

Hydrolysis of Naptalam and Structurally Related Amides: Inhibition by Dissolved Metal Ions and Metal (Hydr)Oxide Surfaces

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In metal ion-free solutions, the secondary amide naptalam hydrolyzes more rapidly as the pH is decreased; intramolecular nucleophilic attack by a carboxylate side group is very likely involved. Millimolar levels of dissolved Cu^{II} and Zn^{II} inhibit hydrolysis between pH 3.6 and pH 6.5. Metal ion–naptalam complex formation is important since addition of the competitive ligand citrate lessens the inhibitory effect. The metal (hydr)oxide surfaces Al_2O_3 and FeOOH inhibit naptalam hydrolysis to a lesser degree; inhibition is proportional to the extent of naptalam adsorbed. Secondary amides (propanil, salicylanilide, and *N*-1-naphthylacetamide) and tertiary amides (*N*-methyl-*N*-1-naphthylacetamide, furalaxyl, and *N,N*-diethylsalicylamide) that lack carboxylate side groups do not hydrolyze within 45 days of reaction, even when millimolar Cu^{II} concentrations are present. Tertiary amides possessing carboxylate side groups (*N,N*-diethyl-3,6-difluorophthalamic acid and *N,N*-dimethylsuccinamic acid) do hydrolyze but are insensitive to the presence or absence of Cu^{II} . The inhibitory effect is believed to occur via metal coordination of (1) the carbonyl group of naptalam, which induces deprotonation of the amide group and makes the substrate less reactive toward nucleophilic attack; (2) the free carboxylate group of naptalam, which blocks intramolecular nucleophilic attack; or (3) a combination of the two.

Keywords: *Naptalam; amide hydrolysis; metal catalysis; metal inhibition; phthalamic acid derivatives.*

INTRODUCTION

Several important classes of agrochemicals possess amide and anilide functional groups. Naptalam (*N*-(1-naphthyl)phthalamic acid, Figure 1) and other anilides possessing an ortho-carboxylic acid group are used to regulate plant growth and improve fruit quality (Green et al., 1987). Naptalam is used in pre-emergence control of grass and broadleaf weeds (Ashton and Crafts, 1981), mainly for perennial and deep-sown annual crops (Green et al., 1987). A total of 160 000 lb of naptalam is used annually in the United States (Gianessi and Anderson, 1995). The chloroanilide propanil (3',4'-dichloropropionanilide, Figure 1) is used as a post-emergence contact herbicide (Green et al., 1987). The systemic fungicide furalaxyl (methyl *N*-2,6-dimethylphenyl-*N*-furoylalaninate, Figure 1) (Green et al., 1987) possesses both an anilide and a carboxylic acid ester functional group. Naptalam and propanil are secondary anilides, while furalaxyl is a tertiary anilide.

Amides and anilides degrade primarily via hydrolysis to yield carboxylic acid and amine products, although far more slowly than corresponding carboxylic acid esters (Pollack and Bender, 1970; Brown et al., 1992; Fife, 1993). Dissolved divalent metal ions have been reported to catalyze the hydrolysis of some simple amides and anilides but to inhibit the hydrolysis of others (Fife and Przystas, 1986; Sayre, 1986; Reddy et al., 1991; Fife, 1991; Sayre et al., 1992; Fife and Bembi, 1993). Agrochemicals often possess functional groups in

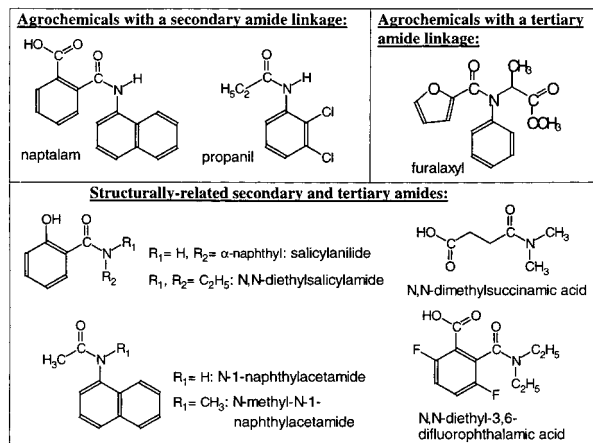


Figure 1. Structures of agrochemicals and related secondary and tertiary amides examined in this study.

the vicinity of amide and anilide linkages; participation by these groups makes interpretation of hydrolysis experiments more complex than in the case of simple amides and anilides.

Relatively little is known about the catalytic or inhibitory effects of dissolved metal ions, mineral surfaces, and other chemicals encountered in environmental media on the hydrolysis of amide and anilide agrochemicals. Granados et al. (1995) reported no significant effects of dissolved divalent metal ions and cyclodextrin on naptalam hydrolysis. The pH value employed (pH = 2.0) may have been unsuitable for catalysis or inhibition however. Recent studies with agrochemicals possessing carboxylic acid ester and

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organophosphorus ester groups have however demonstrated significant catalysis in the presence of dissolved divalent metal ions and metal oxide surfaces (Torrents and Stone, 1991, 1994; Smolen and Stone, 1997, 1998; Dannenberg and Pehkonen, 1998).

The objective of this study is to examine whether the hydrolysis of amide and anilide agrochemicals is susceptible to catalysis or inhibition by dissolved divalent metal ions (Ni^{II} , Cu^{II} , and Zn^{II}) and by metal (hydroxide) surfaces (Al_2O_3 , FeOOH , and TiO_2). Naptalam serves as the focus of this study, although results are also reported for propanil and furalaxyl. Five additional amides and anilides (Figure 1) are included in the study to provide insight into the reactions of the agrochemicals. Citric acid additions were made in a small number of experiments to explore how complexation by naturally occurring organic ligands may influence metal ion catalysis and inhibition.

AMIDE AND ANILIDE HYDROLYSIS: CATALYSIS AND INHIBITION BY DISSOLVED METAL IONS

Amide and anilide hydrolysis begins by nucleophilic attack by water or hydroxide ions at the carbonyl carbon, forming a tetrahedral intermediate. Resonance between the amide nitrogen atom and the carbonyl group decreases the electrophilicity of the carbonyl carbon and thus lowers the reactivity of the carbonyl group toward hydrolysis. Hydrolysis is completed by cleavage of the C–N bond and exit of the amine or aniline leaving group. Due to their high basicities, negatively charged amines are extremely poor leaving groups; protonation is usually necessary to facilitate their exit from the tetrahedral intermediates (Sayre, 1986).

The effects of metal ions on the hydrolysis of simple amides and anilides have been extensively studied, largely because of interest in the action of peptidase metalloenzymes (Buckingham et al., 1985; Sayre, 1986; Groves and Baron, 1989; Chin, 1990; Fife, 1991; Sayre et al., 1992; Fife, 1993). Most postulated mechanisms are one or a combination of the three generalized mechanisms below:

Mechanism 1: The metal ion coordinates the *substrate* in a manner that raises or lowers its susceptibility toward nucleophilic attack.

Mechanism 2: The metal ion coordinates the *nucleophile* in a manner that raises or lowers its reactivity toward electrophilic sites.

