

# Kinetic Study on the Hydrolysis of 1-*N*-Naphthylphthalamic Acid (Naptalam)

Alejandro Granados, Mirtha Nassetta, and Rita H. de Rossi\*

Instituto de Investigaciones en Físico-Química de Córdoba (INFIQC), Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Suc. 16, C.C. 61, 5016 Córdoba, Argentina

The hydrolysis rate of 1-*N*-naphthylphthalamic acid (**Nap**) was measured as a function of pH in the range of 0.9–5 and proceeds via undissociated neighboring carboxyl group participation as was proposed for other phthalamic acid derivatives. One of the main hydrolysis products is naphthylamine, which is a known carcinogenic agent. **Nap** is as reactive as phthalamic acid but is less reactive than phthalanilic acid. MMX calculations on phthalamic acid derivatives showed that phthalanilic acid has the closest distance for a most efficient intramolecular catalysis. Additives such as cyclodextrin or metal ion do not affect the kinetics of the reaction.

**Keywords:** *Naptalam; amide hydrolysis; intramolecular catalysis; cyclodextrin*

## INTRODUCTION

Phthalamic acid derivatives 1 ( $R = H, Ph, 2-$  and  $4-ClC_6H_4, 2,4-Cl_2C_6H_3, 3-MeC_6H_4$  and  $\alpha$ -naphthyl) constitute an important group of plant growth regulators (Hoffmann and Smith, 1949). The nature and degree of the growth response shown by plants treated with these chemicals depend on the type and age of the plant and on the concentration and identity of the phthalamic acid derivative used. Naptalam ( $R = \alpha$ -naphthyl) (**Nap**) has found a place in herbicidal practice for the pre-emergence control of grass and broadleaf weeds, but it is less effective in foliage applications (Ashton and Crafts, 1981). Nevertheless, studies on the chemistry of **Nap** are scarce, even though phthalamic and phthalanilic acids ( $R = H$  and phenyl, respectively) have been widely studied (Bender et al., 1958; Hawkins, 1976). One of the main degradation products of **Nap** is naphthylamine, a known carcinogenic agent (*The Merck Index*, 1989); therefore, we investigated the chemical reactivity of **Nap** at different pH values and in the presence of additives such as cyclodextrins and metal ions which are known to catalyze (Fife and Bembi, 1993) or inhibit (Granados and de Rossi, 1993) the hydrolysis of amides. The results are reported in this paper.

## MATERIALS AND METHODS

**Nap** was obtained from a commercial sample of Alanap (Uniroyal Quimica Argentina S.A.C.I.) and purified by recrystallization from ethanol, mp 184–185 °C [lit. mp 185 °C (*The Merck Index*, 1989)]. Aqueous solutions were made up from deionized water obtained from a Millipore apparatus. Acetonitrile, Sintorgan HPLC grade, was used as received.

$\beta$ -Cyclodextrin (Roquette) was a gift from Ferromet S.A., Buenos Aires, Argentina, and used as received, but the purity was periodically checked by UV spectroscopy.

Hydroxypropyl- $\beta$ -cyclodextrin (HPCD) (Roquette) has an average substitution of 0.46.

Cobalt chloride, aluminum chloride, and copper chloride were of commercially available analytical grade and were used without further purification.

**Kinetic Procedures.** *pH Profile Measurements.* The reactions were initiated by adding the substrate dissolved in acetonitrile to a solution containing all of the other constituents. The total acetonitrile concentration was 4%. All reac-

tions were run at  $40.0 \pm 0.1$  °C and at constant ionic strength (0.5 M) using sodium chloride as compensating electrolyte. The reactions were measured at least up to 98% conversion, and the spectra of the solutions after 10 half-lives were compared with a mock solution containing 1-naphthylamine and phthalic acid. The spectra and their first- and second-order derivative were compared, and from this we estimated that the amount of 1-naphthylamine formed was about 10–15% lower than expected. The observed rate constants were determined by following the disappearance of **Nap** at 285 nm and the appearance of naphthylamine at 300 nm. The value obtained was wavelength independent. The change in absorbance during a kinetic run was recorded on a Shimadzu 260 recording spectrophotometer with a thermostated cell compartment. All reactions followed pseudo-first-order kinetics.

