ature. Workup gave the product (0.02 g, 100%): mp 200–204 °C (methylene chloride); ^{1}H NMR δ 3.93 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.03 (s, 3 H, NCH_3), 4.03 (s, 3 H, OCH_3), 7.20 (s, 1 H, H-1), 7.48 (s, 1 H, H-4), 7.50 (s, J = 10 Hz, 1 H, H-12), 7.85 (s, 1 H, H-7), 9.90 (d, J = 10 Hz, 1 H, H-11); mass spectrum, m/e 395 (M^+), 380, 364, 337, 266; exact mass calcd for $C_{22}H_{21}NO_4$ 395.1294, found 395.1331.

Registry No. **1a**, 39959-51-8; **1b**, 98799-33-8; **1c**, 98799-35-0; **1d**, 98799-40-7; **2a**, 529-34-0; **2b**, 1078-19-9; **2c**, 41303-45-1; **2d**, 13575-75-2; **2e**, 98799-45-2; **2f**, 98799-46-3; **3a**, 98799-47-4; **3b**, 98799-48-5; **3c**, 98799-49-6; **3d**, 98799-50-9; **3e**, 98799-51-0; **3f**, 98799-52-1; **3g**, 98799-53-2; **3h**, 98799-54-3; **3i**, 98799-55-4; **3j**, 54022-61-6; **3k**, 98799-56-5; **3l**, 94656-27-6; **3m**, 98799-57-6; **3n**, 98799-58-7; **3o**, 98799-59-8; **3p**, 98799-60-1; **4a**, 218-38-2; **4b**, 98799-61-2; **4c**, 214-09-5; **4d**, 56517-13-6; **4e**, 98799-62-3; **4f**, 56517-12-5; **4g**, 98799-63-4; **4h**, 214-06-2; **4i**, 98799-64-5; **4j**, 18034-03-2; **4k**, 52259-71-9; **4k'**, 52259-72-0; **4l**, 217-52-7; **4m**, 51116-29-1; **4n**, 15462-10-9; **4o**, 98799-65-6; **4p**, 98799-66-7; **4q**, 98799-77-0; **5c**, 62848-88-8; **5d**, 98799-43-0; **5e**, 98799-44-1; **6c**, 41303-44-0; **6c** (acid chloride), 98799-42-9; **6d**, 13575-74-1; **6e**, 57596-01-7; **7e**, 15288-02-5; **7f**, 15288-01-4; **11a**, 88-67-5; **11c**, 98799-41-8; **12a**, 98799-76-9; **12b**, 98799-67-8; **12c**, 98799-68-9; **13a**, 55377-55-4; **13b**, 98799-69-0; **13c**, 98799-70-3; **14a**, 98799-71-4; **14b**, 98799-72-5; **14c**, 98799-73-6; **15b**, 98838-09-6; **15c**, 98799-75-8; **15d**, 98799-74-7; $Ph_3P^+(CH_2)_2CO_2H\cdot Br^-$, 51114-94-4; *N*-acetylveratrylamine, 65609-25-8; veratrylamine, 5763-61-1; piperonylamine, 2620-50-0; *N*-acetylpiperonylamine, 59682-83-6; 6-iodo-*N*-acetylpiperonylamine, 98799-34-9; vanillin, 121-33-5; 4-isopropoxybenzaldehyde, 2538-98-9; 3-methoxy-4-isopropoxybenzaldoxime, 98799-36-1; 3-methoxy-4-isopropoxybenzylamine, 98799-37-2; 3-methoxy-4-isopropoxy-*N*-acetylbenzylamine, 98799-38-3; 2-iodo-5-methoxy-4-isopropoxy-*N*-acetylbenzylamine, 98799-39-4; 3,4,5-trimethoxybenzoic acid, 118-41-2; piperonaldehyde, 120-57-0; veratraldehyde, 120-14-9; isovanillin, 621-59-0.

Supplementary Material Available: ^{1}H NMR spectral data for **3a–p**, **4a–p**, **13a,c**, **14a–c**, and **15a–c** (8 pages). Ordering information is given on any current masthead page.

Copper(II)-Promoted Aqueous Decomposition of Aldicarb

Shelton Bank* and R. Jeffrey Tyrrell

Department of Chemistry, State University of New York at Albany, Albany, New York 12222

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The copper(II)-promoted decomposition of aldicarb, 2-methyl-2-(methylthio)propanal *O*-[(methylamino)carbonyl]oxime, was investigated over the pH region 2.91 to 5.51. The products are 2-methyl-2-(methylthio)propionitrile (82%) and 2-methyl-2-(methylthio)propanal (18%). Thus in contrast to many acyl compounds Cu^{2+} promotes the same reaction as that observed in acid rather than the base-catalyzed process. From the effects of Cu^{2+} concentration and temperature upon the rate of reaction a scheme is proposed. Cu^{2+} complexation leads to a β-thioiminium ion whose special stability provides fragmentation as the predominant pathway.