Mechanism 3: The metal ion coordinates the *leaving group*, facilitating its exit from the tetrahedral intermediate.

The effects of metal ions on amide hydrolysis via mechanism 1 are best illustrated by the hydrolysis of a number of amide derivatives of picolinic acid reported by Sayre et al. (1992). As illustrated in Figure 2, picolinyl amides possess a pyridyl nitrogen that improves the ability of the carbonyl oxygen to coordinate metal ions by making five-membered chelate ring formation possible. With tertiary picolinyl amides, the shift in electron density accompanying metal ion coordination activates the carbonyl carbon toward nucleophilic attack, and thus catalysis is observed. With secondary picolinyl amides, metal ion coordination of the carbonyl oxygen can induce the deprotonation of the amide nitrogen. Deprotonation shifts electron density onto the carbonyl carbon, and hence metal ion coordination can actually have an *inhibitory* effect on hydrolysis.

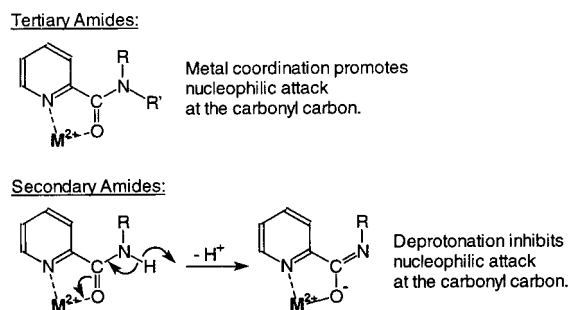


Figure 2. Metal ion coordination of tertiary and secondary amides and its effect on the carbonyl carbon-centered nucleophilic attack [mechanism 1, adapted from Sayre et al. (1992)].

With regards to mechanism 2, metal ions can induce deprotonation of coordinated water molecules, yielding metal–hydroxo species (MeOH^+ , $\text{Me}(\text{OH})_2^0$, etc.) that can serve as nucleophiles. A number of investigators have concluded that nucleophilic attack by metal–hydroxo species is at least partially responsible for observations of metal ion-catalyzed amide hydrolysis (Buckingham et al., 1970; Duerr and Czarnik, 1990; Takasaki et al., 1993). Mechanism 2 is also observed in systems where the metal ion coordinates a side group of the substrate that can serve as an intramolecular nucleophile (Sigman and Jorgensen, 1972; Groves and Baron, 1989; Koike et al., 1995).

Metal ions may simultaneously coordinate with the substrate and the nucleophile, making it possible for mechanisms 1 and 2 to occur concurrently. When metal ion-catalyzed amide hydrolysis is observed, a combined mechanism of this kind is usually proposed (Grove and Barrons, 1989; Chin et al., 1990; Tang and Sayre, 1993; Fife and Bembi, 1993).

Mechanism 3 involves metal ion coordination of the leaving group, which weakens the bond between the leaving group and the carbonyl carbon and facilitates leaving group exit. This type of catalysis is important for amides with poor leaving groups and has been discussed by Sayre (1986) and Fife (1991). Metal ion coordination facilitates the exit of amine leaving group from the tetrahedral intermediate either by stabilizing the amine leaving group through coordination or by promoting the protonation of the amine leaving group.

MATERIALS AND METHODS

Chemical Reagents. The inorganic reagents $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{Pb}(\text{NO}_3)_2$, ZnCl_2 , and NaCl were purchased from Aldrich Chemical Co. Acetic acid, sodium acetate (from J. T. Baker), and MOPS (4-morpholinepropanesulfonic acid, from Aldrich) were employed as pH buffers. Tetradecyltrimethylammonium bromide (TTAB, Aldrich) is an additive to the phosphate buffer that serves as the capillary electrophoresis electrolyte.

Naptalam (*N*-(1-naphthyl)phthalamic acid) was purchased from ChemService at greater than 98% purity and used without further purification. The hydrolysis product 1-naphthylamine was obtained from Aldrich and used without further purification. Several structurally related amides and anilides were included in this study: *N,N*-dimethylsuccinamic acid, furalaxyl (methyl *N*-2,6-dimethylphenyl-*N*-furoylalaninate), propanil (3',4'-dichloropropionanilide), *N*-methyl-*N*-1-naphthylacetamide, and *N*-1-naphthylacetamide (from ChemService); *N,N*-diethyl-3,6-difluorophthalamic acid, *N,N*-diethylsalicylamide, and salicylanilide (from Aldrich). The following hydrolysis products were purchased from Aldrich and used without further purification: 3,4-dichloroaniline, 3,6-difluorophthalic acid, salicylic acid, and succinic acid.

Table 1. Characteristics of Metal (Hydr)Oxides

	surface area (m ² /g)	pH _{ZPC}	site density (sites/nm ²)
Al ₂ O ₃	90.1 ^a	8.9 ^c	3.81 ^a
TiO ₂	39.5 ^a	6.3 ^d	3.81 ^a
FeOOH	47.5 ^b	8.45 ^b	7 ^b

^a Vasudevan and Stone (1998). ^b Coughlin and Stone (1995) [from Hayes and Leckie (1986)]. ^c Torrents and Stone (1994). ^d Torrents and Stone (1991).

Metal (Hydr)Oxides. Aluminum oxide (Al₂O₃, type C) and titanium dioxide (primarily anatase, type P25) were obtained from Degussa Corp. (Teterboro, NJ). The two oxides were stored in an oven at 70 °C and used without further purification. FeOOH (goethite) used in this study had been synthesized and characterized as part of an earlier study (Coughlin and Stone, 1995). A modification of the synthesis method of Atkinson et al. (1967) was employed: 6.5 L of 0.5 M Fe(NO₃)₃ in 0.21 M HNO₃ was added to 12.6 L of 1.55 M KOH while sparging with 20% O₂/80% N₂. The FeOOH particles were washed using sonication and centrifugation and stored in aqueous suspension prior to use.

The characteristics of the metal (hydr)oxides used in this study are summarized in Table 1. The specific surface area (*S*, m²/g) was determined using BET nitrogen adsorption. The number of fluoride-binding surface sites (sites/m²) was determined following the method of Sigg and Stumm (1981) as described in Vasudevan and Stone (1996). A fluoride adsorption isotherm was conducted at pH 4.0 and yielded an adsorption maximum of 2.5 × 10⁻⁴ mol of F⁻/g of TiO₂ and 5.69 × 10⁻⁴ mol of F⁻/g of Al₂O₃. Based upon the measured BET surface area, the site density of both oxides was calculated to be 3.8 sites/nm². For the site density of FeOOH (goethite), the value reported by Hayes and Leckie (1986) was used. The pH_{ZPC} (pH of zero proton condition) of each (hydr)oxide was determined by conducting acid/base titrations at different electrolyte (NaNO₃) concentrations (Torrents and Stone, 1991).

Hydrolysis Experiments. Reagent-grade water (18 MΩ-cm resistivity) was prepared using a glass distillation apparatus and a Milli-Q reagent-grade water system (Millipore Corp.). All glassware was soaked in 6 N HNO₃ and rinsed several times with reagent-grade water prior to use. The brown glass amber vials used for hydrolysis experiments were autoclaved prior to use, and reaction solutions were filter-sterilized to inhibit biotic reactions. At 5–10 mM concentrations, acetate buffer was used for experimental pH range of 3.6–5.5, while the MOPS buffer was used for pH 5.8–7.5.

