

KINETICS OF REACTIONS OF N-ARYLPYRIDINIUM SALTS WITH CYANIDE ION

J.KAVÁLEK, A.LYČKA, V.MACHÁČEK and V.ŠTĚRBA

*Organic Chemistry Department,
Institute of Chemical Technology, 532 10 Pardubice*

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Reaction of N-arylpiperidinium salts with cyanide in methanol and ethanol produces reversibly 4-cyano-1,4-dihydropyridine derivatives. Rate constants of the formation and reverse reaction have been determined and correlated with σ^0 constants. Hydrogen cyanide slows down the formation of the products. The influence of medium on the rate and equilibrium constants has been discussed.

Reactions of substituted phenylpyridinium salts with cyanide ion have attracted much attention recently¹⁻³, the reason being (besides others) in their biochemical importance⁴. The reactions are reversible. The influence of pyridine N-substituents^{2,5} eventually 3-substituents on equilibrium constants and that of N-substituents on the rate constants of formation of the products² were studied in aqueous media. The addition takes place at 4-position, which was proved mainly by NMR spectra of the reaction products^{2,6,7}. In some cases a rapid attack was supposed at 2(6)-position followed by a gradual conversion into more stable 1,4-dihydro derivative⁸, or, on the contrary, a slow conversion of a primary 4-isomer into 2(6)-isomer². These assumptions were made only on the basis of the observed changes in electronic spectra of the reaction mixtures.

In the present work the reactions have been studied of N-arylpiperidinium salts with cyanide in methanol and ethanol. The aim was to determine quantitatively the influence of substituents and medium on the reaction rate constants and find structure of the products.

EXPERIMENTAL

Reagents

N-(3- resp. 4-Substituted phenyl)pyridinium chlorides *Ia-e* (*Ie* = 4-CH₃, *Ib* = 3-CH₃, *Ic* = H, *Id* = 4-Br, *Ie* = 3-Cl) resp. bromides *If,g* (*If* = 3-NO₂, *Ig* = 4-NO₂) were prepared by a method described previously⁹. The other chemicals used were commercial products of *p.a.* purity grade. Anhydrous ethanol was obtained from 96% ethanol by repeated distillation with sodium metal.

1-(4-Bromophenyl)-4-cyano-1,4-dihydropyridine (II). 1 g (3.7 mmol) 1-(4-bromophenyl)pyridinium chloride in 10 ml water was treated with 0.4 g (6.2 mmol) potassium cyanide in 5 ml water. The product separated after 6 hours was collected by suction, washed with water and dissolved in ether. The ether solution was dried over sodium sulphate and filtered with charcoal. Evaporation of ether at 30°C gave 0.32 g (33%) colourless needles melting at 81–82°C with decomposi-

tion. For $C_{12}H_9N_2Br$ (261.0) calculated: 55.19% C, 3.47% H, 10.73% N; found: 55.00% C, 3.45% H, 10.70% N.

1H -NMR spectrum of 1-(4-bromophenyl)-4-cyano-1,4-dihydropyridine was measured in tetrachloromethane (10% solution of the substance) using hexamethyldisiloxane as internal standard (9.95 τ). The measurement was carried out with a Tesla BS 487 B apparatus at 80 MHz at the room temperature. The spectrum consists of AA'XX' spectrum of 1,4-disubstituted benzene ring (within 2.5 and 3.5 τ) and of three multiplets of the intensities 2 : 2 : 1. These multiplets were ascribed to the protons of dihydropyridine nucleus forming an AA'MM'X system. Correctness of this interpretation was proved by spin decoupling from the protons H_A (the protons 2 and 6), resulting in simplification of AA'MM'X into M_2X . The coupling constants and chemical shifts found after this simplification of spectrum have the following values: $\nu_{2,6} = 3.63\tau$; $\nu_{3,5} = 5.32\tau$; $\nu_4 = 5.75\tau$; $J_{2,3} = J_{5,6} = 8.1$ Hz; $J_{3,4} = J_{4,5} = 3.4$ Hz; $J_{2,4} = J_{4,6} = 1.3$ Hz.