*Interaction with Metal Ions and Cyclodextrins.* Reactions with metal ions, with cyclodextrins, and with metal ions and cyclodextrins were carried out at  $25.0 \pm 0.1$  °C and at constant ionic strength (0.5 M). In the reactions with  $Cu^{2+}$ , the ionic strength was not maintained constant because the complex formed between  $Cu^{2+}$  and sodium chloride absorbs strongly at the wavelengths where the measurement was done.

Various concentrations of the metal ions were employed, and the ratio of metal ion to substrate concentration was greater than 20.

The pH of all solutions was adjusted by adding a drop of dilute acid or base. In the range 0.9–2 the pH was maintained with hydrochloric acid at the appropriate concentration, at pH 2–3.8 the buffer was  $1 \times 10^{-2}$  M chloroacetic acid, and at pH above 3.8 the buffer was acetic acid  $1 \times 10^{-2}$  M.  $[H^+]$  is defined as  $10^{-pH}$ .

Solution pH was measured with an Orion 720A pH meter appropriately calibrated before use.

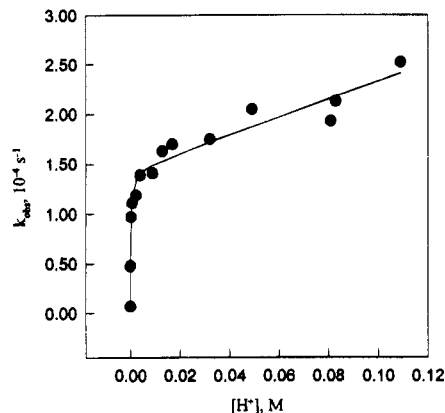
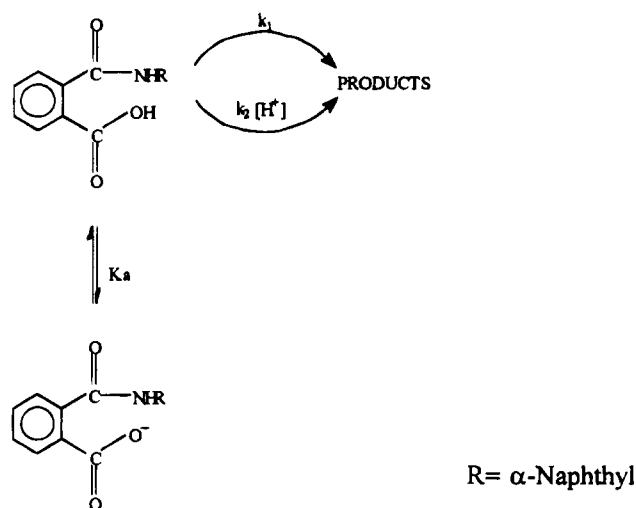
## RESULTS AND DISCUSSION

The hydrolysis rate of **Nap** was measured as a function of pH in the range of 0.9–5. The results collected in Table 1 show that this dependence is characterized by a steady decrease of the rate constant from pH 0.9 to 3 and an abrupt decrease from pH 3 to 5 as the **Nap** ionizes. In Figure 1  $k_{obs}$  is plotted vs hydrogen ion concentration ( $10^{-pH}$ ). The small difference in absorption at the maximum wavelength of 1-naphthylamine was attributed to the formation of *N*-1-naphthylphthalimide (Galeano Díaz et al., 1994). The formation of this product and 1-naphthylamine must take place in parallel pathways because good isosbestic