Hydrolysis reaction solutions were initially prepared with buffer, metal chloride salt, or a predetermined amount of (hydr)oxides (10 g/L). NaCl was added to all solutions to yield a concentration of 0.10 M. Solution pH was adjusted by adding a very small amount of strong acid (HCl) or base (NaOH). After 3–4 h of stirring, an appropriate amount of freshly prepared stock solution of naptalam (or structurally related compound) was added to initiate hydrolysis. The naptalam stock solution was prepared by dissolving 3.0 mg of naptalam in 100 mL of reagent-grade water with continuous stirring for 30 min, followed by filtering through a 0.2-μm filter. It is worth noting that keeping solution pH constant for naptalam reactions is very important since naptalam hydrolysis rates are strongly dependent upon pH. As the reactions took place, changes of pH were less than 0.05 log of units. Vials containing TiO₂ were wrapped with aluminum foil to prevent photochemical oxidation. Reaction solutions were continuously stirred in a 25 °C water bath, and aliquots of solution were periodically collected for analysis. For hydrolysis in metal (hydr)oxide suspensions, aliquots of solution were centrifuged at 5000 rpm for 12 min using a Sorvall SS-34 rotor and then filtered through 0.2-μm filters (Nuclepore Corp.) to remove metal (hydr)oxide particles before analysis.

Hydrolysis reactions were primarily followed using a reversed-phase HPLC system (μ-Bondapac-C₁₈ column, Waters Corp., MA) with UV detection. Naptalam hydrolysis can be followed by either monitoring loss of naptalam at 210 nm or generation of 1-naphthylamine hydrolysis product at 300 nm

over time. HPLC conditions employed for analyzing naptalam, structurally related compounds, and hydrolysis products are described in the Supporting Information. A Waters Quantum 4000 capillary electrophoresis system (CE) with 185 nm UV detector was used to monitor loss of the parent compounds *N,N*-diethyl-3,6-difluorophthalamic acid and *N,N*-dimethylsuccinamic acid and production of the corresponding hydrolysis products 3,6-difluorophthalic acid and succinic acid. The CE was run in anion mode using a 60 cm long fused-silica capillary column, 30–60 s hydrostatic sample time, and 18 kV applied voltage. The electrolyte consisted of 25 mM phosphate buffer (pH 7.4) and 0.5 mM TTAB.

To determine the concentration of naptalam in stock solutions, an aliquot was acidified to pH 2.0, and the concentration of the hydrolysis product 1-naphthylamine was measured after 5–7 days of reaction time. Under these conditions, the hydrolysis reaction went to completion.

Preliminary experiments performed in blank solutions and in solutions containing divalent metal ions indicated that decreases in the concentration of naptalam always matched increases in the concentration of 1-naphthylamine, indicating good mass balance. In subsequent experiments, 1-naphthylamine concentrations were monitored and converted into naptalam concentrations using a mass balance equation. Plots of the log of naptalam concentration versus time were not linear, indicating that pseudo-first-order kinetics did not apply. (The amount hydrolyzed at long reaction time is less than expected from first-order kinetics.)

A separate set of experiments were performed to examine the adsorption of the hydrolysis product 1-naphthylamine to metal (hydr)oxide surfaces. 1-Naphthylamine (29.7 μM) was added to metal (hydr)oxide suspensions containing 10 g/L Al₂O₃, FeOOH, or TiO₂. The solutions contained 5.0 mM acetate (pH 3.6–5.5) or MOPS (pH 5.8–7.5) buffer and 0.10 M NaCl. After 4–5 h of stirring, aliquots of solution were centrifuged and filtered before analysis. Adsorption was determined by comparing the concentrations of 1-naphthylamine in supernatant solutions with those in metal (hydr)oxide-free solutions.

RESULTS AND DISCUSSION

pK_a Values for Naptalam. The acid–base properties of naptalam play a crucial role in its behavior and reactivity. Since the measured pK_a values of the functional groups of naptalam are not available in the literature, we employed the computer program SPARC (Karickhoff et al., 1991) to estimate the pK_a values of the carboxylic acid group, the amide nitrogen, and the carbonyl oxygen of naptalam. SPARC uses computational algorithms based on the fundamental chemical structure theory to estimate a variety of reactivity parameters such as pK_a (Hilal et al., 1994, 1996). Molecular structures of compounds are broken into functional units with known intrinsic reactivity. This intrinsic behavior is modified for a specific molecule in question with mechanistic perturbation models (Karickhoff et al., 1991).

The estimated pK_a values (infinite dilution scale) for deprotonation of the carboxylic acid group of naptalam is 3.2 and for the deprotonation of the amide nitrogen is 10.24. The pK_a for the protonation of the carbonyl oxygen is -5.6. These pK_a values were used as input into the equilibrium computer program HYDRAQL (Papelis et al., 1988). At the ionic strength of our experiments (0.10 M NaCl), a neutral species is predominant below pH 3.5, a monoanion is predominant between pH 3.2 and pH 10.35, and a dianion is predominant above pH 10.35.

Naptalam Hydrolysis in the Absence of Metal Ions. Hydrolysis experiments in the absence of metals were performed at 25 °C in solutions buffered between

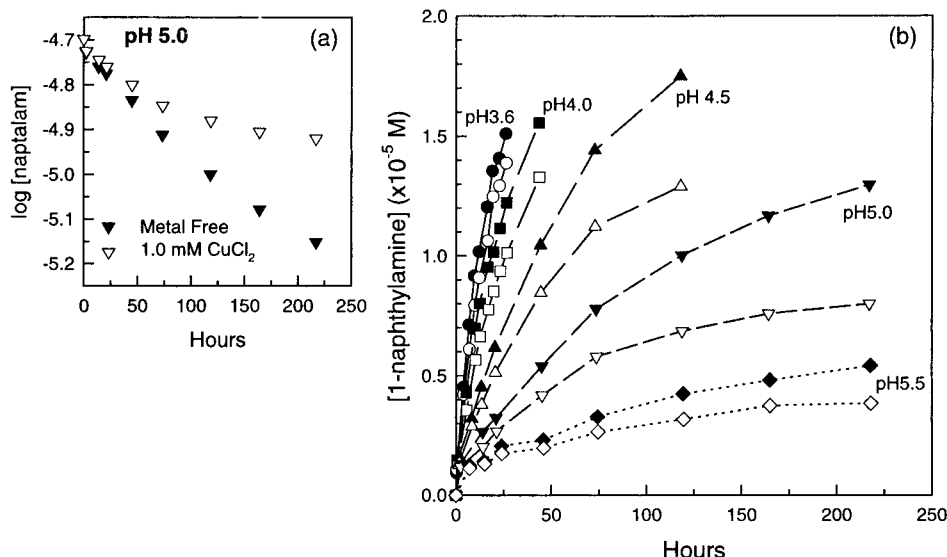


Figure 3. Loss of naptalam (a) and production of 1-naphthylamine (b) as a function of time in the presence and absence of Cu^{II}. Filled symbols represent metal ion-free solutions, while open symbols represent solutions containing Cu^{II}. Reaction conditions: 2.0×10^{-5} M naptalam, 1.0 mM CuCl₂, 10 mM acetate buffer, 0.1 M NaCl, 25 °C.

pH 3.6 and pH 7.5. Stoichiometric conversion of naptalam to 1-naphthylamine was observed throughout the pH range examined. Plots of log[naptalam] versus time are not linear (Figure 3a); hydrolysis rates inexplicably slow as the reaction progresses. The rate of 1-naphthylamine production significantly decreases with increasing pH (Figure 3b).