Aldicarb, 2-methyl-2(methylthio)propanal *O*-[(methylamino)carbonyl)] oxime (I), is a widely used systemic pesticide which acts on the central nervous system. Both aldicarb and its toxic metabolites contaminate the aquifers in various parts of the United States,[1] and in many instances levels in drinking water wells exceed the current federal guideline of 10 ppb.[2] Recent studies in our lab-

$$CH_3SC(CH_3)_2CH{=}CNOC(O)NHCH_3$$
I

oratory[3] and by others[4,5] have determined the effects of pH and temperature on the hydrolysis rate and the reaction products of aldicarb. At pH values above 7.0 a characteristic base-catalyzed carbamate decomposition via methyl isocyanate dominates, and the principal products are the oxime (II) of 2-methyl-2-(methylthio)propanal (III), methylamine, dimethylurea, and carbon dioxide.[3] At pH

$$CH_3SC(CH_3)_2CH{=}NOH$$
II

values below 5.0 an unusual acid-catalyzed reaction occurs, leading principally to 2-methyl-2-(methylthio)propionitrile (IV) and methylamine.[3] The acid-catalyzed process is peculiar since most *N*-methylcarbamates react orders of magnitude more slowly in acid media than in basic media.[6] Minor products in both reactions come in part from the small amount (~9%) of the *Z* isomer present in I.

The characterization of the acid-catalyzed component in the hydrolysis of aldicarb (I)[3] led us to speculate on the interesting possibility of catalysis by divalent metal ions. Multivalent ions, acting as Lewis acids,[7-9] catalyze a variety of organic reactions and have several advantages over the proton in assisting reaction.[8] For example, the metal often carries more than a single positive charge, and in solutions near neutrality the concentration of divalent metal can usually be brought to 10^{-2} M, some 4 to 5 orders of magnitude greater than the hydronium ion concentration. More complex mechanisms for metal ion catalysis have been reported for hydrolysis of acyl derivatives, such as esters, amides, and anhydrides.[10-19] These studies provide

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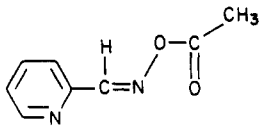
Table I. Effect of M^{2+} on Aqueous Decomposition[a] of Aldicarb[b]

pD	M^{2+}	$10^5 k_{obsd}$, s^{-1} [e]	k rel
5.0	none	2.30	1
	Zn^{2+} [c]	5.78	2.51
	Cu^{2+} [d]	52.0	22.6
5.6	none	2.40	1
	Zn^{2+} [c]	3.78	1.56
	Cu^{2+} [d]	29.1	12.1

[a] At 90 °C in deuterated citrate phosphate buffer, 0.05 M: ionic strength raised to 0.7 M with potassium chloride. [b] Aldicarb concentration 0.087 M. [c] $ZnCl_2$, 0.087 M. [d] $Cu(NO_3)_2 \cdot 3H_2O$, 0.087 M. [e] Reactions were followed for 3 half-lives by FT NMR. Products in all metal-promoted reactions are the nitrile IV and the aldehyde III.

models for the roles of metal ions in biologically related reactions of hydrolytic metalloenzymes. In these reactions catalysis occurs because metal ions polarize the carbonyl bond by binding to the carbonyl oxygen or because metal-coordinated water molecules (or hydroxide ions) attack the carbonyl carbon through template effects. Sometimes further enhancement results from decreases in the basicity of the leaving groups due to metal coordination.

Reports by Olofson[20] and Suh and Kaiser[14,19] are significant to our investigation of metal-promoted hydrolysis of aldicarb (I). Olofson found a major rate enhancing effect of Cu^{2+} and Zn^{2+} ions in the deprotonation of 1-methyltetrazoles to form carbanion intermediates. Suh et al. found that these same metal cations catalyze nucleophilic attack by either metal-bound water or hydroxide ion and enhance the hydrolysis rate in the pH range 2.0–7.0 of *O*-acetyl-2-pyridinecarboxaldoxime, a molecule structurally related to aldicarb. These reactions are similar to the



hydrolysis of aldicarb. However, unlike these systems, aldicarb can react by either acid- or base-catalyzed pathways. Therefore, in our investigation of metal ion catalysis, we consider whether the possibility that the metal ions promote the hydroxide (water) pathway or whether the reaction mechanism is analogous to that catalyzed by hydronium ions.