**Table 1. Effect of pH on the Rate Constants for the Hydrolysis of Nap<sup>a</sup>**

pH	$k_{\text{obs}}, 10^{-4} \text{ s}^{-1}$	$\log k_{\text{obs}}$	pH	$k_{\text{obs}}, 10^{-4} \text{ s}^{-1}$	$\log k_{\text{obs}}$
0.96	2.52 <sup>b</sup>	-3.60	2.41	1.39 <sup>c</sup>	-3.85
1.08	2.13 <sup>b</sup>	-3.67	2.61	1.31 <sup>b</sup>	-3.88
1.09	1.93 <sup>b</sup>	-3.71	2.61	1.19 <sup>c</sup>	-3.92
1.31	2.05 <sup>b</sup>	-3.68	3.10	1.11 <sup>c</sup>	-3.95
1.49	1.75 <sup>b</sup>	-3.75	3.40	0.976 <sup>c</sup>	-4.01
1.77	1.70 <sup>b</sup>	-3.77	4.07	0.503 <sup>c</sup>	-4.32
1.88	1.63 <sup>b</sup>	-3.79	5.01	0.0667 <sup>c</sup>	-5.15
2.03	1.41 <sup>b</sup>	-3.85			

<sup>a</sup> Temperature 40 °C, ionic strength 0.5 M with NaCl as compensating electrolyte, AcN 4%,  $[\text{Nap}]_0 = 5 \times 10^{-5} \text{ M}$ . <sup>b</sup> The pH values were regulated using hydrochloric acid. <sup>c</sup> Rate constants extrapolated to  $[\text{buffer}] = 0$  using the data in Table 2.

**Figure 1.** Effect of  $[\text{H}^+]$  on the hydrolysis of **Nap**; data from Table 1.**Scheme 1**

point and pseudo-first-order plots are obtained in the kinetic runs. Besides, rate constants determined at different wavelengths gave the same results (Bernasconi, 1976).

On the basis of literature data regarding the hydrolysis of phthalanilic acids (Hawkins, 1976), the hydrolysis of **Nap** can be represented as shown in Scheme 1.

For Scheme 1, the rate of formation of products can be expressed by

$$dP/dt = (k_1 + k_2[\text{H}^+])[\text{Nap}] \quad (1)$$

from which eq 2 could be derived:

$$k_{\text{obs}} = (k_1 + k_2[\text{H}^+]) / (1 + K_a/[\text{H}^+]) \quad (2)$$

Adjusting the values of the observed rate constants at the different  $[\text{H}^+]$  concentration to eq 2 (Enzfitter, 1987), we obtained the values of  $k_1$ ,  $k_2$ , and  $K_a$ , namely  $(1.46 \pm 0.05) \times 10^{-4} \text{ s}^{-1}$ ,  $(9 \pm 1) \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ , and  $(2.13 \pm 0.01) \times 10^{-4} \text{ M}$ , respectively. These values gave theoretical rate profiles in good agreement with the experimental results (Figure 1).

No significant buffer catalysis was observed in the concentration range studied. The results are summarized in Table 2.

The hydrolysis of phthalamic acid is about  $10^5$  times faster than the hydrolysis of benzamide with a comparable concentration of hydrogen ion (Bender et al., 1958). Besides, the pseudo-first-order rate constants obtained for the hydrolysis of benzanilide and for phthalanilic acid indicates that the neighboring carboxyl group results in a 3600-fold rate increase (Hawkins, 1976). The rate of hydrolysis of benzanilide at 1.0 M HCl and 65.8 °C is  $4.95 \times 10^{-6} \text{ s}^{-1}$ , and that of **Nap** at the same HCl concentration can be calculated using the value of  $k_1$  and  $k_2$  given above as  $1 \times 10^{-3} \text{ s}^{-1}$ . This 200-fold difference can be attributed to the presence of the neighboring group.

Therefore, we suggest that the mechanism of the major reaction pathway is similar to that proposed for phthalanilic acid (Hawkins, 1976), which is shown in Scheme 2. The formation of *N*-1-naphthylphthalimide must involve nucleophilic attack of the amide nitrogen on the neighboring carboxylic group followed by water expulsion (Scheme 3). Since this reaction pathway represents only 10–15% of the total reaction, it will not be further discussed.

It is known from previous studies (Hawkins, 1976) that the rate-determining step occurs at some point in the reaction chain after the formation of the tetrahedral intermediate but before the hydrolysis of the anhydride. Assuming that  $k_5$  and  $k_6$  are the rate-determining steps, the expression of  $k_{\text{obs}}$  can be obtained using standard procedures (eq 3) (Bunnett, 1974).