To illustrate the pH dependence of the naptalam hydrolysis reaction, the percent naptalam converted into 1-naphthylamine after 43.5 h of reaction has been calculated. As shown in Figure 4, the percent conversion is negligible during a 14-day period at pH 7.5 but rises dramatically as the pH is decreased to 4.5. The percent conversion levels out slightly below pH 4.

A mechanism involving intramolecular attack has been postulated for the hydrolysis of monoamide derivatives of phthalic acid (a group to which naptalam is a member) (Hawkins, 1976; Fife and Squillacote, 1978) and succinic acid (Higuchi et al., 1966; Kluger and Hunt, 1989a,b) in dilute aqueous media. The free carboxylic acid group may serve as an intramolecular nucleophile, attacking the amide carbonyl carbon to form a tetrahedral intermediate as illustrated in Scheme A of Figure 5. Elimination of the amine moiety from the tetrahedral intermediate generates an anhydride, which hydrolyzes much faster than the parent amide. In this way, intramolecular catalysis occurs.

The neutral species (I) or the kinetically equivalent zwitterion (II) (Figure 5) is considered to be the most reactive species based on the observation that hydrolysis rates reach a maximum at pH values near the p*K*_a of the carboxylic acid group and decrease at pH values either higher or lower than the p*K*_a (Hawkins, 1976; Fife and Squillacote, 1978). Furthermore, transfer of a proton to the leaving group from the carboxylic acid group or from the medium is considered as a requirement since loss of an amine anion from the tetrahedral intermediate is highly unfavorable.

A pathway involving nucleophilic attack of the amide nitrogen on the carboxylate carbonyl carbon to form a phthalimide (Scheme B of Figure 5) has been reported to be important for a few substituted phthalamic acids [e.g., *N*-(2-aminophenyl)phthalamic acid] (Perry, 1997). In the study by Granados et al. (1995), the intramo-

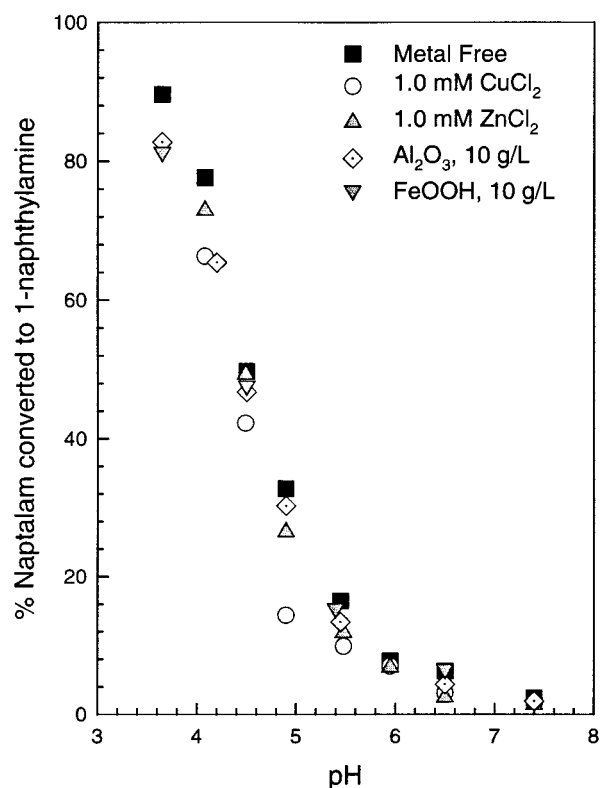


Figure 4. Percent naptalam converted into 1-naphthylamine after 43.5 h of reaction as a function of pH. Reaction conditions: $2.0\text{--}2.7 \times 10^{-5}$ M naptalam, 1.0 mM CuCl₂ or ZnCl₂, 10 g/L Al₂O₃ or FeOOH, 5.0–10 mM acetate (pH 3.7–5.5) or MOPS (pH 5.8–7.5) buffer, 0.1 M NaCl, 25 °C.

lecular catalysis mechanism was considered the predominant hydrolysis pathway of naptalam, and formation of *N*-1-naphthylphthalimide was suggested to explain 10–15% of the shortfall between the amount of 1-naphthylamine produced and the amount expected after reaching nearly complete hydrolysis of naptalam.

The observed pH dependence of naptalam hydrolysis is in accordance with the previous studies by Hawkins (1976), Fife and Squillacote (1978), and Granados et al. (1995). As pH decreases, the concentration of the neutral

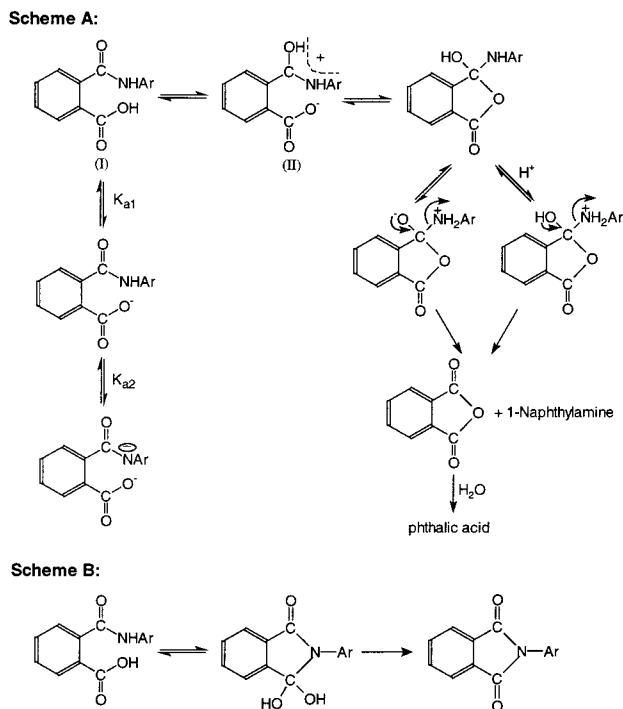


Figure 5. Proposed mechanisms of naptalam hydrolysis in the absence of metal ions [adapted from Hawkins (1976) and Granados et al. (1995)]. Ar = α -naphthyl.

species increases, and the stabilization of the amine leaving group is enhanced. For this reason, naptalam hydrolysis rates increase as the pH is decreased.