Results and Discussion

The initial screening experiments using Zn^{2+} and Cu^{2+} in citrate buffers and having been analyzed by FT NMR demonstrated that Cu^{2+} produced a large rate enhancement whereas Zn^{2+} gave a considerably smaller effect (Table I). However, the high binding constants of the metals to the buffers likely moderated the effect, and in all other studies acetate buffers were used. Also, although proton NMR signals of the starting material and product appeared normal in the presence of Cu^{2+} ion, there was concern about quantitative NMR analysis in the presence of the paramagnetic species. Accordingly the experimental design for further studies utilized GLC analysis after extraction. (See Experimental Section).

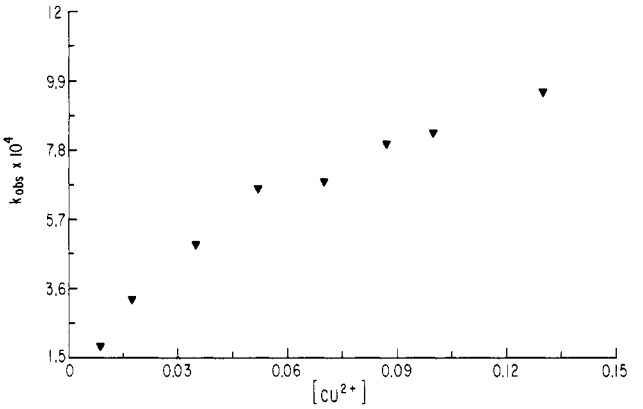


Figure 1. Plot of observed pseudo-first-order rate constant vs. copper(II) concentration for reaction of aldicarb at pH 3.92 and 60 °C.

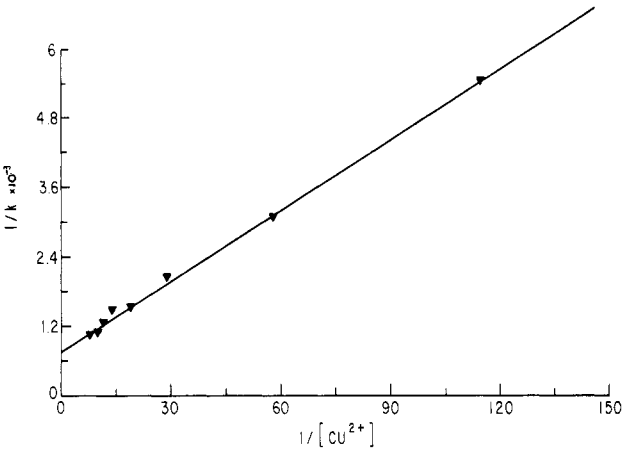


Figure 2. Plot of reciprocal of observed pseudo-first-order rate constant vs. reciprocal of copper(II) concentration for reaction of aldicarb at pH 3.92 and 60 °C.

Table II. Effect of Concentration of Cu^{2+} on Observed Rate Constant[a] at Constant pH

$10^2[Cu^{2+}]$,[b] M	$10^4 k_{obsd}$, s^{-1}	mole ratio $[Cu^{2+}]$/aldicarb
0.0	0.075	0
0.87	1.85	1
1.74	3.25	2
3.50	4.90	4
5.20	6.60	6
7.00	6.80	8
8.70	7.94	10
10.0	8.30	12
13.0	9.50	15

[a] At 60 °C with aldicarb at 0.0087 M in a 0.1 M acetate buffer at pH 3.92 and ionic strength raised to 0.7 M with KCl. [b] $Cu(NO_3)_2 \cdot 3H_2O$. [c] Analysis by GLC and followed for 2 to 3 half-lives.

The effect of Cu^{2+} concentration on the rate of reaction at constant pH is shown in Table II and Figure 1. As indicated by the plateau, saturation effects are observed at a Cu^{2+} concentration of 1.3×10^{-1} M with the aldicarb concentration maintained at 8.7×10^{-3} M. These effects suggest coordination of Cu^{2+} by aldicarb. Rate expressions have been derived[18] for similar systems and lead to the following formula:

$$\frac{1}{k_o} = \frac{1}{k_{cat}} + \frac{(1 + [H^+]/K_a)}{k_{cat}K_f} \frac{1}{[Cu^{2+}]}$$

where k_o is the pseudo-first-order rate constant, K_a is the acid dissociation constant of aldicarb, K_f is the equilibrium binding constant of aldicarb with Cu^{2+}, and k_{cat} is the rate

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Table III. Effect of pH and Temperature on Cu^{2+}-Promoted Aqueous Decomposition of Aldicarb[a]

pH	temp, °C	10^4k, s^{-1}
2.91	70	4.86
3.41	70	4.68
3.92	80	16.85
	70	5.26
	60	1.85
	50	6.34
	30	5.73
4.55	70	6.77
4.95	70	9.92
5.20	70	11.60
5.51	70	14.80

[a] Analysis by GLC. Concentration of $Cu(NO_3)_23H_2O$ was 0.087 M. k is observed rate constant. Using a 0.1 M acetate buffer with ionic strength raised to 0.7 with potassium chloride.

constant for complexed aldicarb. Figure 2 depicts the predicted linear relationship between $1/k_o$ and $[Cu^{2+}]$. The intercept value of 7.8×10^2 s^{-1} yields a k_{cat} of 1.3×10^{-3} s^{-1} ($\tau_{1/2}$ = 8.9 min) at pH 3.92 and 60 °C. In view of the close fit of the data to the theoretical expression, multiple complexation between Cu^{2+} and aldicarb is unlikely.