Measurements

The reaction course was followed spectrophotometrically with a Unicam SP 800 apparatus in the wavelength range 200 to 400 nm in 1 cm quartz cells. The rate constants of formation of products and their retrogression were determined with the use of a Zeiss VSU-2P apparatus at 25°C at λ_{max} 270 nm (*Ila*–*b*), 285 nm (*Ilc*–*e*), and at the isosbestic point 305 nm of compound *IIf* and its decomposition products (λ_{max} of *IIf* was 285 nm). The rate constants of formation of the 1,4-dihydropyridines were measured as it follows: 0.5 ml $10^{-3}M$ pyridinium salt solution was added to 9.5 ml tempered methanolic solution of sodium cyanide, and a part of the resulting mixture was poured into a 1 cm quartz cell located in the thermostated cell compartment of the apparatus. The rate constants were obtained from the time dependence of $\log(A_\infty - A_t)$. In two series of experiments the pyridinium salt solutions were added into tempered solutions of mixtures hydrogen and sodium cyanides resp. sodium cyanide and lithium chloride. The reverse reaction was followed with the solutions of the respective 1,4-dihydropyridines prepared by mixing 0.5 ml $10^{-3}M$ pyridinium salt solution, 1 ml 0.1M-NaCN and 7.5 ml methanol at 25°C. When the formation of the dihydropyridines *II* was practically complete (at least five half-lives), the reaction mixture was treated with 1 ml 0.1 to 0.5M- CH_3CO_2H in alcohol. The further procedure was the same as in the experiments studying the formation of 1,4-dihydropyridines. The rate constant was obtained from the time dependence of $\log(A_t - A_\infty)$. In the case of 4-bromoderivative the rate constant of the reverse reaction was measured also with the use of the crystalline derivative dissolved in pure methanol, in 0.01M methanolic acetic acid or in methanolic lithium chloride of the ionic strength 0.08.

pK_a of methanolic hydrogen cyanide was measured as it follows: absorbance of solutions having total concentrations of phenol and sodium cyanide $3 \cdot 10^{-4}M$ and 0.01 to 0.1M, respectively, were measured at λ 294 nm at 25°C. From the absorbance values found and known phenolate extinction coefficient the ratio $[C_6H_5OH]/[C_6H_5ONa] = I$ was calculated and introduced into Eq. (1), where pK_A and pK_s are the dissociation constant of phenol and the ionic product of methanol¹⁰, respectively; therefrom the methoxide ion concentrations were calculated and introduced into Eq. (2) to give K_B (assumption: $[CH_3O^-] = [HCN]$).

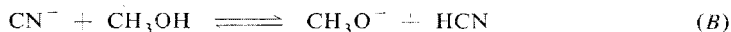
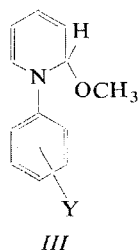
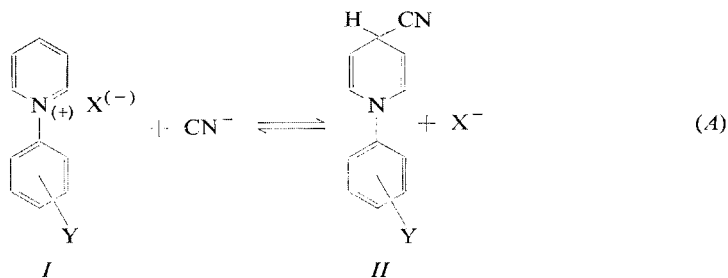
$$pK_A = pK_s + \log [CH_3O^-] + \log [I], \quad (1)$$

$$K = [CH_3O^-][HCN]/[CN^-]. \quad (2)$$

The K_B value increases practically linearly with increasing cyanide concentration. At 0.08M cyanide concentration the K_B value is $1.55 \cdot 10^{-4}$ mol/l, and extrapolation to zero cyanide concentration gives $K_B = (1.35 \pm 0.10) \cdot 10^{-4}$ mol/l.

RESULTS AND DISCUSSION

The reaction of the compounds *Ia–e* with cyanide ion is accompanied by a gradual change in spectra from that characteristic for a pyridinium salt to that of addition product having λ_{\max} 270 and 285 nm in the case of *Ia,b* and *Ic–f*, respectively. All the spectral records showed well-developed isosbestic points. After reaching the maximum absorbance at λ_{\max} of the respective product the spectra of the reaction mixtures do not further change, which indicates stability of the product under the given reaction conditions. Electronic spectrum of the product formed from the compound *Id* is identical with that of the crystalline 1(4-bromophenyl)-4-cyano-1,4-dihydropyridine the structure of which was determined by NMR spectroscopy. Therefrom it follows that the reaction (A) involves only addition at the position 4.