Inhibitory Effects of Dissolved Metal Ions on Naptalam Hydrolysis. Ni^{II} , Cu^{II} , and Zn^{II} -containing solutions exhibited good mass balance for the conversion of naptalam to 1-naphthylamine. Figure 3b shows that the hydrolysis reaction is significantly slower in the presence of 1.0 mM Cu^{II} than in metal ion-free solutions throughout the pH range examined ($3.6 < \text{pH} < 5.5$). The greatest inhibitory effect of Cu^{II} occurs at pH 5.0, followed by pH 4.5. This pH effect is most clearly seen when the percent hydrolytic conversion at a fixed time is plotted as a function of pH, as shown in Figure 4. The 1.0 mM Zn^{II} yields a smaller, inhibitory effect, and 1.0 mM Ni^{II} yields a still smaller inhibitory effect (not shown). Figure 6 shows the percent hydrolytic conversion at pH 5.0 as a function of Cu^{II} and Zn^{II} concentration. When 4.0 mM Cu^{II} has been added, the hydrolytic conversion of naptalam into 1-naphthylamine after 189 h of reaction is only 45% the amount observed in metal ion-free solutions. When 4.0 mM Zn^{II} has been added, the hydrolytic conversion is 86% the amount observed in metal ion-free solutions.

It was noted earlier that plots of $\log[\text{naptalam}]$ as a function of time were not linear in metal ion-free solutions. As shown in Figure 3a, these plots are even less linear in the presence of Cu^{II} and other ions. The inhibitory effect of Cu^{II} appears to grow as the reaction progresses.

Effects of metal ions on the hydrolysis of amides and carboxylic acid esters where carboxylate and acetamido side groups participate in hydrolysis as intramolecular nucleophiles have been reported (Fife and Squillacote, 1978; Fife et al., 1988; Fife, 1991). Metal ions have been found to inhibit the hydrolysis of secondary amides, while catalyzing hydrolysis of carboxylic acid esters. Although the compounds in those studies possess sig-

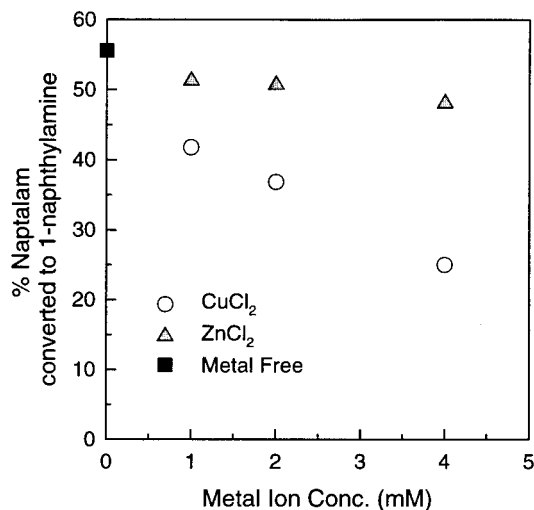


Figure 6. Percent naptalam converted into 1-naphthylamine after 189 h of reaction as a function of metal ion concentration (pH 5.0). Reaction conditions: 2.0×10^{-5} M naptalam, 10 mM acetate buffer, 0.1 M NaCl, 25 °C.

nificantly different structures from naptalam, the studies do provide a good basis for understanding the influence of metal ions on intramolecular reactions.

Before we discuss the mechanisms of metal ion-inhibited hydrolysis, it is useful to explore possible modes of metal ion coordination by naptalam. There are three possible donor groups on naptalam to coordinate with metal ions: the carboxylate group, the carbonyl oxygen, and the amide nitrogen. Within the pH range in our study, the carboxylic acid group is predominantly in its anionic form and is a much better donor ligand than the carbonyl oxygen and the amide nitrogen. If the metal ion is already coordinated to the carboxylate group, then coordination to either the carbonyl oxygen or the amide nitrogen would yield a seven-membered chelate ring. Coordination to the carbonyl oxygen is considered to be more likely since many studies have shown that metal ions coordinate amides preferentially via the carbonyl oxygen rather than via the amide nitrogen (Angus et al., 1993; Connolly et al., 1995).

The inhibitory effect of metal ions on naptalam hydrolysis can be approached using the three mechanisms outlined earlier:

Mechanism 1 corresponds to metal ion coordination to the carbonyl oxygen of naptalam (probably with participation of the carboxylate group). As mentioned earlier, metal ion-induced deprotonation at the amide nitrogen yields an inhibitory effect, while metal binding without deprotonation yields a catalytic effect. Therefore, metal ion inhibition of naptalam hydrolysis via mechanism 1 would arise from deprotonation as illustrated in Figure 2. Metal ion complex formation with the carbonyl oxygen must occur in order for inhibition by this mechanism to take place. Since complex formation constants for carbonyl oxygen groups are not available in the literature, another neutral ligand will be used as an analogy [a similar approach was used by Smolen and Stone (1997)]. Cu^{II} complexes ammonia (NH_3) 20 times more strongly than Ni^{II} and 63 times more strongly than Zn^{II} (for the reaction $\text{Me}^{2+} + \text{NH}_3 = \text{MeNH}_3^{2+}$; Smith et al., 1995). We can predict that complex formation by the carbonyl oxygen follows the same trend: $\text{Cu}^{\text{II}} > \text{Ni}^{\text{II}} > \text{Zn}^{\text{II}}$.

Once a complex has formed, the ability of each metal ion to induce deprotonation of the amide nitrogen is a

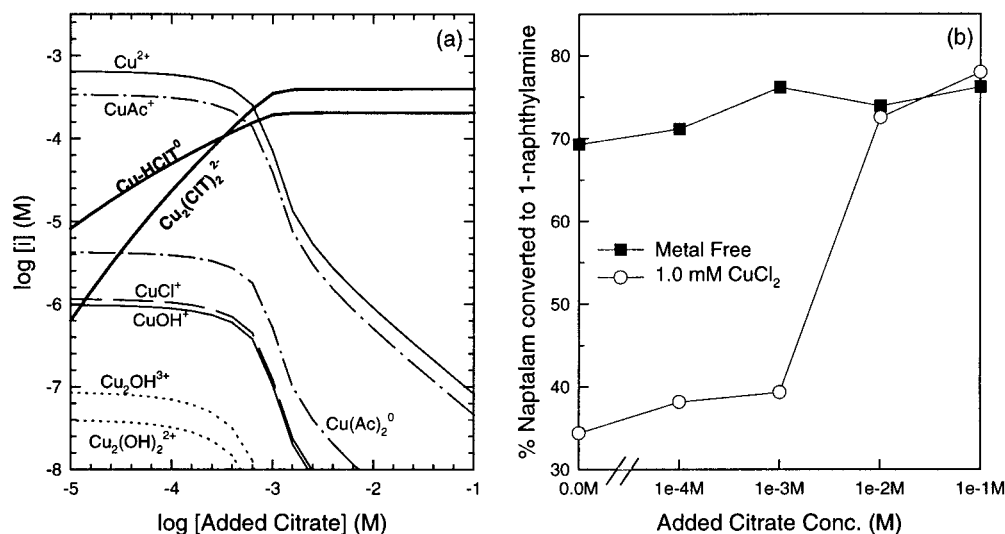


Figure 7. (a) Cu^{II} speciation with increasing citrate concentration calculated using HYDRAQL. (b) Effect of citrate addition on the Cu^{II} -inhibited hydrolysis of naptalam. Reaction conditions: 1.0 mM CuCl_2 , 20 mM acetate buffer (pH 5.0), 0.1 M NaCl, 25 °C. Percent naptalam converted into 1-naphthylamine was calculated after 103 h of reaction.

function of its ability to alter the electronic distribution of the coordinated substrate (Hay, 1984; da Silva and Williams, 1991). Cu^{II} , with the highest electron affinity (i.e., ionization potential), should perform better than Zn^{II} , with a moderate electron affinity, and Ni^{II} , with the lowest electron affinity of the three metal ions (da Silva and Williams, 1991).