Table III and Figure 3 record the pH dependency of Cu^{2+}-promoted reaction of aldicarb in the range of pH 2.91 to 5.51. Precipitation of copper species precluded studies at higher pH values. Below pH 4.0 the reaction rate is independent of pH at equimolar concentrations of Cu^{2+} and aldicarb. In contrast, for reaction in the absence of metal ion this is a region of marked change of rate with pH. Above pH 4.0 the Cu^{2+}-promoted reaction shows a moderate pH dependency, whereas in this region the reaction rate in the absence of metal ion is essentially insensitive to pH variation.

The product composition for the metal-promoted reaction is notable. First, in the pH range 4.0 to 5.6, the product composition of the Cu^{2+}-promoted reaction is pH independent in contrast to reaction without metal. Second, the products of the Cu^{2+}-promoted reaction are the nitrile (82.1%) and the aldehyde (17.9%). These products are the same as those of the acid-catalyzed reaction and different from those of the base-catalyzed reaction. Therefore the metal promotes the acid-catalyzed reaction, in contrast to findings reported by Suh.[19]

Activation parameters determined from the temperature dependence of the promoted rate of hydrolysis reveal yet another important difference. The linear plot of ln k/T vs. $1/T$ leads to values of $\Delta G^{\ddagger}$ at 303 K, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ of 25.0 kcal/mol, 23.6 kcal/mol, and −4.6 eu, respectively. The values of $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ are unexceptional, but the observed activation entropy is quite different from the usual metal-catalyzed bimolecular reaction value of ~−20 eu.[19]

As previously described, the catalytic role of metal ions in hydrolytic reactions involving acyl derivatives is thought to occur mainly by two kinetically equivalent processes: (a) direct coordination of the carbonyl oxygen to the metal ion with subsequent activation to nucleophilic attack by either external hydroxyl ions or water molecules; (b) nucleophilic attack by metal-coordinated nucleophiles (^-OH, H_2O) through template effects on the complex.[10-19,22,23] Of the many systems that have been studied, the Cu^{2+}-catalyzed ester hydrolysis of the ester *O*-acetyl-2-pyridinecarboxaldoxime reported by Suh et al.[14,18] is most similar to the aldicarb reaction. Catalysis in the pyridine compound takes place by nucleophilic attack of a metal-bound

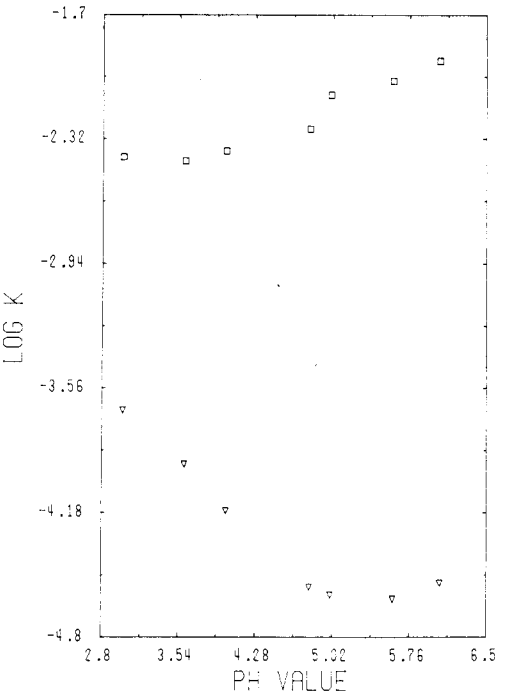
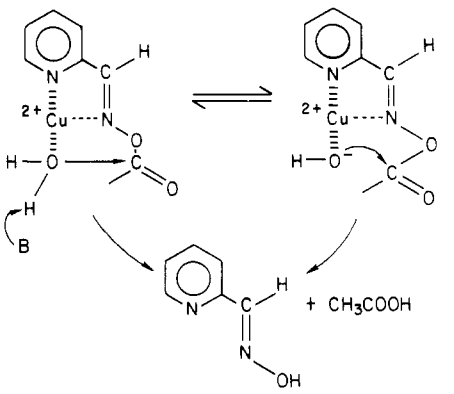


