



# Kinetics and mechanism of acid-catalyzed hydrolysis of cyclohexyl isocyanide and $pK_a$ determination of *N*-cyclohexylnitrilium ion

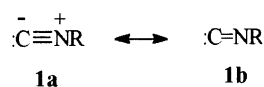
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**Abstract**—A novel mechanism for acid-catalyzed hydrolysis of cyclohexyl isocyanide is proposed. It is specific acid/general base catalysis, involving a fast, pre-equilibrium *C*-protonation of the isocyanide, followed by a rate-determining attack of water on the electron-deficient carbon of the protonated isocyanide. The  $pK_a$  of *N*-cyclohexylnitrilium ion was determined to be  $0.86 \pm 0.05$ . © 2001 Elsevier Science Ltd. All rights reserved.

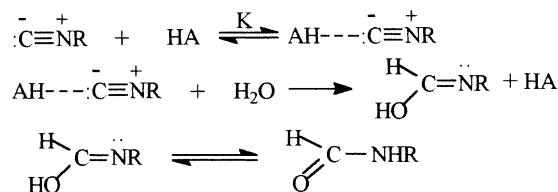
A correct structure **1a** for isocyanides was first proposed by Lindemann and Wiegrebé in 1930.<sup>1</sup> Based on microwave and IR studies, **1a** resonance structure gives more contribution than **1b** resonance structure.<sup>2</sup> The resonance structure **1a** has a nucleophilic carbon carrying a negative charge and a lone pair of electrons, while the resonance structure **1b** has an electron-deficient carbon, which behaves as an electrophile.<sup>3</sup> Whether the isocyano carbon behaves as a nucleophile or an electrophile depends on reaction conditions, reagents, and its substituents.<sup>3</sup>



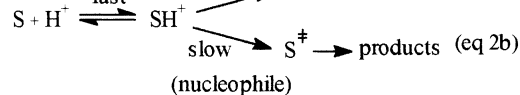
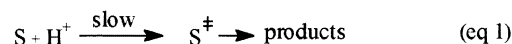
To understand a mechanism for the isocyano carbon to behave as an electrophile, alkaline hydrolysis of aromatic isocyanides has been studied.<sup>4a,b</sup> To understand a mechanism for the isocyano carbon to behave as a nucleophile, acid-catalyzed hydrolysis of isocyanides has been studied and it was reported that acid-catalyzed hydrolysis of methyl isocyanide forming methyl formamide is a general-acid catalyzed process, in which there is a reversible hydrogen bonding between a general acid and the isocyano carbon, followed by a rate determining nucleophilic attack at the same carbon by water.<sup>4c</sup> (Scheme 1) However, after doing more experi-

ments on the issue, we reach a different conclusion for the mechanism.

The isocyano carbon was confirmed to form hydrogen bonding with water or alcohols,<sup>5</sup> but both water and alcohols hardly react with isocyanides without any catalyst.<sup>3</sup> It turns out that the hydrogen-bonding complexes don't activate the isocyanide functional group enough for further nucleophilic attack by a nucleophile. Furthermore, the hydrogen-bonding complex of isocyanide with an acid molecule is unlikely to form in a polar protic solvent like water.<sup>6</sup> Therefore, it seems unlikely that the mechanism of Scheme 1 is correct.



Scheme 1.



Scheme 2.

**Keywords:** isocyanide; mechanism; hydrolysis; specific acid catalysis; nitrilium ion.

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Acid-catalyzed reactions can be divided into two main classes (eq 1, 2a, and 2b) involving the proton transfer occurring before or during the rate-determining step of the reaction<sup>7</sup> (Scheme 2). Eq 1 involves a slow, rate-determining proton transfer, which is more likely to transfer to substrates containing carbon atoms as the basic center. The type of reactions is supposed to be general-acid catalyzed and they show normal solvent isotope effect ( $k_{\text{H}^+}/k_{\text{D}^+}>1$ ).<sup>7</sup> Both eq 2a and 2b, including a fast, pre-equilibrium protonation before a rate-determining step, are expected to apply to substrates containing oxygen or nitrogen atoms as the basic center. Eq 2a involves an A1 mechanism and eq 2b belongs to an A2 mechanism. Both eq 2a and eq 2b are expected to be specific-acid catalyzed and they show inverse solvent isotope effect ( $k_{\text{D}^+}/k_{\text{H}^+}>1$ ).<sup>7</sup>