We can conclude that Cu^{II} possesses properties most suited for inhibition via mechanism 1. Because Ni^{II} and Zn^{II} rank differently in terms of complex formation and electron affinity, it is difficult to predict a priori which metal ion is more suited for inhibition by this mechanism.

Mechanism 2 corresponds to metal ion coordination of the free carboxylate group. This eliminates its ability to serve as an intramolecular nucleophile. The divalent metal ions with the highest complex formation constant with the carboxylate group should yield the greatest inhibition by this mechanism. Although thermodynamic data are not available for naptalam, complex formation constants for the analogous ligand benzoate are available. Cu^{II} complexes benzoate 5.9 times more strongly than Zn^{II} and 9.1 times more strongly than Ni^{II} (for the reaction $\text{Me}^{2+} + \text{L}^- = \text{MeL}^+$; Smith et al., 1995). Thus, trends in complex formation constants match the trends observed in the inhibition experiments.

An equilibrium calculation was performed using the computer program HYDRAQL (Papelis et al., 1988) and thermodynamic data from Smith et al. (1995) under the following set of conditions: 20 μM benzoic acid, 1.0 mM Cu^{II} , 0.10 M NaCl, 2 < pH < 10. The maximum extent of Cu^{II} -benzoate complex formation occurred at pH 5.7. At pH values below this, protons compete with Cu^{II} for complex formation with benzoate. At higher pH, hydroxide ions compete with benzoate for complex formation with Cu^{II} . Since Cu^{II} -naptalam complex formation may involve another ligand donor group within the naptalam molecule, it is not surprising that the maximum inhibitory effect (which we observed at a pH of 5.0) occurred at a lower pH than calculated here for complexation by benzoate.

Mechanism 3 does not appear to be operative, since facilitating leaving group exit should catalyze hydrolysis, rather than inhibit it.

The experimental observation that Cu^{II} is the best inhibitor of naptalam hydrolysis is consistent with either mechanism 1 or mechanism 2. The greater inhibitory effect of Zn^{II} relative to Ni^{II} is also consistent with either mechanism. It is possible that both mechanisms contribute to the observed inhibitory effects.

Effects of Citric Acid Addition on Inhibition by Cu^{II} . Natural organic matter is ubiquitous in aquatic environments and forms complexes with dissolved metal ions. To examine whether complex formation could affect the ability of Cu^{II} to inhibit the hydrolysis of naptalam in natural environment, citric acid was included in one set of experiments. Citric acid possesses three carboxylate groups and one alcohol group; these functional groups are commonly found in natural organic matter (Mopper et al., 1980; Fox and Comerford, 1990).

Thermodynamic data from CRITICAL (Smith et al., 1995) and the equilibrium speciation computer program HYDRAQL (Papelis et al., 1988) were used to calculate Cu^{II} speciation under the conditions employed in this set of experiments. In these calculations, the acetate monoanion is presented as Ac^- , while the citrate trianion is represented as CIT^{3-} . CIT_T represents total added citrate, while Cu_T represents total added Cu^{II} .

As shown in Figure 7a, total concentrations of free Cu^{II} species (e.g., Cu^{2+} , CuAc^+ , $\text{Cu}(\text{Ac})_2^0$, CuCl^+ , CuOH^+) are not significantly affected when $\text{CIT}_T \ll \text{Cu}_T$. When enough citrate has been added to match Cu_T , citrate-complexed Cu^{II} species (primarily CuHCIT^0 and $\text{Cu}_2(\text{CIT})_2^{2-}$) become more important. Cu^{II} -citrate complexes predominate when $\text{CIT}_T > \text{Cu}_T$.

In the absence of Cu^{II} , citrate addition did not significantly affect the hydrolysis of naptalam. When $\text{CIT}_T \ll \text{Cu}_T$, citrate addition has little effect on Cu^{II} inhibition of naptalam hydrolysis. However, when $\text{CIT}_T \gg \text{Cu}_T$, citrate addition causes the naptalam hydrolysis rate to be the same as observed in Cu^{II} -free solutions (Figure 7b). The switchover takes place at added citrate concentrations that match added Cu^{II} concentrations, in agreement with the HYDRAQL calculations.

Comparison of Figure 7, panels a and b, indicates that free Cu^{II} species inhibit naptalam hydrolysis, while Cu^{II} -citrate complexes do not. When added citrate

concentrations are high enough to depress free Cu^{II} species concentrations, less Cu^{II} -naptalam complex presumably forms, resulting in less inhibition.

Hydrolysis of Other Secondary Amides in the Presence and Absence of Cu^{II} . After 45 days of reaction at pH 5.0, no hydrolysis of the three other secondary amides (propanil, salicylanilide, and *N*-1-naphthylacetamide) listed in Figure 1 could be detected in either the presence or the absence of 1.0 mM Cu^{II} .

Naptalam, salicylanilide, and *N*-1-naphthylacetamide all possess a 1-naphthylamine leaving group with a $\text{p}K_{\text{a}}$ of 3.92 (Lide, 1997), while propanil possesses a 3,4-dichloroaniline leaving group with a $\text{p}K_{\text{a}}$ near 2.05 (Lide, 1997). Both 1-naphthylamine and 3,4-dichloroaniline are weaker bases and thus are good leaving groups; however, 3,4-dichloroaniline is a better leaving group than 1-naphthylamine due to its lower basicity. *N*-1-Naphthylacetamide and propanil do not possess side groups that can participate in intramolecular attack at the amide linkage. The phenolic $-\text{OH}$ group of salicylanilide is too basic to serve as a general acid or base catalyst below pH 7. In addition, the phenolate anion derived from this group is not a suitable intramolecular nucleophile, since its $\text{p}K_{\text{a}}$ is too high and since the resultant four-membered ring is sterically unstable. Thus, only naptalam possesses a functional group capable of serving as an intramolecular nucleophile, which explains why it hydrolyzes substantially more rapidly than the other three amides.

Since there was no observed hydrolysis of the three other secondary amides in the presence of Cu^{II} , it is not possible to say whether Cu^{II} inhibits or catalyzes the hydrolysis reactions.

Hydrolysis of Tertiary Amides in the Presence and Absence of Cu^{II} . *N*-Methylated naptalam, prepared from phthalic anhydride and *N*-methyl-1-naphthylamine, would serve as an interesting tertiary amide analogue to the secondary amide naptalam. Unfortunately, two synthesis attempts failed (performed in ethyl ether and in tetrahydrofuran solvents). For this reason, our work was restricted to the five commercially available tertiary amides listed in Figure 1.

