

Kinetic Studies on the Addition of Potassium Cyanide to α,N -Diphenylnitrone

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The rate constants for the nucleophilic addition of potassium cyanide to α,N -diphenylnitrone and its derivatives (p -OCH₃, p -CH₃, p -Cl, and p -NO₂) were determined by ultraviolet spectrophotometer at 25 °C, and the rate equations which can be applied over a wide pH range were obtained. On the basis of pH-rate profile, adduct analysis, general base catalysis and substituent effect, a plausible mechanism of this addition reaction was proposed: At high pH, the cyanide ion to carbon-nitrogen double bond was rate controlling, however, in acidic media, the reaction proceeded by the addition of hydrogen cyanide molecule to carbon-nitrogen double bond after protonation at oxygen of α,N -diphenylnitrone. In the range of neutral pH, these two reactions occurred competitively.

Introduction

The nucleophilic addition of activated carbon-carbon double bond and carbon-nitrogen double bond has been subjected to extensive mechanistic and synthetic studies.¹⁻⁴ Nitrone, having carbon-nitrogen double bond and oxygen attached to nitrogen is very reactive and used as an intermediate in organic synthesis.⁵ It easily reacts with nucleophiles such as Grignard reagent,⁶ thiol,^{7,8} and HCN.⁹⁻¹²

In general, nitrones formed a 1,3-adduct with nucleophiles.¹³ It has been known that the structures of adducts vary depending upon the reaction conditions.

Masui and coworkers¹² have reported the first isolation of N -(α -cyanobenzyl)- N -phenylhydroxylamines formed by reactions of α,N -diphenylnitrone with liquid hydrogen cyanide. These hydroxylamines are stable in acidic media and nonpolar solvents, but they are readily dehydrated to give the corresponding cyanoimines in basic media and polar solvents. Bellavita¹⁴ also found that α -phenyl- N - p -tolyl nitrone, when treated with potassium cyanide in methanol, afforded the cyanoanil in good yields, though the intermediate hydroxylamine could not be isolated.

In spite of many uses of nitrone as dye, medicament, sensitizer and intermediates in organic synthesis,^{12,14} nitrone has been the subject of only a few kinetic studies. In the previous report,¹⁶ we described the hydrolysis mechanism of nitrone over a wide pH range. In this study, we have investigated the rate and mechanism of the addition of potassium cyanide to nitrone.

Experimental Section

General procedure. All chemicals were reagent grade unless otherwise specified. UV spectra were obtained by a Varian Cary 14 spectrophotometer. IR spectra were taken with a Perkin-Elmer Infrared 710B. NMR spectra were obtained with a Varian Model EM 360 (60 MHz) and melting points were measured with a Haake Buchler apparatus.

Synthesis of α,N -diphenylnitrone and its derivatives.

α,N -diphenylnitrone and its derivatives were prepared by condensation of corresponding benzaldehyde derivatives and N -phenylhydroxylamine.¹⁷

Identification of adducts. In acidic media, α,N -diphenylnitrone (1.0 mmol) and potassium cyanide (1.0 mmol) were dissolved in 20 mL of HCl solution (pH = 3). The reaction mixture was stirred for 24 h at room temperature under nitrogen atmosphere. The mixture was extracted with CH₂Cl₂, washed with water, dried over anhydrous MgSO₄ and concentrated. The product recrystallized from ethanol to give N -(α -cyanobenzyl)- N -phenylhydroxylamine. IR (KBr pellet, cm⁻¹): 3100-3500 (OH), 2260 (C≡N); ¹H NMR (CDCl₃, δ) 7.8-8.9 (m, 10H, phenyl), 5.9 (s, 1H, C₆H₅(CN)CH), 1.6 (s, 1H, OH).

In basic media, product analysis was carried out by the same method as in the acidic media except using buffer solution (pH = 9.0) of boric acid and sodium hydroxide. The product was recrystallized from ethanol to give α -cyanobenzylideneaniline. IR (KBr pellet, cm⁻¹): 2230 (C≡N), 1600 (C=N); ¹H NMR (CDCl₃, δ) 7.1-8.4 (m, 10H, phenyl).