If, after finishing the reaction, methanolic solution of acetic acid is added to the reaction mixture, the reaction product is converted into the starting substance, and, on addition of excess cyanide ion, again the dihydropyridine *II* is formed. In the same way the reverse reaction and subsequent formation of *IId* take place, if the crystalline compound *IId* is dissolved in methanol. These results prove the reversibility of the reaction (A). If, instead of acetic acid, methanolic hydrochloric acid

is used, the transformation of the dihydropyridine *II* is much faster, but the final spectrum does not correspond to the compound *I*. Subsequent addition of excess cyanide does not result in formation of the dihydropyridine *II*, or only a slight amount is formed. The reaction of the 3-nitro derivative has a similar course, however, the product formed is unstable, its decomposition rate being lower by about one order of magnitude than the rate of formation. With the 4-nitro derivative, the decomposition rate of the product is comparable with the rate of its formation. In addition to it, the reaction is complicated in this case by a very rapid formation of an addition complex of the type *III* through the reaction with the methoxide ion¹¹ formed by alcoholysis of cyanide ion (Eq. (B)).

$$k_{\text{exp}} = k_2[\text{CN}^-] + k_{-1} = k_1 + k_{-1} \quad (3)$$

The rate constants of formation of the dihydropyridines *II* were determined with an at least two hundredfold excess of cyanide ions, so that the reaction took always a pseudomonomolecular course. The time dependence of $\log(A_\infty - A_t)$ was always linear in the whole range studied (at least three half-lives). As the reaction is reversible, the experimental rate constant is a sum of the rate constants of formation and decomposition of the complex (Eq. (3)). The effect of the reverse reaction is particularly significant with less reactive pyridinium salts *Ia-c* at lower cyanide ion concentrations. The rate constant k_{-1} of the reverse reaction was subtracted from the experimentally found constant, and the rate constant k_1 thus obtained was plotted against cyanide ion concentration. The dependence obtained is not linear, as it should be, if the reaction were 1. order in cyanide ion, but the increase is gradually smaller and smaller. This phenomenon is obviously due to the

TABLE I

Values of Measured and Corrected (for ionic strength 0.01) Rate Constants k_1 (s^{-1}), k_{corr} (s^{-1}) and k ($1 \text{ mol}^{-1} \text{ s}^{-1}$) of Reaction (A) at Various Analytic Concentrations of Cyanide Ions (mol/l)

$[\text{CN}^-] \cdot 10^2$	$k_1 \cdot 10^3$	k/k_x	$k_{\text{corr}} \cdot 10^3$	$k \cdot 10^1$
1	5.43	1.000	5.43	5.43
2	9.02	1.186	10.69	5.34
3	11.90	1.305	15.53	5.18
4	12.49	1.661	20.75	5.19
5	15.43	1.834	28.29	5.66
6	17.02	2.146	36.52	6.08
7	19.27	2.291	44.15	6.31
8	20.64	2.446	50.04	6.25

influence of increasing ionic strength on reaction between two oppositely charged ions. This influence of ionic strength was followed by measuring the rate of the reaction (A) at constant cyanide ion concentration ($10^{-2}M$) at various lithium chloride concentrations. The rate constants k_1 found at various cyanide ion concentrations were multiplied by the corresponding factors k/k_x (where k is the rate constant k_1 of the reaction with mere 0.01M cyanide ion, and k_x is the rate constant for the same cyanide concentration in the presence of lithium chloride to make the total ionic strength equal to that of the k_1 constant to be multiplied). The values k_{corr} (corrected to the ionic strength 0.01) increase practically linearly with increasing cyanide ion concentration (Table I).

The alcoholysis taking place in the reaction solutions results in a decrease of effective concentration of cyanide ion and in formation of the products type III (in the case of more reactive compounds). In order to lower the negative effect of alcoholysis (reaction (B)), the kinetics of formation of the dihydropyridines II was measured in the presence of added hydrogen cyanide. The rate constants should have been greater, but the reverse was true: the more hydrogen cyanide was added the slower was the reaction (A). A probable reason of this rate decrease is the formation of a hydrogen bonding between hydrogen cyanide and cyanide ion giving thus much less reactive associates than the free cyanide ions are. Table II gives the rate constants for various amounts of the added hydrogen cyanide and the rate constants k' calculated therefrom and related to free cyanide ion. The equilibrium constant 30.5 l/mol of the reaction (C) was used in the calculation, and there resulted the k' values which were, within experimental error, independent of hydrogen cyanide concentration.



TABLE II

Values of Measured and Calculated Rate Constants k_1 (s^{-1}) and k' (s^{-1}) of Reaction (A) at Various Analytical Concentrations of Hydrogen Cyanide (mol/l) and Free Cyanide Ion (mol/l)

[HCN]. 10^2	$k_1 \cdot 10^3$	[CN ⁻]. 10^2	$k' \cdot 10^3$
0	5.44	1.00	5.44
0.5	4.74	0.89	5.31
1	4.32	0.80	5.37
2	3.81	0.66	5.74
4	3.01	0.49	6.20
6	2.21	0.38	5.83
8	1.71	0.31	5.51

The rate constants k_1 found at 10^{-2}M concentration of cyanide ion were divided by the effective cyanide ion concentration (obtained from the analytical cyanide concentration and K_B) and used for quantitative evaluation of substituent effects on the rate of formation of the dihydropyridines *II*: the correlation obtained is given in Eq. (4). The time dependence of $\log(A_t - A_\infty)$ found for the reverse reactions

$$\log k = (1.08 \pm 0.06) \sigma^0 - (0.63 \pm 0.02); \quad r = 0.99368, \quad (4)$$

$$\log k_{-1} = -(1.63 \pm 0.17) \sigma^0 - (2.01 \pm 0.04); \quad r = 0.9837 \quad (5)$$

of the dihydropyridines *Ia-e* were again linear in the whole range studied. In the range studied the k_{-1} values were independent of ionic strength and acetic acid concentration; *i.e.* the reverse reaction is not acid-catalyzed under the conditions used. The logarithms of k_{-1} correlate according to Eq. (5).