Acid-catalyzed hydrolysis of cyclohexyl isocyanide was measured by time-scan of UV at 210 nm, where there is no absorption change for acid-catalyzed hydrolysis of cyclohexyl formamide. As shown in Table 1, hydrolysis of the isocyanide was catalyzed by hydronium ion,  $\text{H}_3\text{O}^+$ . At  $[\text{H}_3\text{O}^+]=0.06\sim 0.002$  M, the pseudo-first-order rate constants were linearly proportional to the concentration of hydronium ion with a slope of  $7.77\times$

$10^{-2} \text{ M}^{-1} \text{ S}^{-1}$ , i.e.  $k_{\text{H}^+}=7.77\times 10^{-2} \text{ M}^{-1} \text{ S}^{-1}$ . Similarly, the reaction was also catalyzed by  $\text{D}_3\text{O}^+$ , and  $k_{\text{D}^+}=1.77\times 10^{-1} \text{ M}^{-1} \text{ S}^{-1}$ . The ratio  $k_{\text{D}^+}/k_{\text{H}^+}$  is 2.28. The inverse solvent isotope effect indicates the reaction is specific-acid catalyzed and involves a fast, pre-equilibrium protonation before a rate-determining step.

Normally, in the case of specific hydronium-ion catalyzed reactions, the reaction rate does not depend on the concentration of any acid other than hydronium ion.<sup>7</sup> However, as shown in Table 2, hydrolysis of the isocyanide at the  $\text{CH}_3\text{CO}_2\text{H}/\text{CH}_3\text{CO}_2\text{Na}$  buffer systems was catalyzed by undissociated acetic acid ( $k_{\text{AcOH}}=2.94\times 10^{-3} \text{ M}^{-1} \text{ S}^{-1}$ ) Since  $k_{\text{AcONa}}$  is smaller than a standard deviation, it is statistically insignificant. It is known that general acid catalysis can not be kinetically distinguished from specific acid followed by general base catalysis.<sup>7</sup> Therefore, the reaction may involve fast pre-equilibrium hydronium-ion catalysis (specific acid catalysis) followed by slow hydration catalyzed by  $\text{CH}_3\text{CO}_2\text{Na}$  (general base catalysis) (Scheme 3).

After pre-equilibrium protonation of the isocyanide, there are three possible species (chloride,  $\text{AcOH}/\text{AcO}^-$ , and water) involving their rate-determining attack on

**Table 1.** Rate constants for acid-catalyzed hydrolysis of cyclohexyl isocyanide in  $\text{HCl}/\text{H}_2\text{O}$  or  $\text{DCl}/\text{D}_2\text{O}$  solutions<sup>a</sup>

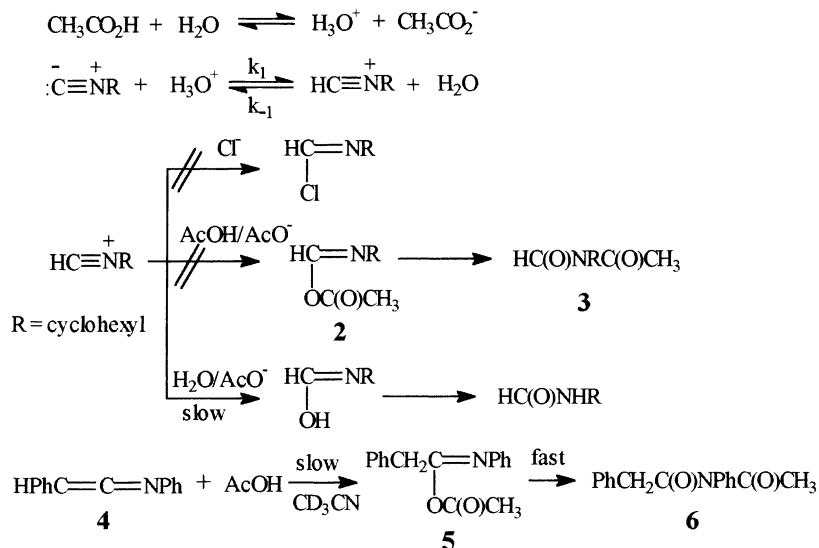
$[\text{H}^+]$ (M)	$T$ ( $^\circ\text{C}$ )	$k_{\text{obs}}$ ( $\text{s}^{-1}$ )	$[\text{D}^+]$ (M)	$T$ ( $^\circ\text{C}$ )	$k_{\text{obs}}$ ( $\text{s}^{-1}$ )
0.06	26	$4.73\times 10^{-3}$	0.06	26	$1.05\times 10^{-2}$
0.06	35	$1.01\times 10^{-2}$			
0.06	45	$1.74\times 10^{-2}$			
0.06	50	$2.35\times 10^{-2}$			
0.04	26	$3.15\times 10^{-3}$			
0.02	26	$1.70\times 10^{-3}$	0.02	26	$3.38\times 10^{-3}$
0.01	26	$8.35\times 10^{-4}$			
0.008	26	$7.27\times 10^{-4}$			
0.006	26	$5.61\times 10^{-4}$	0.006	26	$9.09\times 10^{-4}$
0.004	26	$3.56\times 10^{-4}$			
0.002	26	$1.72\times 10^{-4}$	0.002	26	$2.74\times 10^{-4}$