Kinetic studies. A buffer solution (98 mL) of known concentration in a 100 mL volumetric flask was immersed into the thermostat at 25 °C and allowed to equilibrate for 20 min. Each methanolic solution (1.0 mL) of nitrone and potassium cyanide was introduced to 98 mL aqueous buffer solution and the flask was vigorously shaken. Each aliquot (3.0 mL) of the solution was removed from the volumetric flask at time intervals and was placed in a quartz cuvette. The decrease of absorption at the wavelength of maximum absorption (λ_{max} = 315-350 nm) for the nitrone derivatives with time was monitored.

Results and Discussion

Determination of rate constants. The observed rates of reaction with excess potassium cyanide concentration were always pseudo-first order. Plots of the pseudo-first order rate constants against various potassium cyanide concentrations were straight lines passing through the origin, showing the

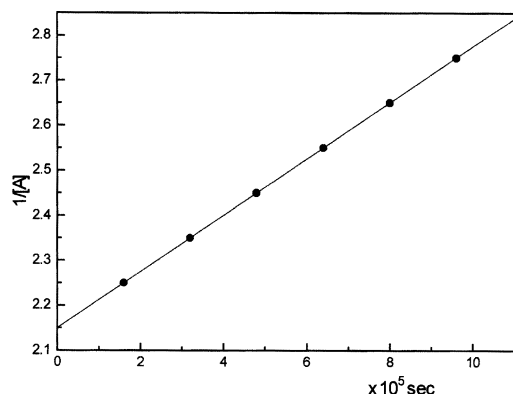


Figure 1. Plot of 1/Absorbance of α,N -diphenylnitrone vs. time at pH 7.0 and 25 °C.

reactions are first order to nitrone and potassium cyanide, respectively. Thus, the second-order rate constants could be calculated from the slope of the plot of $1/A$ against time for the reaction between equal initial concentration (2.0×10^{-5} M) of nitrone and potassium cyanide (Figure 1). The second-order rate constants (k_t) determined at various pHs are given Table 1 and Figure 2.

Table 1. Rate constants for the addition reaction of potassium cyanide to α,N -diphenylnitrone at various pH and 25 °C

pH	Buffer Solution	k_t ($M^{-1} \text{ sec}^{-1}$)	
		obsd	calcd
3.0	HCl	206	206
4.0	HOAc + NaOAc	11.4	20.6
5.0		2.00	2.11
6.0		1.76×10^{-1}	2.52×10^{-1}
7.0	$\text{KH}_2\text{PO}_4 + \text{K}_2\text{HPO}_4$	2.00×10^{-2}	6.70×10^{-2}
8.0	$\text{H}_3\text{BO}_3 + \text{NaOH}$	2.10×10^{-2}	4.90×10^{-2}
9.0		3.80×10^{-2}	6.40×10^{-2}
10.0		1.40×10^{-1}	2.28×10^{-1}
11.0	NaOH	3.69	1.87
12.0		18.4	18.3
13.0		182	182

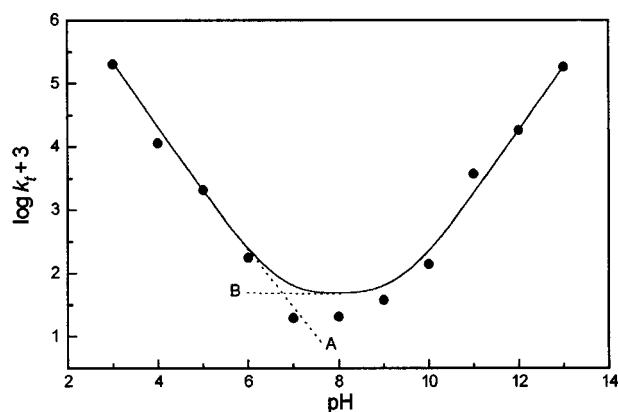


Figure 2. pH-rate profile for the addition reaction of potassium cyanide to α,N -diphenylnitrone at 25 °C. Circles are experimental points and the curve is drawn according to equation (3). Dashed line represents acid and base catalyzed rate constant.