The course of reaction (*A*) in ethanol is similar to that in methanol, however, with more reactive pyridinium salts the formation of adducts type *III* becomes more significant. Therefore, the kinetics of formation (and the respective retrogression) of only the three dihydropyridines *Ila, Ilc, Ild* were studied. Logarithms of the rate constants k_2 and k_{-1} correlate with σ^0 constants according to Eqs (6) and (7), respectively.

$$\log k_2 = 0.95 \sigma^0 + 0.43, \quad (6)$$

$$\log k_{-1} = -1.52 \sigma^0 - 3.63. \quad (7)$$

All the rate constants found for the derivatives *Ia-f* are summarized in Table III.

TABLE III

Values of Rate Constants k_2 ($1 \text{ mol}^{-1} \text{ s}^{-1}$), k_{-1} (s^{-1}) and Equilibrium Constants K ($1/\text{mol}$) of Reaction (*A*) of Compounds *Ia-f* in Ethanol and Methanol at 25°C

Compound	Methanol			Ethanol		
	$k_2 \cdot 10^1$	$k_{-1} \cdot 10^4$	$K \cdot 10^{-2}$	k_2	$k_{-1} \cdot 10^4$	$K \cdot 10^{-2}$
<i>Ia</i>	1.65	23.26	0.71	2.07	11.00	18.80
<i>Ib</i>	1.90	16.38	1.16	—	—	—
<i>Ic</i>	2.30	12.69	1.81	2.68	6.14	43.64
<i>Id</i>	5.43	4.64	11.70	5.19	2.18	238.07
<i>Ie</i>	6.67	2.78	23.99	—	—	—
<i>If</i>	11.70	—	—	—	—	—

The above results can be summarized as it follows: Reactions of the pyridinium salts *Ia-g* with methoxide ion in methanol give the respective 2-methoxy-1,2-dihydropyridine derivatives as the only products. On the contrary, the reactions with cyanide ion give only the products type *II*. Both the spectral records of the reaction course and the kinetic relations exclude a transient formation of products having the CN group bound at 2-position of the pyridinium ring. Lyle and Gauthier⁸ and Lindquist and Cordes³ suppose (with respect to changes in electronic spectra of the reaction mixture of pyridinium ions and CN^-) an initial attack at 2-position with a rapid conversion into 4-isomer⁸ resp. a slow subsequent conversion of 4-isomer into 2-isomer³; in the both cases, however, the 2-isomer would absorb at a shorter wavelength, whereas the opposite is true in all the cases studied so far¹. In addition to it, in the second case³ it was not possible to isolate 2-isomer or confirm its structure by some means.

The influence of substituents on the value of equilibrium constant of the reaction of the compounds *I* with CN^- is practically the same¹¹ as that in the reaction with CH_3O^- , however, the equilibrium constants of the reaction with CN^- in methanol are by about two orders of magnitude greater, in spite of CN^- being a far weaker base. The decisive role is played in this case by the reverse reaction which is by 7 to 8 orders of magnitude faster¹² in the case of the adduct with CH_3O^- . The rate constants of formation of the dihydropyridines *II* in ethanol are by about one order of magnitude greater than those in methanol, but the reverse reaction rates are only about two times smaller. The overall influence on the equilibrium constants (an about twenty-fivefold increase) is comparable with the estimated influence of the change of medium (about one order of magnitude) on the reaction of the compounds *I* with RO^- ions in methanol and ethanol¹¹. The reaction course can simply be represented as it follows: solvated ions \rightarrow intimate ionic pair \rightarrow activated complex \rightarrow product *II*. The observed much greater influence of polarity of medium on k_2 than that on k_{-1} is caused by that the formation of a dipolar activated complex from two solvated ions involves a much greater change in charge distribution than that encountered during the conversion of the neutral molecule *II* into activated complex; the ρ value of the reverse reaction is 1.5 times greater than that of the formation of the dihydropyridine *II*. As the magnitude of ρ constant depends, first of all, on the extent of formation resp. splitting of bonds (C—C bonds in this case) in the activated complex, it can be presumed that the structure of the activated complex resembles more the intimate ionic pair than the product.

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