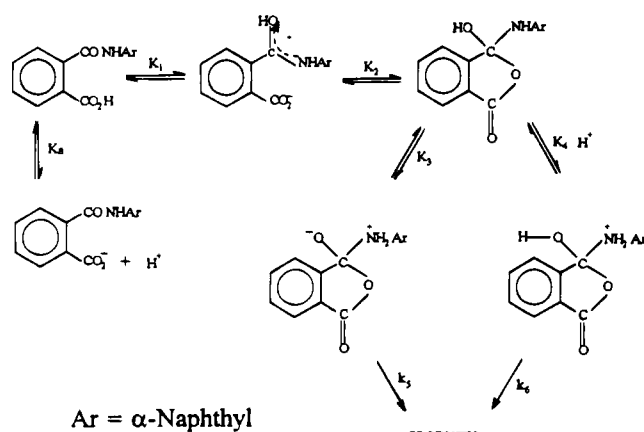
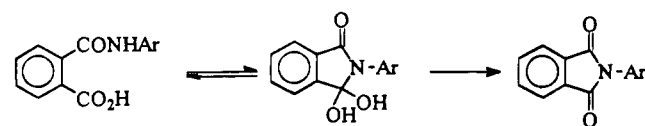
$$k_{\text{obs}} = K_1 K_2 (K_3 k_5 + K_4 k_6 [\text{H}^+]) / (1 + K_a [\text{H}^+]) \quad (3)$$

The ratio  $k_1/k_2 = K_3 k_5 / K_4 k_6 = 0.16$  implies that at hydrogen ion concentrations lower than 0.16 M (pH 0.69) the pathway involving the zwitterion intermediate predominates over that involving external protonation of the nitrogen of the leaving group. It is well-known that the equilibrium constant for the formation of cyclic anhydride from an aliphatic dicarboxylic acid is profoundly affected by the pattern of substitution on the intervening carbon chain. Alkyl substituents favor the cyclic form (Kirby and Lancaster, 1972). The formation from half-esters and half-amides of dicarboxylic acids might be expected to be affected in the same way, and Higuchi et al. (1966) have observed such effects in the hydrolysis of the various methylsuccinilic acids. The rate of hydrolysis and thus the efficiency of intramolecular catalysis by the carboxyl group increase with the number of methyl substituents until tetramethylsuccinilic acid is 1200 times more reactive than the unsubstituted compound. Similar effects have been observed by Bruce (Bruce and Bradbury, 1968, and references cited therein) and others (Oreskes and Morawetz, 1958) in intramolecular nucleophilic catalysis by the carboxyl group. Bruce draws the general conclusion that alkyl substitution decreases the popula-

**Table 2. Effect of Buffer Concentration on the Observed Rate Constants for the Hydrolysis of Nap<sup>a</sup>**

buffer, 10 <sup>-2</sup> M	<i>k</i> <sub>obs</sub> , 10 <sup>-4</sup> s <sup>-1</sup>					
	pH 2.41	pH 2.61	pH 3.10	pH 3.40	pH 4.07	pH 5.01
0.50	1.32 ± 0.03 <sup>b</sup> (1.64 ± 0.05) <sup>c</sup>	1.23 ± 0.051 <sup>b</sup>	1.12 ± 0.05 <sup>b</sup>	0.96 ± 0.02 <sup>b</sup>	0.49 ± 0.01 <sup>d</sup>	0.058 ± 0.002 <sup>d</sup>
0.70	1.60 ± 0.08 <sup>b</sup>					
1.0	1.43 ± 0.04 <sup>b</sup> (1.75 ± 0.09) <sup>c</sup>		1.08 ± 0.06 <sup>b</sup>	0.99 ± 0.02 <sup>b</sup>	0.48 ± 0.01 <sup>d</sup>	0.078 ± 0.007 <sup>d</sup>
3.0	1.7 ± 0.1 <sup>b</sup>	1.1 ± 0.1 <sup>b</sup>				
5.0	(1.57 ± 0.05) <sup>c</sup>	1.30 ± 0.04 <sup>b</sup>	1.02 ± 0.07 <sup>b</sup>	0.98 ± 0.03 <sup>b</sup>	0.54 ± 0.01 <sup>d</sup>	0.064 ± 0.002 <sup>d</sup>
7.0	2.0 ± 0.1					
10		1.59 ± 0.03 <sup>b</sup>				

