinase,[2] it is very likely a chemical necessity that the acyl phosphate *not* be complexed to the metal ion. From a chemical standpoint the reaction should

(43) The hydrolysis of the acylimidazole intermediate produced by attack of imidazole at the carbonyl of PCOP would also be metal ion catalyzed[35] and would be very rapid. Attack of imidazole at phosphorus would give phosphorylimidazole, which would be reasonably stable under the present reaction conditions at 30 °C and would build up in concentration. Lloyd, G. J.; Cooperman, B. S. *J. Am. Chem. Soc.* **1971**, *93*, 4883. No evidence was found indicating the formation of such a species.

(44) High concentrations of Mg^{2+} or Ca^{2+} (0.33 M) were recently reported to have only a small accelerating effect on the pyridine-catalyzed hydrolysis of *p*-nitrophenyl phosphate. Herschlag, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 4665. See also references therein. It was concluded that metal ion binding to the phosphate oxygens has little effect on the ability of pyridine to attack phosphorus as a nucleophile.

(45) (a) Mildvan, A. S. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1979**, *49*, 103. (b) Chapman, B. E.; O'Sullivan, W. J.; Scopes, R. K.; Reed, G. H. *Biochemistry* **1977**, *16*, 1005.

proceed via an enzyme–ADP–metal ion complex as suggested.[45]

Acknowledgment. This work was supported by a research grant from the National Science Foundation. We would also like to thank Professors S. P. Bessman and P. J. Geiger for their expert assistance in carrying out the phosphate analysis with the automated phosphate analyzer.

Registry No. PCOP, 125830-06-0; PCOP(hydrochloride), 125830-05-9; Cu^{2+}, 15158-11-9; Ni^{2+}, 14701-22-5; Co^{2+}, 22541-53-3; Zn^{2+}, 23713-49-7; Mg^{2+}, 22537-22-0; Ca^{2+}, 14127-61-8; 1,10-phenanthroline-2-carboxylic acid chloride hydrochloride, 37067-11-1; orthophosphoric acid, 7664-38-2.

Stereoelectronic Effects on Chemoselectivity in the Free Radical Bromination of Arylcyclopropanes

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Abstract: The reaction of atomic bromine with several arylcyclopropanes has been investigated. For systems where the aryl moiety is phenyl or α- or β-naphthyl, the expected S_H2 pathway leading to cyclopropane ring cleavage is observed. In the case of 9-cyclopropylanthracene, however, an unprecedented hydrogen atom abstraction reaction is observed. These observations are explicable on stereoelectronic grounds. For the 9-anthryl system, the lowest energy perpendicular conformation finds the α-C–H bond aligned with the π-system, and consequently hydrogen abstraction is facile. In this conformation, the α-C–C bonds are deactivated toward bromine atom attack. For phenyl- and β-naphthylcyclopropane, the bisected conformation is preferred and ring opening predominates. The ground-state conformation of α-cyclopropylnaphthalene is unique in that it is midway between bisected and perpendicular. Although cyclopropane ring opening is the only detected process, quantitative data are presented which demonstrate that the *rate* of this process is diminished because of unfavorable stereoelectronic factors. Analysis of this reaction system with the Curtin–Hammett principle leads to a general statement of the requirements for α-hydrogen abstraction from cyclopropylarenes by bromine atom.

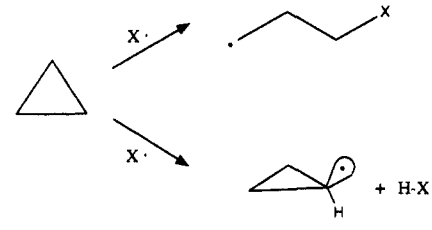
Introduction

The reaction of a free radical with cyclopropane results in hydrogen abstraction and/or ring opening (Scheme I), the observed chemoselectivity being dependent on the nature and identity of the attacking radical. Imidyl[1,2] and *tert*-butoxy[3] radicals yield exclusively hydrogen abstraction products. Chlorine atom[3,4] yields both hydrogen abstraction and ring-opened products, the product ratio being temperature dependent. Bromine atom produces ring-opened products exclusively.[5-7]

The free radical bromination of alkylcyclopropanes has been studied in considerable detail and shown to involve the backside attack of bromine atom on the least-hindered position of the cyclopropane (with inversion of configuration), resulting in formation of the most-stable radical (Scheme II).[5,6] This S_H2 process represents a formal carbon atom abstraction by Br• and derives its thermodynamic driving force from the relief of cyclopropane ring strain.