Figure 3. Plot of log of the pseudo-first-order rate constant vs. pH for reaction of aldicarb. ▽, for reaction without added metal; □, reaction with Cu^{2+} at 0.087 M.

hydroxide ion (or water molecule) on the complexed ester. The mechanism (eq 1) is characterized as involving in-



(1)

creased effective concentrations of attacking nucleophiles via template effects as well as enhanced leaving group ability due to metal complexation. Additionally, the value of $\Delta S^{\ddagger}$ of −21 eu is characteristic of a bimolecular reaction. Cu^{2+}-promoted hydrolysis of aldicarb has two fundamental differences from that of the above pyridine compound. The major product is nitrile and not oxime, and the value of $\Delta S^{\ddagger}$ is much smaller. These observations point to a major difference in mechanism due to the different substituents attached to the imine carbons of the two aldoxime derivatives. For aldicarb, the β-thio substituent is the important contributor.

The mechanism for the metal ion (and proton) catalyzed aldicarb reaction, shown in Scheme I, involves complexation with the formation of β-thioiminium ion (V). This species then undergoes an intramolecular elimination to yield the nitrile and the substituted carbamic acid which decomposes as expected to carbon dioxide and methylamine. Two features of the species V are notable: first, hydrolysis is not an important pathway; second, fragmention is the predominant pathway. There is considerable precedence for both the enhanced stability of β-thioiminium ions[24] and the enhanced fragmenation of

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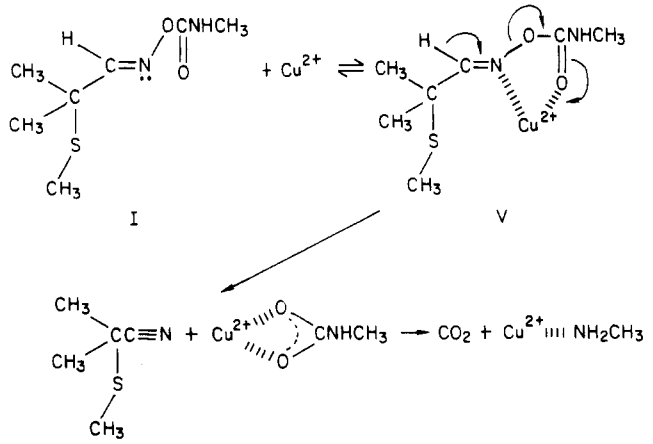
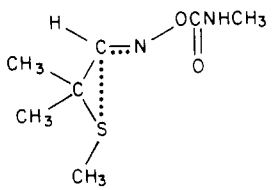
Scheme I



α-alkyl thioketoximes in the Beckmann reaction.[25]

Other work supports the proposal that an ion such as V would be special. LaLonde finds the β-thioiminium ions are stabilized against solvolysis by an intramolecular charge-transfer interaction between the sulfide sulfur atom and the neighboring iminium ion.[24] From equilibrium constants, the magnitude of the effect is slightly more than a power of 10.[24] Fragmentation estimates of the effect of sulfur are greater. For example, in α-alkyl thioketoximes of anti stereochemistry for sulfur, fragmentation is enhanced by 10^2 to 10^3 over rearrangement.[25] Complexed aldicarb V has the appropriate geometry to exhibit both of these effects and thus lead principally to the nitrile.

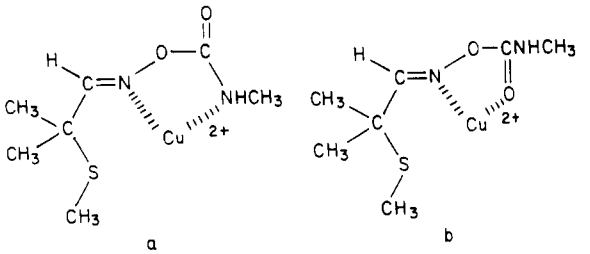
Somewhat removed but relevant analogies can be made from recent studies of the chemical ionization (CI) mass spectroscopy (MS)[26] and phototransformations of aldicarb.[27] Whereas the electron-impact (EI) MS studies of aldicarb reveal no molecular ions, in CIMS strong $(M + H)^+$ signals are observed,[26] as well as large peaks due to the ions of the protonated oxime and nitrile. Protonation apparently reduces fragmentation by stabilization, quite possibly by way of β-thioiminium species. In a related vein, phototransformations of aldicarb depend on the presence of sulfur. Model compounds without the sulfur atom exhibit no photochemical transformation; consequently interaction between the sulfur and imino group is proposed.