<sup>a</sup> Temperature 40 °C, ionic strength 0.5 M (NaCl as compensating electrolyte). The error limits indicated are the standard deviations of the kinetic plot. <sup>b</sup> Chloroacetic acid/chloroacetate buffer. <sup>c</sup> Phosphoric acid/diacid phosphate buffer. <sup>d</sup> Acetic acid/acetate buffer.

**Scheme 2****Scheme 3****Table 3. MMX Distances and Rate Constants for the Hydrolysis of 1<sup>a</sup>**

R	<i>a</i> , Å	<i>b</i> , Å	<i>c</i> , Å	<i>k</i> <sub>obs</sub> , 10 <sup>-4</sup> s <sup>-1</sup>
H	2.89	4.22	2.89	2.35 <sup>b</sup>
phenyl	2.79	2.49	2.77	8.77 <sup>c</sup>
naphthyl	2.93	4.07	3.86	2.13 <sup>d</sup>

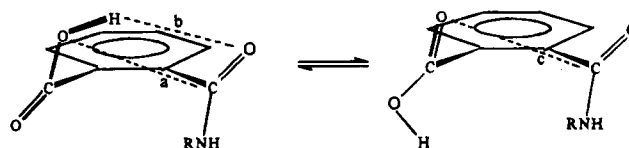
<sup>a</sup> The distances *a*, *b*, and *c* are defined in Figure 2. <sup>b</sup> Data at 47.3 °C (Bender, 1957). <sup>c</sup> Value at 40 °C calculated using the data reported at 25 and 66 °C (Hawkins; 1976). <sup>d</sup> This work, 40 °C.

tion of extended chain conformations of these compounds, thus bringing the reacting groups into close proximity most of the time. Consistent with this interpretation, the largest effects are observed in cases having groups held close together in conformationally rigid molecules.

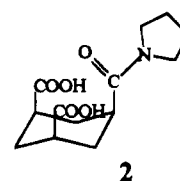
Kirby (Kirby and Lancaster, 1972) has shown that the closest distance of approach between the carboxyl oxygen and the amide carbon atom in the ground state is less for more reactive compounds, increasing from about 2.6 Å for the unsubstituted maleamic acid to 3 Å for the cyclopentenyl compound and to 3.8 Å for the cyclobutenyl compound.

At pH 1 and 40 °C phthalanilic acid (R = phenyl) is hydrolyzed 4 times more rapidly than phthalamic acid (R = H) (Bender et al., 1958; Hawkins, 1976) and naptalam (R = naphthyl) (Table 3). At pH 2 and 25 °C the same trend is observed.

Menger (Menger and Ladika, 1988) described an intramolecular catalyzed cleavage of the aliphatic amide **2** under biological conditions with a half-life of 8 min

**Figure 2. MMX derived conformation for phthalamic acid derivatives.**

at neutral pH and room temperature.



Menger's diacid amide **2** reacts more rapidly than phthalamic acid (Bender, 1957) and *N*-*n*-propyl-diisopropylmaleamic acid (Kirby and Lancaster, 1972, and references cited therein). Diacid amide **2** has a nearly ideal geometric disposition between amide and carboxyl group as shown by molecular mechanic calculations (MM2). These calculations on Menger's diacid amide (Menger and Ladika, 1988) show a global minimum that has an acid carbonyl oxygen distance of 2.78 Å from the amide carbonyl carbon. A second minimum has an acid hydroxyl 2.8 Å from the amide carbonyl atom. We used another molecular mechanic method (MMX) for Menger's diacid amide and obtained similar results. We therefore used this calculation method for phthalamic acid derivatives. The results are collected in Table 3 and Figure 2. It can be seen from Table 3 that phthalanilic acid (R = phenyl) has the closest distance for a most efficient intramolecular catalysis as measured experimentally. A similar explanation was given for the high reactivity of Menger's diacid amide.