For arylcyclopropanes, free radical bromination also yields ring-opened products.[8-10] The effect of substituents on the aromatic ring has been examined, and the reaction is found to correlate with σ^+ ($\rho = -1.84$).[10] This substituent effect is remarkably similar to that observed for hydrogen abstraction from substituted toluenes by bromine atom (correlation to σ^+, $\rho = -1.76$),[10] which is not unreasonable because both processes involve

Scheme I



Scheme II

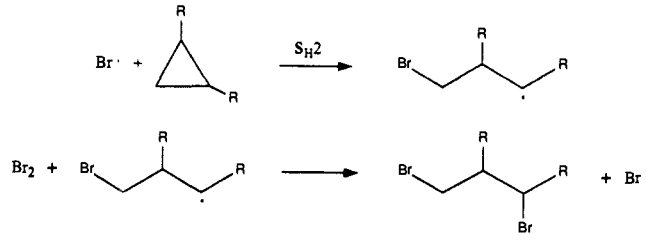


Table I. Bromination of Phenylcyclopropane under a Variety of Conditions

entry	brominating agent/ conditions	time, min	temp, °C	% $PhCHBrCH_2CH_2Br$
1	$Br_2/CCl_4/h\nu$[a]	5	15	100
2	$Br_2/CH_2Cl_2/h\nu$[a]	5	−78	100
3	Br_2/CCl_4/dark[b]	5	15	0[c]
4	Br_2/CH_2Cl_2/dark[b]	5	−78	0[c]
5	NBS/Bz_2O_2/CCl_4[d]	90	80	0[c]

[a] Irradiated with a 400-W medium pressure mercury-arc lamp at a distance of 1–2 ft through Pyrex. [b] Nondegassed solution, protected from light. Excess Br_2 quenched with a suitable olefin before analysis. [c] >95% recovered starting material. [d] NBS = *N*-bromosuccinimide; Bz_2O_2 = 2–3% benzoyl peroxide.

formation of a benzyl radical (presumably via a polar transition state).

Irrespective of the substituents present on the cyclopropyl ring, there are no reported examples of abstraction of a cyclopropyl

(1) Traynham, J. C.; Lee, Y.-S. *J. Am. Chem. Soc.* **1974**, *96*, 3590.
(2) Tanko, J. M.; Skell, P. S.; Seshadri, S. *J. Am. Chem. Soc.* **1988**, *110*, 3221.
(3) Walling, C.; Fredricks, P. S. *J. Am. Chem. Soc.* **1962**, *84*, 3326.
(4) Roberts, J. D.; Dirstine, P. H. *J. Am. Chem. Soc.* **1945**, *67*, 1281.
(5) Maynes, G. G.; Applequist, D. E. *J. Am. Chem. Soc.* **1973**, *95*, 856.
(6) Shea, K. J.; Skell, P. S. *J. Am. Chem. Soc.* **1973**, *95*, 6728.
(7) The gas-phase photobromination of cyclopropane with a Br_2/Cl_2 mixture yields ca. 10% cyclopropyl bromide, undoubtedly with Cl• serving as H-abstractor. When Cl_2 is omitted, only 1,3-dibromopropane is formed. Dedio, E. L.; Kozak, P. J.; Vinogradov, S. N.; Gunning, H. E. *Can. J. Chem.* **1962**, *40*, 820.
(8) Kuivila, H. G.; Caywood, S. C.; Boyce, W. F.; Langevin, F. L., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 5175.
(9) LaLonde, R. T.; Ferrara, P. B.; Debboli, A. D., Jr. *J. Org. Chem.* **1972**, *37*, 1094.
(10) Applequist, D. E.; McKenzie, L. F. *J. Org. Chem.* **1976**, *41*, 2262.

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