While the value of $\Delta S^{\ddagger}$ is surprising for a bimolecular reaction, the value is consistent with the proposed elimination reaction (Scheme I). The reaction bears some similarity to the Chugaev and acetate pyrolyses reactions, for which values for $\Delta S^{\ddagger}$ of −4.3 and −4.7 eu, respectively, were found.[28] Finally, this same elimination is the thermal reaction of aldicarb at higher temperatures and longer times.[29] Metal coordination lowers the activation energy for the process in analogy with other known metal-catalyzed decompositions.[30]

Attention is next focused on experiments designed to probe the likely site of metal complexation. Complexation to divalent metals is particularly favorable when the chelating atoms are four atoms apart.[12-14,22,23] Perhaps the most likely binding site is the imine nitrogen,[31] and for aldicarb binding at several other additional sites is possible. UV–vis spectroscopy revealed that the sulfur of the metal thio group is not a prime candidate for strong bonding. The complete absence of an intense ligand to metal charge-transfer (LMCT) absorption band in the region 325–380 nm,[32-34] characteristic of $S\sigma Cu^{2+}(dx^2 - y^2)$, argues against strong coordination of Cu^{2+} to sulfur. This is not unexpected since in dipolar solvents thio ether coordination to Cu^{2+} is nearly always very weak.[35]

Alternatively binding to the metal ion could occur either through chelation of the metal ion to the imine and carbamate nitrogen atoms (a) or to the imine nitrogen and carbonyl oxygen atoms (b) as illustrated below.



To evaluate the importance of the carbamate nitrogen for binding and catalysis by Cu^{2+} ion, the hydrolysis of 2-methyl-2-(methylthio)propanal *O*-acetyloxime (VI), the *O*-acetyl derivative of aldicarb (I) was investigated. In

$$CH_3SC(CH_3)_2CH{=}N{-}O{-}(O){=}CCH_3$$
VI

VI binding to the Cu^{2+} ion can occur only through the carbonyl oxygen, and, therefore, the importance of the carbamate nitrogen to catalysis would be evidenced by the extent of the rate enhancement in its absence. In fact, Cu^{2+} promotion for hydrolysis of ester VI is virtually the same as that for aldicarb. At 70 °C and Ph 3.92 the Cu^{2+}-catalyzed hydrolysis of ester VI has a rate constant of 3.0×10^{-3} s^{-1}. The estimated rate constant for the metal-free reaction of this ester at these conditions is 6.3×10^{-5} s^{-1}. Thus the Cu^{2+} promotion of a factor of 47 is virtually the same as that found for aldicarb. Importantly, the major product (approximately 80%) of the reaction in both instances is the nitrile IV.

The role of copper ion for the aldicarb reaction does not appear to be related to those acyl systems in which the metal ion acts as a Lewis acid to polarize a scissile carbonyl bond or coordinates hydroxide attack or decreases the basicity of the leaving group. On the other hand, the

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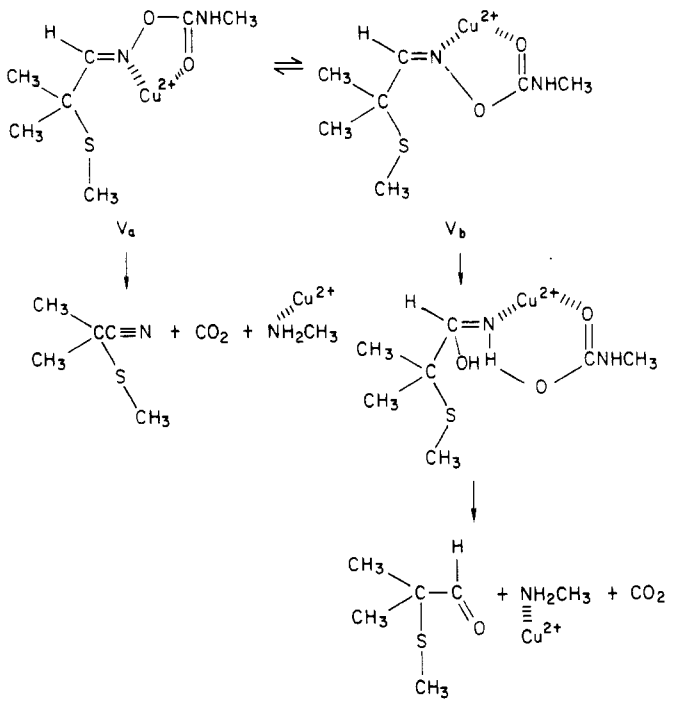
Scheme II



observed metal-complexed carbon–nitrogen double-bound activation has many analogies,[36-39] and in particular binding to the nitrogen lone pair of a CN double bond is well-known.[40] Two kinds of processes are promoted by this complexation: namely, nucleophilic addition to carbon and proton removal. An example of the former process is the activation of the CN double bond of tosylhydrazones by Cu(I) toward nucleophilic addition of a lithium reagent.[36] Additionally, the Cu(II)- and Ni(II)-catalyzed isomerization of aldoximes to amides is reasonably accounted for by this path,[37] and the Pb^{2+}-catalyzed addition of methyl isocyanate to carbamates provides another example.[30] Deprotonation catalyzed by metal ion complexation is similarly known for a variety of systems,[38] and important examples of this route include heterocyclic anion formation. Finally, the known metal-catalyzed elimination of oximes and their derivatives are reasonably accounted for by such a scheme.[39]