<sup>a</sup>  $\mu$  (ionic strength)=0.06 (NaCl);  $k_{\text{H}^+}=7.77\times 10^{-2}\pm 8.45\times 10^{-4} \text{ M}^{-1} \text{ S}^{-1}$ ;  $k_{\text{D}^+}=1.77\times 10^{-1}\pm 2.94\times 10^{-3} \text{ M}^{-1} \text{ S}^{-1}$ ;  $k_{\text{D}^+}/k_{\text{H}^+}=2.28$ ;  $\Delta H^\ddagger=12.0\pm 0.8$  kcal/mol,  $\Delta S^\ddagger=-29.0\pm 2.5$  cal/mol K,  $\Delta G^\ddagger=21.0\pm 1.6$  kcal/mol at  $[\text{H}^+]=0.06$  M,  $T=26\text{--}50^\circ\text{C}$ . All rate constants are measured at least in duplicate with maximum deviations of  $\pm 5\%$ .

**Table 2.** Rate constants for acid-catalyzed hydrolysis of cyclohexyl isocyanide in  $\text{CH}_3\text{CO}_2\text{H}/\text{CH}_3\text{CO}_2\text{Na}$  aqueous buffer solutions<sup>a</sup>

$\alpha_{\text{Ha}}$	$[\text{CH}_3\text{CO}_2\text{H}]$ (M)	$[\text{CH}_3\text{CO}_2\text{Na}]$ (M)	$[\text{CH}_3\text{CO}_2\text{H}]+[\text{CH}_3\text{CO}_2\text{Na}]$ (M)	$k_{\text{obs}}$ ( $\text{s}^{-1}$ )
0.8	0.008	0.002	0.01	$5.81\times 10^{-5}$
	0.016	0.004	0.02	$7.93\times 10^{-5}$
	0.024	0.006	0.03	$9.86\times 10^{-5}$
	0.032	0.008	0.04	$1.30\times 10^{-4}$
0.5	0.005	0.005	0.01	$1.80\times 10^{-5}$
	0.010	0.010	0.02	$2.76\times 10^{-5}$
	0.015	0.015	0.03	$4.50\times 10^{-5}$
	0.020	0.020	0.04	$6.16\times 10^{-5}$
0.375	0.006	0.010	0.016	$1.35\times 10^{-5}$
	0.009	0.015	0.024	$2.52\times 10^{-5}$
	0.012	0.020	0.032	$3.31\times 10^{-5}$
	0.015	0.025	0.040	$4.01\times 10^{-5}$

<sup>a</sup>  $\alpha_{\text{Ha}}=[\text{HA}]/([\text{HA}]+[\text{A}^-])$ ;  $\mu$  (ionic strength)=0.6 (NaCl);  $T=26^\circ\text{C}$ ;  $k_{\text{AcOH}}=2.94\times 10^{-3}\pm 4.69\times 10^{-5} \text{ M}^{-1} \text{ S}^{-1}$ ;  $k_{\text{AcONa}}=5.20\times 10^{-8}\pm 2.75\times 10^{-5} \text{ M}^{-1} \text{ S}^{-1}$ . All rate constants were measured at least in duplicate with maximum deviations of  $\pm 5\%$ .