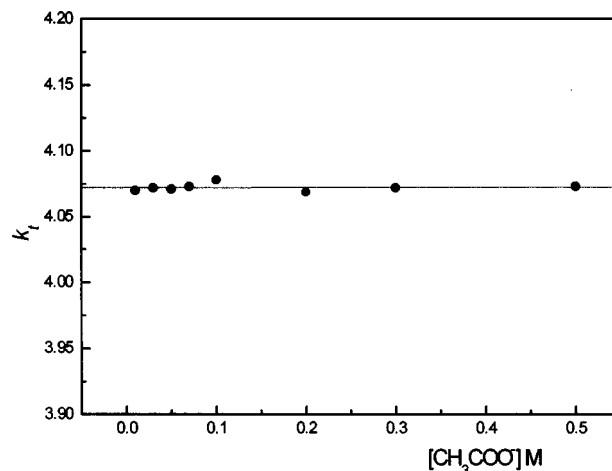


Figure 3. Plot rate constant vs. concentration of acetate ion at pH 4.78 and 25 °C.

General base catalysis. To make sure that this reaction is catalyzed by general base, the rate constants were determined at various acetate ion concentrations at pH 4.78. As shown in Figure 3, this reaction is not catalyzed by general base.

Substituent effect. As shown in Figure 4, The effect of substituents on the rate of addition was found to conform to the Hammett σ -constant with ρ is 0.527, 1.46 and 1.52 at pH 3.0, 8.0, and 12.0, respectively. This result indicates that the rate of addition is accelerated by electron withdrawing groups at all pH ranges.

Rate equation and mechanism. As shown in Figure 2, the rate of addition of potassium cyanide to α,N -diphenylnitrone is given by an expression of the following equation (1).

$$\begin{aligned} \text{Rate} &= k_t[\text{S}][\text{KCN}]_T \\ &= \{k_0 + k_H[\text{H}_3\text{O}^+] + k_{OH}[\text{OH}^-]\}[\text{S}][\text{KCN}]_T \\ &= k_0[\text{S}][\text{KCN}]_T + k_H[\text{H}_3\text{O}^+][\text{S}][\text{KCN}]_T + \\ &\quad k_{OH}[\text{OH}^-]\left\{1 + \frac{[\text{H}_3\text{O}^+]}{K_a}\right\}[\text{CN}^-][\text{S}] \end{aligned} \quad (1)$$

Where, $[\text{KCN}]_T$ is the total concentration of $[\text{CN}^-]$ and

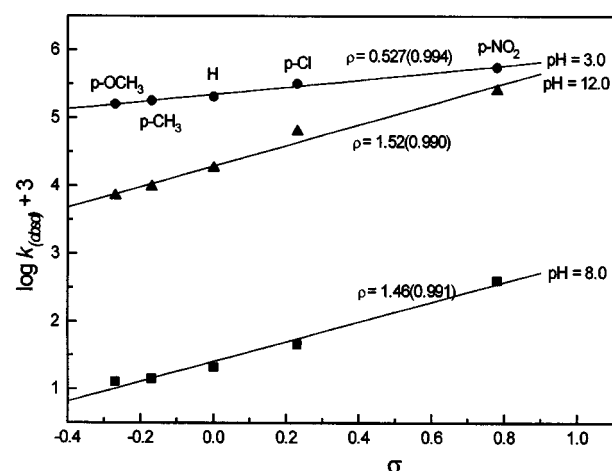


Figure 4. Hammett plots for the addition reaction of potassium cyanide to α,N -diphenylnitrone derivatives at various pH.

[HCN] at equilibria, k_0 is the pH independent part, it is the constant due to catalysis of H_2O , and k_H and k_{OH} are the hydronium and hydroxide ion dependent rate constant, respectively. K_a is the acid ionization constant of hydrogen cyanide.

