

KINETICS AND MECHANISM OF REACTION OF 1-ARYLPYRIDINIUM SALTS WITH ACETONE AND CYCLOHEXANONE

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1-Arylpyridinium ions react with acetone and cyclohexanone in the presence of sodium methoxide to give substituted 1,2- and 1,4-dihydropyridines. The substituted 1,2-dihydropyridines are less stable and are gradually transformed into the derivatives of 1,4-dihydropyridine. The rate constants of the reaction of 1-arylpyridinium salts with cyclohexanone anion and the respective reverse reactions have been measured. The rate constant logarithms were correlated with the σ^0 constants. Increasing dimethyl sulphoxide content causes a decrease in the reverse reaction rate and an increase in the rate constant of formation of the substituted dihydropyridine, the latter effect being stronger than that in similar reactions with cyanide and methoxide ions.

Pyridinium salts can react with carbanions to give derivatives of 1,2- and 1,4-dihydropyridines. The reactions of 1-methyl-3-nitropyridinium iodide with anions of dimethyl malonate, ethyl cyanoacetate, and malono dinitrile gave stable crystalline compounds, the NMR spectra of which suggested that the carbanions added to the position 4 to give the substituted 1,4-dihydropyridines¹. Also in the reactions of 2,6-dichlorobenzyl-, substituted styryl- and substituted stilbylpyridinium ions with anions of acetone and nitromethane, 1,4-dihydropyridines were isolated as the only products²⁻⁴. In none of the above cases the reaction course was followed and the kinetics measured.

The purpose of this paper is the determination of the reaction course of 1-arylpyridinium ions with anions of acetone and cyclohexanone in methanol, determination of structure of the products formed and the rate constants of formation and reverse decomposition of the dihydropyridines. The work is complemented with a study of influence of medium (methanol-dimethyl sulphoxide) on the rate of reactions of 1-arylpyridinium ions with anions of acetone, cyclohexanone and cyanide ion and the respective retrogressions.

EXPERIMENTAL

1-(4-methyl-, 3-methyl-, H-, 4-bromo- and 3-chlorophenyl)pyridinium chlorides (*Ia-e*) and 1-(3-nitro- and 4-nitrophenyl)pyridinium bromides (*If-g*) were prepared by the method described previously⁵. Methanol and acetone were commercial reagents of *p.a.* purity grade. Di-

methyl sulphoxide was refluxed with calcium oxide and distilled. A commercial sample of cyclohexanone was rectified under the normal pressure and the middle fraction boiling at 163–164°C was taken.

NMR Spectra

A) Preparation of solutions of 1-aryl-4-(2-cyclohexanonyl)-1,4-dihydropyridines *IVa, d*. 7.2 ml 1M sodium methoxide solution was added to 2 g (7.4 mmol) 1-(4-bromophenyl)pyridinium chloride in 12 ml methanol and 1 ml (9.65 mmol) cyclohexanone. After 1 hour 1.8 g yellow crystalline compound *IVd* was collected by suction, m.p. 128–135°C. In a similar way the compound *IVa* melting at 99–103°C was prepared; 0.20 g product *IV* was dissolved in about 1 ml deuteriochloroform, 5% hexamethyldisiloxane was added thereto (internal standard 9.95 τ), and the NMR spectra were measured immediately.

B) Preparation of solutions of acetyl derivatives *II* and *III*. 1.3 ml 1M sodium methoxide was added to 1.45 mmol pyridinium salt *Ia* resp. *Id, If, Ig* in 2 ml methanol and 3 ml acetone. After 1 hour 100 ml tetrachloromethane was added, and sodium chloride resp. bromide was collected by suction; the solutions were concentrated *in vacuo*, the final volume being 1.5 to 2 ml, and after addition of about 5% hexamethyldisiloxane they were used for NMR spectra measurements. When preparing the 4-nitrophenyl derivative 0.16 g of deeply red crystalline 1,4-dihydro derivative *Ilg* (m.p. 133–136°C; for C₁₄H₁₄N₂O₃ (258) calculated: 65.1% C, 5.43% H, 10.85% N; found: 64.4% C, 5.25% H, 11.10% N) separated on evaporation of the reaction solution. For NMR spectra measurements the compound *Ilg* was dissolved in deuteriochloroform. The mother liquor contained the practically pure 1,2-dihydro derivative *IIIg* and was used for NMR spectra measurements after concentration to the volume 1 ml. NMR spectra were measured with a Tesla BS 487 apparatus at 80 MHz at the room temperature. In all the cases hexamethyldisiloxane was used as internal standard (9.95 τ).