Hydrolysis reactions were studied as a function of pH over a 45-day period, in both the presence and the absence of 1.0 mM Cu^{II} . Experiments with *N*-methyl-*N*-1-naphthylacetamide, *N,N*-diethylsalicylamide, and *N,N*-diethyl-3,6-difluorophthalamic acid were conducted at pH 5.0; experiments with furalaxyl and *N,N*-dimethylsuccinamic acid were conducted over a wider pH range (pH 3.6–7.5).

The three tertiary amides that lack carboxylate side groups (*N*-methyl-*N*-1-naphthylacetamide, furalaxyl, and *N,N*-diethylsalicylamide) did not hydrolyze to any significant extent, either in the presence or in the absence of 1.0 mM Cu^{II} . In metal ion-free solutions, the two tertiary amides possessing carboxylate side groups (*N,N*-diethyl-3,6-difluorophthalamic acid and *N,N*-dimethylsuccinamic acid) were observed to undergo hydrolysis at measurable rates. *N,N*-Dimethylsuccinamic hydrolysis followed pseudo-first-order kinetics, and hydrolysis rates increased substantially as the pH was decreased, similar to our findings with naptalam. The 129-day half-life observed at pH 6.3, for example, decreases to a half-life of 1.2 days at pH 3.8 (data not shown). *N,N*-Diethyl-3,6-difluorophthalamic acid hydrolyzed much more slowly, with a half-life greater than 250 days at pH 5.0.

Addition of 1.0 mM Cu^{II} to *N,N*-diethyl-3,6-difluorophthalamic acid-containing solutions and 1.5 mM Cu^{II} to *N,N*-dimethylsuccinamic acid-containing solutions had no effect on hydrolysis rates. Thus, tertiary amides with carboxylate side groups are insensitive to the presence of Cu^{II} , while secondary amides with carboxylate side groups (naptalam) are inhibited by the presence of Cu^{II} .

First let us consider the hydrolysis in the absence of $\text{Cu}(\text{II})$. As far as formation of the tetrahedral intermediate is concerned, the tertiary amides with a carboxylate group capable of serving as an intramolecular nucleophile hydrolyze substantially more rapidly than those without (similar to the findings with naptalam and related secondary amides). Although furalaxyl possesses a furan oxygen and a carbonyl oxygen that is a part of a carboxylic acid ester linkage; apparently neither group is sufficiently basic to yield appreciable intramolecular reaction. *N,N*-Diethylsalicylamide possesses the same (albeit weak) phenolic $-\text{OH}$ side group as salicylanilide. As far as the rates of leaving group exit are concerned, the compounds with aniline leaving groups (*N*-methyl-*N*-1-naphthylacetamide and furalaxyl) should hydrolyze more rapidly than those with aliphatic amine leaving groups (*N,N*-diethylsalicylamide, *N,N*-diethyl-3,6-difluorophthalamic acid, and *N,N*-dimethylsuccinamic acid).

Observations regarding the hydrolysis of tertiary amides in the presence of Cu^{II} can be interpreted using the three mechanisms presented earlier:

Mechanism 1 corresponds to metal ion coordination to the carbonyl oxygen. Since tertiary amides do not possess an amide hydrogen, metal ion-induced deprotonation cannot occur. Metal ion coordination serves only to withdraw electron density from the carbonyl carbon, and hence catalysis should be observed, not inhibition.

Mechanism 2 corresponds to metal ion coordination of the attacking nucleophile. Generation of MeOH^+ and other hydroxo species catalyzes amide hydrolysis. On the other hand, metal ion coordination to the carboxylate group of *N,N*-dimethylsuccinamic acid and *N,N*-diethyl-3,6-difluorophthalamic acid could block the intramolecular nucleophilic attack.

Mechanism 3 catalyzes the exit of leaving group and should be more relevant when the leaving group is an aliphatic amine than when the leaving group is an aniline.

For the tertiary amides that lack carboxylate side groups, because hydrolysis rates could not be measured, no conclusions can be drawn about Cu^{II} catalysis or inhibition. For the hydrolysis of *N,N*-dimethylsuccinamic acid and *N,N*-diethyl-3,6-difluorophthalamic acid, metal ion coordination could result in both catalysis and inhibition. It is possible that these two effects offset each other, which may explain the insensitivity to the presence of $\text{Cu}(\text{II})$.

Inhibitory Effects of Metal (Hydr)Oxide Surfaces on Naptalam Hydrolysis. Metal (hydr)oxide surface sites contain metal atoms that can participate in complex formation reactions with solute species. In heterogeneous aquatic environments such as soils, sediments, and aquifers, the abundance of metal (hydr)oxide surface sites may exceed that of dissolved metal ions. For this reason, analogies between dissolved metal ion and surface site catalysts for the hydrolysis of carboxylic acid esters (Stone, 1989; Torrents and Stone, 1991) and organophosphorus esters (Torrents and Stone,

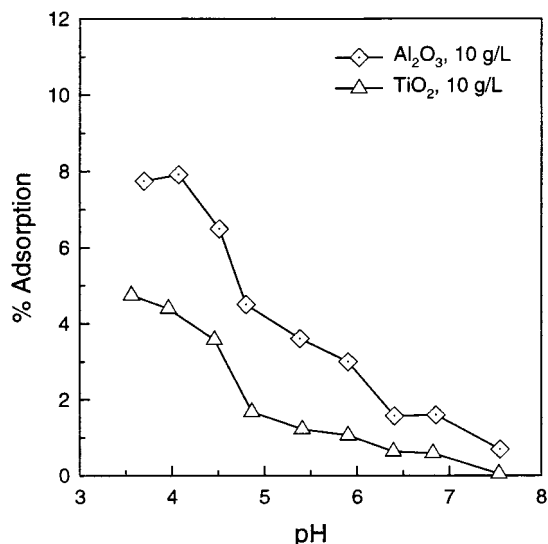


Figure 8. Adsorption of naptalam onto Al₂O₃ and TiO₂ oxide surfaces as a function of pH. Reaction conditions: 2.7×10^{-5} M naptalam, 10 mM acetate (pH 3.6–5.7) or MOPS (pH 5.8–7.5) buffer, 0.1 M NaCl, 25 °C.

1994; Smolen and Stone, 1998; Dannenberg and Pehkonen, 1998) have been explored.

The experiments described in this section investigate whether metal (hydr)oxide surfaces can inhibit naptalam hydrolysis in the same way as dissolved Ni^{II}, Cu^{II}, and Zn^{II}. Reaction progress was monitored by measuring changes in the concentrations of either naptalam or the hydrolysis product 1-naphthylamine in the supernatant solution as a function of pH. In order for this method to be reliable, adsorption of naptalam and 1-naphthylamine must be properly accounted for.

1-Naphthylamine Adsorption. The adsorption of 1-naphthylamine to metal (hydr)oxide surfaces were examined in Al₂O₃, FeOOH, and TiO₂ suspensions consisting of the same chemical composition as those used in the hydrolysis experiments. Throughout the pH range considered (3.6 < pH < 7.5), 1-naphthylamine concentration in supernatant solutions were not measurably different than concentrations measured in metal (hydr)oxide-free solutions, indicating negligible adsorption. Therefore 1-naphthylamine concentration measurements can be used to determine how much naptalam hydrolysis has taken place in metal (hydr)oxide suspensions.