Reactions carried out in alkaline solutions were too slow to measure conveniently as was observed by Bender (1957) for phthalamic acid.

The knowledge of the rate of hydrolysis of **Nap** under different conditions is important because one of the main hydrolytic product is 1-naphthylamine, which is known to have carcinogenic effects (*The Merck Index*, 1989). It is known that the rate of hydrolysis of some amides is catalyzed by metal ions (Fife and Bembi, 1993) and that cyclodextrins can catalyze or inhibit them (Granados and Rossi, 1993). The reactions of **Nap** in the presence of Cu<sup>2+</sup>, Al<sup>3+</sup>, and Co<sup>2+</sup> were measured at 25 °C and at pH 2.03. There was no spectroscopic evidence of interaction of **Nap** with these metal ions in the ground state, nor was the kinetics affected. The results are summarized in Table 4. MMX calculations on **Nap** show a conformer which can act as a guest for metal ions but its energy is not a minimum, so this could

**Table 4. Rate Constants of the Hydrolysis of Nap in the Presence of Metal Ions and Cyclodextrin<sup>a</sup>**

additive	[additive], 10 <sup>-3</sup> M	k <sub>obs</sub> , 10 <sup>-4</sup> s <sup>-1</sup>
		0.32 <sup>b</sup> (1.41) <sup>f</sup>
β-cyclodextrin	1.0	1.52 <sup>c</sup>
	10	1.50 <sup>c</sup>
Cu <sup>2+</sup>	5.0	0.34 <sup>d</sup>
	10	0.34 <sup>d</sup>
	2.5	1.22 <sup>e</sup>
	5.0	1.40 <sup>e</sup>
	7.5	1.40 <sup>e</sup>
Al <sup>3+</sup>	20	0.35 <sup>b</sup>
	40	0.34 <sup>b</sup>
Co <sup>2+</sup>	8.0	0.30 <sup>b</sup>

<sup>a</sup> [Nap] = 5 × 10<sup>-5</sup> M, acetonitrile 4%, and pH 2.03. <sup>b</sup> Temperature 25 °C, ionic strength 0.5 M with NaCl as compensating electrolyte. <sup>c</sup> Temperature 40 °C, ionic strength 0.5 M with NaCl as compensating electrolyte. <sup>d</sup> Temperature 25 °C, without ionic strength control. <sup>e</sup> [CD] = 10 mM, temperature 40 °C, without ionic strength control.

**Table 5 Half-Life of Naptalam at Some Selected pH Values in Water at 40 °C<sup>a</sup>**

pH	t <sub>1/2</sub> , h	pH	t <sub>1/2</sub> , h
2	1.28	5	29.7
3	1.60	6	285
4	4.17	7	2838

<sup>a</sup> Values were calculated using using k<sub>obs</sub> calculated from eq 2 with k<sub>1</sub> = 1.46 × 10<sup>-4</sup> s<sup>-1</sup>, k<sub>2</sub> = 9 × 10<sup>-4</sup> s<sup>-1</sup>, and K<sub>a</sub> = 2.13 × 10<sup>-4</sup> M.

be the reason why there is no interaction between Nap and metal ions.

The rate of hydrolysis was not affected by β-CD or HPCD. Besides, the presence of metal ions and cyclodextrin together does not affect the rate, in contrast to what was found in the hydrolysis of esters and amides (Fornasier et al., 1989; De Santi et al., 1990) in vesicles and micelles (Broxton and Cox, 1993, and references therein) containing metal ions.

## CONCLUSIONS

The hydrolysis of Nap is intramolecularly catalyzed by the participation of the undissociated neighboring carboxyl group. Nap is more reactive than other amides with no neighboring carboxyl groups, and its degradation rate is not affected by cyclodextrins or metal ions. The half-life is highly dependent on pH as is shown in Table 5 and the main hydrolysis product is naphthylamine, which is a known carcinogenic compound.

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