Scheme 3.

the protonated isocyanide. Hydrolysis of the isocyanide in a series of buffer solutions with fixed buffer ratio and buffer concentration was carried out in a fixed ionic strength, which was made with varied ratio of NaCl and NaClO<sub>4</sub>. The hydrolysis rate did not change as the salt was switched from NaCl to NaClO<sub>4</sub>. Therefore, it turns out that chloride does not join the rate-determining attack. In addition, hydrolysis of the isocyanide in the presence of AcOH/AcO<sup>-</sup> and a little bit water in CDCl<sub>3</sub> was monitored by proton NMR spectrometer, and it was found that no reaction occurred at room temperature. When the deuteriated solvent was switched from CDCl<sub>3</sub> to CD<sub>3</sub>CN, the reaction did occur at room temperature, and one can see that, as the reaction progressed, the amount of water was getting decreased and the amount of the product (cyclohexyl formamide) was getting increased. However, there is no evidence that AcOH/AcO<sup>-</sup> join the rate-determining attack because compound **3** can not be detected at all as a product of the reaction by means of proton NMR and mass spectrometer. It is known that **2** can undergo intramolecular isomerization to **3** very fast at room temperature.<sup>8</sup> Presumably, it is faster than bimolecular intermolecular hydrolysis of **2**. We also did a similar reaction of ketenimine **4** with acetic acid in CD<sub>3</sub>CN and monitored it by proton NMR at room temperature. The reaction lasted for a few minutes but intermediate **5** could not be detected during the whole process. It turns out that the isomerization rate of **5** to **6** is much faster than that of the first step. Therefore, it is clear that water is the only nucleophile to attack the protonated isocyanide at the rate-determining step.

Solvent isotope effect is a good criterion to distinguish between specific-acid and general-acid catalysis, but it is not sensitive enough to tell A-2 from A-1 mechanism.<sup>7</sup> Therefore, entropy of activation was measured for the purpose. It was reported that A-1 mechanism gives  $\Delta S^\ddagger \cong 0$  to 10 eu, whereas the A-2 mechanism gives  $\Delta S^\ddagger \cong -15$  to  $-30$  eu in systems of 1 M of [H<sub>3</sub>O<sup>+</sup>].<sup>6</sup> As shown in Table 1, at [H<sub>3</sub>O<sup>+</sup>]=0.06 M and temperature

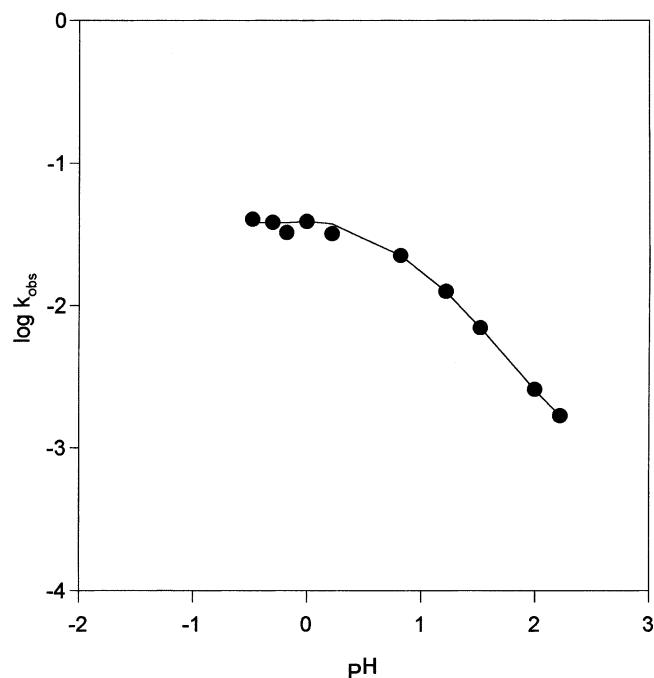
range of 25–50°C, entropy of activation ( $\Delta S^\ddagger$ ) of acid-catalyzed hydrolysis of the isocyanide is  $-29.0$  cal/mol K. Since the A1 and A2 mechanisms are specific-acid catalyzed reactions and protonation on the isocyanide carbon is not the rate-determining step, presumably hydronium ion concentration has limited influence on activation entropy of the reaction.<sup>7b</sup> Besides, the highly negative activation entropy indicates the reaction involves an A-2 mechanism instead of an A-1 mechanism, and the result is consistent with the mechanism we propose in Scheme 3.