Then k_t is given as following;

$$k_t = k_0 + k_H[\text{H}_3\text{O}^+] + k_{OH}[\text{OH}^-] \left\{ 1 + \frac{[\text{H}_3\text{O}^+]}{K_a} \right\} \quad (2)$$

Substituting the numerical values obtained from the fit of experimental data to equation (2),

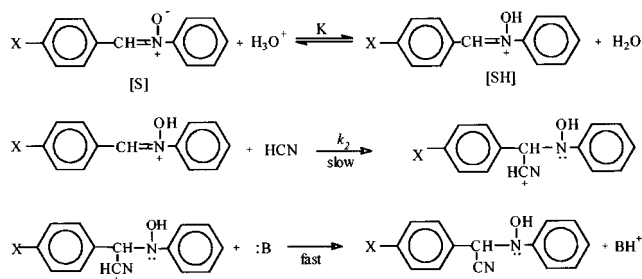
$$k_t = 4.57 \times 10^{-2} + 2.06 \times 10^5 [\text{H}_3\text{O}^+] + 1.82 \times 10^3 [\text{OH}^-] \quad (3)$$

Table 1 and Figure 2 show that the overall rate constant (k_t) calculated by equation (3) were good a agreement with the observed values. The curve A and B in Figure 2 represent the acid and base catalyzed rate constant in equation (2).

Similarly, the rate equation obtained for the addition of potassium cyanide to nitron derivatives;

$$\begin{aligned} p\text{-OCH}_3: k_t &= 1.09 \times 10^{-2} + 1.58 \times 10^5 [\text{H}_3\text{O}^+] + 4.32 \times 10^2 [\text{OH}^-] \\ p\text{-CH}_3: k_t &= 3.04 \times 10^{-2} + 1.99 \times 10^5 [\text{H}_3\text{O}^+] + 1.21 \times 10^3 [\text{OH}^-] \\ p\text{-Cl}: k_t &= 1.01 \times 10^{-1} + 3.66 \times 10^5 [\text{H}_3\text{O}^+] + 4.05 \times 10^3 [\text{OH}^-] \\ p\text{-NO}_2: k_t &= 2.26 \times 10^{-1} + 5.53 \times 10^5 [\text{H}_3\text{O}^+] + 9.01 \times 10^3 [\text{OH}^-] \end{aligned}$$

In low pH, *N*-(α -cyanobenzyl)-*N*-phenylhydroxylamine was isolated as a product. The rate of addition of HCN to α ,*N*-diphenylnitrone is not subject to general base catalysis (Figure 3) and is proportional to the hydronium ion concentration (Figure 2). Therefore, it can be proposed that the reaction proceeds by the attack of HCN to α -carbon after protonation at oxygen of nitron.

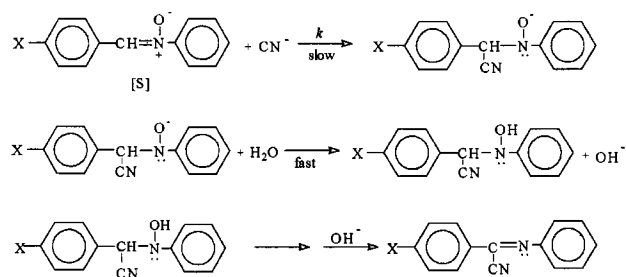


In the acidic solution, the concentration of [SH] is increased by the electron donating, but k_2 is enhanced by the electron withdrawing substituent. since the two effect are in opposition, the rate constant k_H should be insensitive to change to σ .

However, the observed $\rho = 0.527$ at pH = 3.0, indicated that the second step must be the rate determining step in this reaction.

In the basic media, it is expected that the cyanide ion and hydroxide ion could add to nitron. However, the spectral and analytical data indicated that the product obtained under basic condition (pH = 9.0) was the cyanide adduct (cyanoimine). Moreover, the kinetic data show that the rate for addition of cyanide ion was approximately 10^6 times faster

than that of hydrolysis of nitron at basic media.¹⁶ Therefore, the following addition reaction mechanism was proposed:



In alkaline pHs, where the rate limiting step is the direct attacking of cyanide ion at carbon atom, we expected that the rate constant, k_{OH} should be more sensitive to change σ than k_H ($\rho = 0.527$ at pH = 3.0, $\rho = 1.52$ at pH 12.0).

As shown in above, the rate equations which can be applied over a wide pH range were obtained. On the basis of various kinetic results, a reaction mechanism was proposed. However, to better understand the theory for the exact transition state and intermediate, it seems necessary to probe the influence of β -substituent variation from nitron as well as the change of the nucleophiles.

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