Spectral method for following the reaction of compounds Ia–f with acetone. The respective pyridinium salt 0.35 mmol was dissolved in the mixture 5 ml methanol and 2.5 ml acetone, and 2.5 ml 0.1M-CH₃ONa was added thereto. At regular time intervals 0.05 ml samples were withdrawn and diluted with 5 ml methanol. A part of the diluted sample was placed in 0.2 cm quartz cell and its spectrum was measured immediately in the wavelength range 230 to 400 nm with a Unicam SP 800 apparatus.

Spectral method for following the reaction of compounds Ia–g with cyclohexanone. The compound *I* (0.2 ml 10⁻³M) was added to 1.5 ml methanol in 1 cm quartz cell, and 0.1 to 0.2 ml 5 · 10⁻¹M cyclohexanone and 0.2 ml 0.01 to 1.0M (according to reactivity of the pyridinium salt) sodium methoxide were added thereto. At regular time intervals spectra were recorded in the wavelength range 230 to 400 nm (230 to 500 nm for the compound *Ig*) with the Unicam SP 800 spectrophotometer. In the same way the reaction of the compound *Ig* with acetone was followed, 2M acetone solution in methanol being used. In some cases the reaction mixture was, after finishing the reaction, acidified with a 20% excess (with respect to sodium methoxide) of acetic acid in methanol, and again spectra were recorded in the same wavelength range at regular time intervals.

Kinetic Measurements

The measurements were carried out with the use of a Zeiss VSU-2P spectrophotometer at 25°C in 0.5 and 1 cm cells at constant ionic strength 0.1. The reaction rates of the pyridinium salts with cyclohexanone were measured as it follows: the thermostated methanolic solution of pyridi-

nium salt, cyclohexanone and lithium chloride was mixed with thermostated sodium methoxide solution. The final volume of the solutions was 10 ml, and final concentrations of pyridinium salts, cyclohexanone and methoxide were within $(0.5 \text{ to } 1.5) \cdot 10^{-4} \text{ mol/l}$, $(2 \text{ to } 7.5) \cdot 10^{-2} \text{ mol/l}$ and $10^{-3} \text{ to } 10^{-1} \text{ mol/l}$, respectively. A part of the solution was placed in a cell in the thermostated cell compartment of the spectrophotometer and the time-absorbance dependence was followed at the wavelengths 285, 295 and 420 nm for the compounds *Ia*–*b*, *Ic*–*f* and *Ig*, respectively. The rate constants were determined from the time dependence of $\log(A_{\infty} - A_t)$. The reverse reaction rate constants were determined in similar way as those of the formation rates, however, the volume was adjusted to make 10 ml after addition of 10% excess methanolic acetic acid (with respect to sodium methoxide). The acetic acid was added after at least six half-lives of the reaction of pyridinium salts with cyclohexanone. Again a part of the solution was placed in a quartz cell, and absorbance decreases were measured at the same wavelengths as above. The rate constants were obtained from the time dependence of $\log(A_t - A_{\infty})$.

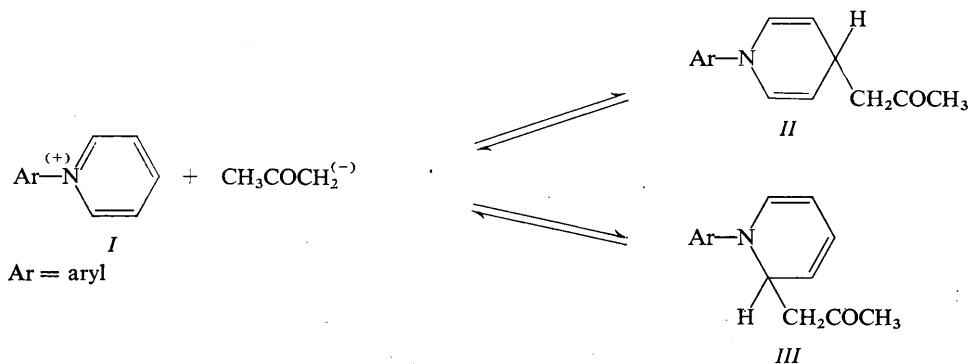
Kinetic measurements of the reaction of compound I with cyclohexanone and the reverse reaction of product IVc in mixtures methanol–dimethyl sulphoxide. The measurements were carried out in the same way as those in pure methanol⁶ with the only difference that 1 to 5 ml methanol was substituted by dimethyl sulphoxide, and the ionic strength was adjusted at 0.1 by addition of lithium chloride.