Naptalam Adsorption. The hydrolysis of naptalam in Al₂O₃ and TiO₂ suspensions was followed by monitoring the loss of naptalam and the production of 1-naphthylamine. When naptalam was added to 10 g/L Al₂O₃ and TiO₂ suspensions, an initial rapid decrease in concentration was followed by a more gradual decrease (data not shown). The initial, rapid decrease did not yield a corresponding increase in the 1-naphthylamine concentration. The later, more gradual decrease did however yield amounts of 1-naphthylamine that corresponded to the stoichiometry of the hydrolysis reaction. It is therefore concluded that the initial decrease of naptalam concentration corresponds to adsorption, while the later decrease corresponds to hydrolysis.

Using this approach, the initial amount of naptalam adsorbed in suspensions containing 10 g/L Al₂O₃ and TiO₂ as a function of pH can be calculated, as shown in Figure 8. Adsorption increases as the pH is decreased and appears to reach a plateau near the pK_a of the

carboxylic acid group (3.5). These results are consistent with carboxylic acid adsorption experiments performed by Kummert and Stumm (1980) and Balistreri and Murray (1981).

The hydrolysis of naptalam in FeOOH suspensions was followed by the production of 1-naphthylamine. The extent of naptalam adsorption onto FeOOH hydroxides was not determined.

Naptalam Hydrolysis in Metal (Hydr)Oxide Suspensions. Al₂O₃ and FeOOH (hydr)oxides exert a small but significant inhibitory effect on naptalam hydrolysis, while TiO₂ has a negligible effect (data not shown). The effect of Al₂O₃ and FeOOH on naptalam hydrolysis as a function of pH is illustrated in Figure 4. The inhibitory effect of Al₂O₃ and FeOOH is most significant at pH 3.7 and decreases as pH increases.

Both adsorption and the inhibitory effect of Al₂O₃ on hydrolysis decrease as pH increases, indicating that adsorption may play an important role in inhibition. From (hydr)oxide properties listed in Table 1, the total available surface sites S_T (in moles of sites per liter) at a loading of 10 g/L can be calculated and is in the order of Al₂O₃ (5.70×10^{-3} M) ~ FeOOH (5.52×10^{-3} M) > TiO₂ (2.50×10^{-3} M). The higher available surface sites of Al₂O₃ relative to TiO₂ may explain the higher adsorption of naptalam to Al₂O₃ and, thus, the higher inhibitory effect. Although the adsorption data with FeOOH were not obtained, the observed inhibitory effects of the three (hydr)oxides are consistent with their total surface site loadings.

Let us assume for the moment that total dissolved metal ion concentration (e.g., Cu_T) and surface site loading (S_T , in mol/L) both provide reasonable estimates of the volume density of metal inhibitors available to naptalam. It is therefore interesting to note that the inhibitory effect arising from 1.0 mM Cu^{II} is substantially greater than that arising from 5.7 mM Al₂O₃ surface sites. In addition, the greatest inhibitory effect from Cu^{II} is observed at pH 5.0; while the greatest inhibitory effect from Al₂O₃ occurs at pH 3.7.

It is possible that metal (hydr)oxide surfaces inhibit naptalam hydrolysis similarly to dissolved metal ions via mechanism 1 (Figure 2), mechanism 2, or a combination of the two mechanisms.

CONCLUSIONS

This work was motivated by earlier studies that demonstrated that secondary amides are subject to metal ion inhibition, while tertiary amides are subject to metal ion catalysis (Fife and Squillacote, 1978; Fife, 1991; Sayre et al., 1992). This study examined whether the same conclusions from previous work can apply to agrochemicals bearing secondary and tertiary amide moieties.

Among the agrochemicals and structurally related secondary and tertiary amides considered here, only those possessing a carboxylate group that can serve as an intramolecular nucleophile exhibited significant hydrolysis, either in the presence or in the absence of metal ions or (hydr)oxide surfaces. This represents a unique group of amide compounds, and this fact must be kept in mind when comparisons to earlier studies are made.

The hydrolysis of the secondary amide naptalam is inhibited by dissolved metal ions (Cu^{II} and Zn^{II}) and by metal (hydr)oxide surfaces (Al₂O₃ and FeOOH). In contrast, the hydrolysis of two tertiary amide *N,N*-

dimethylsuccinamic acid and *N,N*-diethyl-3,6-difluorophthalamic acid is unaffected by the presence of Cu^{II}.

Metal catalysis and inhibition can occur via three primary mechanisms. In this study, results from different metals and structurally related compounds elucidate the responsible mechanism(s). It is concluded that two of the mechanisms may contribute to the observed inhibition. Mechanism 1 involves metal ion coordination of the carbonyl oxygen of naptalam (and possibly other portions of the molecule), which induces deprotonation of the amide group and makes the substrate less reactive toward nucleophilic attack. Mechanism 2 involves metal ion coordination of the free carboxylate group of naptalam, which blocks intramolecular nucleophilic attack. The insensitivity of the two tertiary amides to the presence of metal ions may arise from the tertiary amide versus secondary amide structure or from differences in leaving group basicity.

ENVIRONMENTAL SIGNIFICANCE

The dissolved metal ions included in this study (Ni^{II}, Cu^{II}, and Zn^{II}) are probably not found at high enough concentrations in most environments to significantly perturb rates of amide hydrolysis. The study does, however, provide important information about relationships between metal ion properties and metal ion inhibition and provides an impetus for studying the effects of more abundant dissolved metal ions such as Mg^{II}, Ca^{II}, and Fe^{II}.

Iron(III) (hydr)oxides, which were found to inhibit naptalam hydrolysis in this work, represent an important fraction of the available mineral surface area in soils and sediments (Cornell and Schwertmann, 1996). Al^{III}- and Ti^{IV}-containing metal (hydr)oxides are important in localized regions, such as the tropics. Dissolved metal ions and metal-containing mineral surfaces appear to be analogous in many respects regarding their ability to catalyze (Smolen and Stone, 1997, 1998) and inhibit (this work) hydrolysis reactions.

To illustrate the possible role of metal catalysis and inhibition in the environment, consider the following generalized equation for substrate hydrolysis at a fixed pH:

$$\frac{-d[\text{substrate}]}{dt} = \frac{\text{hydrolysis rate for uncomplexed substrate} + \text{hydrolysis rate for metal-substrate complex}}$$

The largest term on the right-hand side of this equation determines the half-life of the substrate. In order for catalysis to be observed, the fraction of substrate complexed by the metal ion can be small as long as the corresponding rate constant is large enough. In order for inhibition to be observed, the fraction of substrate complexed by the metal ion must be high, since any uncomplexed substrate continues to hydrolyze at the normal, faster rate. For this reason, inhibition is inherently harder to bring about than catalysis.

In the environment, other inorganic and organic ligands are present and may compete with the substrate for available free metal ions. This study demonstrated that citric acid substantially lowers the Cu^{II} inhibitory effect on naptalam hydrolysis. To predict hydrolysis rates, it is therefore necessary to carefully account for the effects of metal speciation on catalysis and inhibition.

Supporting Information Available: A table showing the HPLC conditions and UV wavelengths used in the study (1 page). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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