The metal- and acid-catalyzed reactions of aldicarb lead to 17–20% of the aldehyde. In view of the fact that the product composition of the metal ion catalyzed reaction is invariant with pH, clearly both the major (nitrile) and minor products (aldehyde) result from promoted processes. A mechanism (Scheme II) incorporating a common feature involves isomeric iminium ions. The ion V_a undergoes elimination to give nitrile, and ion V_b undergoes nucleophilic addition to give aldehyde. The geometrical relationships of the sulfur and hydrogen (and many analogies) are consistent with this expectation.

The ratio (80/20) of the products is different from the starting isomer ratio of 90/10 and the isomer ratio of products from the thermal decomposition and CIMS of aldicarb (90/10). It is possible that the starting ratio of isomers of aldicarb governs the thermal and CIMS results, and the product ratios obtained for the catalyzed reactions is the result from an increase in the *Z* form. Such increases of the *Z* form for the conjugate acids of oximes and their derivatives are well-known.[40] Thus, with the assumption that the ratio of ions V_a to V_b is 80/20, the observed results can be rationalized. In support of this, aldicarb, which is initially 90/10 *E*:*Z*, is converted to an 80/20 *E*:*Z* ratio in the presence of acid under conditions where no further reaction has occurred.

Experimental Section

Materials. The preparation of 2-methyl-2-(methylthio)-propanal *O*-[(methylamino)carbonyl]oxime, (aldicarb (I)), followed literature procedures,[29] with certain modifications which were described previously.[3] The product was obtained as long white needles mp 99–101 °C (lit.[29] mp 99–100 °C) and was determined by NMR to be in *E* and *Z* conformations in a ratio of 90/10, respectively.

2-Methyl-2-(methylthio)propanal *O*-Acetyloxime (VI). A 25-mL round-bottomed flask equipped with a stir bar and charged with 0.93 g (7 mmol) of 2-methyl-2-(methylthio)propanal oxime (II) and a tenfold excess of acetic anhydride (6.6 mL) was warmed and stirred for 30 min. The solution was cooled, poured into ice–water, and neutralized with 100 mL of 10% sodium bicarbonate. The aqueous layer was extracted with ether (3 × 10 mL), and the ether extracts were dried over sodium sulfate. The ether was removed, and the resulting oil was distilled (88 °C (0.5 mmHg)) to afford 0.69 g of (4 mmol, 57%) VI: ^1H NMR on an EM 360A gave 1.43 ppm, S, 6 H; 1.95 ppm, S, 3 H; 2.10 ppm, S, 3 H; 7.3 ppm, S, 1 H.

$ZnCl_2$ and $Cu(NO_3)_2 \cdot 3H_2O$ were reagent grade. All buffers used in the kinetic studies were prepared according to the methods described by Gomori.[41] Reagent grade buffer components and distilled water were used throughout. The ionic strength of buffered solutions was adjusted to 0.7 M with potassium chloride.

Kinetics. Gas–liquid chromatography (GLC) afforded a simple and efficient means for determination of rates of the Cu^{2+}-promoted hydrolysis of aldicarb (I). A measured quantity of aldicarb (I) was added to an amount of 0.1 M acetate buffer, pH 3.92, to afford a final concentration of 8.7×10^{-3} M. Vigorous stirring for approximately 90 min was required for complete dissolution of solute. An equimolar amount of $Cu(NO_3)_2 \cdot 3H_2O$ was added with stirring, and the pH of the solution was measured. The addition of the Cu^{2+} salt caused a decrease in the pH of the solution, possibly due to buffer complexation. The pH was adjusted with 1 N potassium hydroxide to the desired value. Aliquots (5 mL) of the reaction mixture were placed in each of eight labeled test tubes which were subsequently capped and sealed with parafilm. Another similarly filled test tube was fitted with a one-hole stopper into which was inserted a thermometer. The tubes were placed into an oil bath whose temperature was controlled by an I^2R Model L7-1180B Thermowatch. The reaction timer was started on immersion of the samples, and the initial sample tube was withdrawn when the tubes had attained thermal equilibrium. The hydrolysis reaction was stopped by quenching the tubes in a large ice–water bath. The reaction product (nitrile III) was extracted from the aqueous buffer with 1.0 mL of hexane which contained a measured quantity of 2-chlorooctane as an internal reference standard. The hexane layer was separated from the aqueous layer essentially quantitatively by slowly freezing the samples to −20 °C and decanting the upper unfrozen hexane layer into sample vials.