The acid-catalyzed hydrolysis of the isocyanide was also carried out in high concentration of HCl aqueous solutions (Table 3). The pH-rate profile (Fig. 1) of the hydrolysis shows a downward bend, which involves gain of a proton by the isocyanide in a rapid equilibrium prior to a rate-determining step.<sup>9</sup> Clearly it involves titration of the isocyanide and the curve in Fig. 1 should fit eq 3.<sup>9</sup> Rearrangement of eq 3 into eq 4 allows us to make a plot of  $(1/k_{\text{obs}})$  versus  $1/[\text{H}^+]$  and to get  $K_a = 0.138 \pm 0.016$  ( $\text{p}K_a = 0.86 \pm 0.05$ ) for *N*-cyclo-

**Table 3.** Rate constants for acid-catalyzed hydrolysis of cyclohexyl isocyanide in high concentration of HCl aqueous solutions<sup>a</sup>

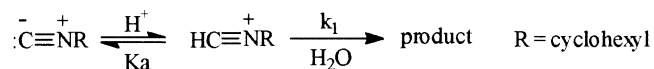
[H <sup>+</sup> ] (M)	T (°C)	k <sub>obs</sub> (s <sup>-1</sup> )
3.00	26	4.02 × 10 <sup>-2</sup>
2.00	26	3.83 × 10 <sup>-2</sup>
1.50	26	3.27 × 10 <sup>-2</sup>
1.00	26	3.89 × 10 <sup>-2</sup>
0.60	26	3.19 × 10 <sup>-2</sup>
0.15	26	2.24 × 10 <sup>-2</sup>
0.06	26	1.25 × 10 <sup>-2</sup>
0.03	26	6.99 × 10 <sup>-3</sup>
0.01	26	2.58 × 10 <sup>-3</sup>
0.006	26	1.68 × 10 <sup>-3</sup>

<sup>a</sup>  $\mu$  (ionic strength)=3.0 (NaCl); UV wavelength for monitoring the reaction=210 nm. All rate constants were measured at least in duplicate with maximum deviations of  $\pm 5\%$ .



**Figure 1.** PH-rate profile for acid-catalyzed hydrolysis of cyclohexyl isocyanide in high concentration of HCl aqueous solutions ( $\mu=3.0$  (NaCl)).

hexylnitrilium ion from the slope and intercept of the plot. The very low  $pK_a$  value indicates the nitrilium ion is a strong acid, which is caused by both sp-hybridized carbon and positive charge on nitrilium nitrogen.



$$k_{\text{obs}} = \frac{k_1 [\text{H}^+]}{\text{K}_a + [\text{H}^+]} \quad \text{eq. 3}$$

$$\frac{1}{k_{\text{obs}}} = \frac{\text{K}_a + [\text{H}^+]}{k_1 [\text{H}^+]} = \left(\frac{\text{K}_a}{k_1}\right) \frac{1}{[\text{H}^+]} + \left(\frac{1}{k_1}\right) \quad \text{eq. 4}$$

It is interesting to compare mechanisms of acid-catalyzed hydrolysis of nitriles, isocyanides, and ketenes. Benzonitrile was reported to involve fast pre-equilibrium *N*-protonation, followed by rate-determining attack of water on cyano carbon.<sup>10a</sup> Cyclohexyl isocyanide, however, involves fast pre-equilibrium C-protonation, followed by rate-determining attack of water on

protonated isocyano carbon. However, acid-catalyzed hydration of ketenes, which have electron-rich  $\text{C}_\beta$  and O and electron-deficient  $\text{C}_\alpha$ , involves slow, rate-determining  $\text{C}_\beta$ -protonation.<sup>10b</sup>

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