Gas–liquid chromatographic analyses were performed on a Hewlett-Packard Model 5750 research chromatograph equipped with a 5 ft × $^1/_8$ in. stainless steel column, packed with 30% SE-30 on Chrom W, 60–80 mesh. The GLC conditions employed were as follows: column temperature, 80 °C for 1 min post injection, then 15 °C increase per minute to 150 °C; injection port temperature, 80 °C; detector temperature, 150 °C. Injections (8 μL)

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of sample employed to produce the kinetic measurements. Generally, eight points (plus initial sample) taken during at least 2 half-lives were obtained. For each sample relative concentration of product at each time period was obtained by integrating the product peak and dividing that value by the integration value obtained for the internal standard peak. The slope of the linear regression analysis of ln concentration vs. time afforded the pseudo-first-order rate constant.

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Reactions of *N*-Halobenzylalkylamines with Sodium Methoxide in Methanol

Bong Rae Cho,* Jong Chan Yoon, and Richard A. Bartsch[1]

Department of Chemistry, Korea University, 1-Anamdong, Seoul, Korea, and Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

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Reactions of *N*-halobenzylmethylamines 1 and 2 (X = Cl and Br) with MeONa–MeOH have been investigated. Eliminations from 1 were quantitative, producing only benzylidenemethylamines. Reaction of 2 with MeONa–MeOH produced benzylidenemethylamines and benzylmethylamines. The yield of benzylidenemethylamine increased with electron-withdrawing aryl substituents and increased base concentration and became quantitative when pentane was used as a solvent. The results are interpreted as competing bimolecular elimination and nucleophilic substitution by methoxide on bromine. Product studies for reaction of *N*-halobenzyl-*tert*-butylamines with MeONa–MeOH and EtSNa–MeOH establish that the substitution reaction is a general reaction pathway available for the *N*-haloamines. Transition states for eliminations from 1 and 2 are characterized by Hammett ρ and primary deuterium isotope effect values.

Base-promoted, alkene-forming reactions have been extensively investigated, and a rather detailed understanding of steric and electronic effects in these reactions has evolved.[2a,3a] In contrast, relatively little is known about the influence of such factors in base-promoted eliminations which form carbon–nitrogen double bonds.[2b,4-11]

Unexpectedly large differences in E2 transition-state structures for base-promoted, imine-forming eliminations from $ArCH_2N(X)R$ compounds have been reported. When the leaving group was chlorine and the base–solvent combination was MeONa–MeOH or *t*-BuOK–*t*-BuOH, E2-central type of transition states were evident with appreciable C_β–H and N_α–Cl bond cleavage and significant double bond character.[8] On the other hand, for arenesulfonate leaving groups and amine bases in H_2O–THF–EtOAc or MeOH, the transition states are E1-like with extensive N_α–OSO_2Ar bond rupture but limited C_β–H bond scission and carbon–nitrogen double bond development.[9-11] At this stage it is not possible to deduce whether these transition-state differences result from the replacement of a poorer (chloride) leaving group by a better one (arenesulfonate)[10] or a variation in strength and charge type of the base or a combination of these two factors. To assess the influence of a change to a better leaving group with a constant base–solvent combination, we have investigated reactions of *N*-chlorobenzylmethylamines **1a–e** and *N*-bromobenzylmethylamines **2a–e** with MeONa–MeOH under the same experimental conditions. It should be noted that bromide is an even better leaving group than

Table I. Rate Coefficients for Eliminations from $ArCH_2N(Cl)CH_3$ Promoted by MeONa–MeOH

entry	compd[a]	temp, °C	[MeONa], M	$10^2k_2^E$,[b] M^{-1} s^{-1}
1	**1a**	25.0	0.0172	1.06
2	**1a**	25.0	0.172	1.13
3	**1b**	25.0	0.172	0.177
4	**1a**	35.0	0.172	2.41
5	**1a**	45.0	0.172	5.42
6	**1c**	25.0	0.172	0.568
7	**1d**	25.0	0.172	5.29
8	**1e**	25.0	0.172	21.1

[a] [Substrate] = 3.0–8.5 × 10^{-5}. [b] Estimated uncertainty, ±3%.

Table II. Effect of Aryl Substituents upon Yields of Elimination Products from Reactions of $YC_6H_4CH_2N(Br)CH_3$ with 0.0172 M MeONa–MeOH at 25.0 °C

Y	yield of **3**,[a] %
p-CH_3O	56.5
H	81.2
m-Br	87.2
m-NO_2	98.2

[a] Estimated uncertainty, ±1%.

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