Kinetics of the acid catalyzed reverse reaction of 1-(4-methylphenyl)-1,4-dihydro-4-acetonilpyridine (IIa). 2.5 ml 0.1M sodium methoxide was added to 0.5 ml 0.1M 1-(4-methylphenyl)pyridinium chloride in the mixture of 3.5 ml methanol and 0.5 acetone. After 10 minutes 0.1 ml of the solution was injected into 10 ml methanol containing acetic acid and sodium acetate resp. chloroacetic acid and sodium chloroacetate in various amounts and ratios (1 : 1 to 6 : 1), concentration of the acid was within $1.5 \cdot 10^{-3}$ and $3 \cdot 10^{-1} \text{ M}$. Ionic strength was adjusted by addition of lithium chloride at the value 0.2. A part of the solution was poured into a 1 cm quartz cell, and the time dependence of the absorbance decrease was measured at the wavelength 290 nm. The rate constant was obtained from the time dependence of $\log(A_t - A_{\infty})$.

RESULTS AND DISCUSSION

Reactions of Arylpyridinium Salts with Acetone

The reaction of the compounds *I* with acetone in methanol in the presence of methoxide ions results in formation of a mixture of two isomeric dihydropyridines *II* and *III* (Scheme 1). The reaction rate increases with increasing both alkoxide and acetone concentrations. With the 4-methyl derivative *Ia* the reaction is practically finished within three minutes at 0.1M methoxide ion and 1.4M acetone concentrations. The mixture of reaction products from the derivatives *Ia*–*e* shows absorption bands with maxima at 290 and 350 nm corresponding to the isomers *II* and *III*, respectively. With the 4-methyl derivative the initial absorbance ratio of the isomers *II* and *III* is 4 : 1 to 5 : 1, however, the value increases with time, because the isomer *IIIa* is transformed into the more stable isomer *IIa*. The isomerization half-life is about 1 minute in methanol. Addition of an aprotic solvent (acetone, chloroform) lowers the isomerization rate. With increasing σ value of the substituent in the benzene ring the reaction half-life increases; in the case of 3-nitro and 4-nitro derivatives the isomers



SCHEME 1

*III*f and *III*g are relatively stable, so that the electronic spectrum of the reaction mixture does not change during half an hour.

Structure of the reaction products was determined on the basis of their NMR spectra. The spectrum of heterocyclic protons of 1-(4-nitrophenyl)-4-acetyl-1,4-dihydropyridine (*II*g) (Fig. 1a) is qualitatively very similar to that of 1-(4-bromophenyl)-4-cyano-1,4-dihydropyridine (ref.⁶). In addition to it, the proton H_4 shows, besides the interactions with $H_{3,5}$ and $H_{2,6}$, also a strong interaction with the proton H_α of the methylene group ($J_{4,\alpha} = 6.3$ Hz). The protons H_α are split by the proton H_4 into a doublet, the protons of the methyl group (H_γ) give a sharp singlet. Spectra of the other studied compounds of this type are quite analogous (Table I). Spectrum of the heterocyclic protons of 1-(4-nitrophenyl)-2-acetyl-1,2-dihydropyridine (*III*g) consists of 5 multiplets belonging to five various types of protons (Fig. 2). A partial analysis of the spectrum gave the following data: $\nu_2 = 5.01\tau$; $\nu_3 = 4.34\tau$; $\nu_4 = 4.02\tau$; $\nu_5 = 4.54\tau$; $\nu_6 = 3.56\tau$; $J_{2,3} = 6.2$ Hz; $J_{3,4} = 9.1$ Hz; $J_{4,5} = 5.5$ Hz; $J_{5,6} = 7.1$ Hz. The values of coupling constants found agree well with those found previously for similar systems⁷. The both methylene protons are non-equivalent, which is due to the presence of three different substituents at the neighbouring carbon atom. The values of the difference in chemical shifts $\Delta\nu_{\alpha,\alpha'} = 29.3$ Hz ($\nu_\alpha = 6.99\tau$; $\nu_{\alpha'} = 7.36\tau$) and coupling constant $J_{\alpha,\alpha'} = 16.7$ Hz were calculated from the AB spectrum formed after spin decoupling from the proton H_2 , the coupling constants $J_{2,\alpha}$ and $J_{2,\alpha'}$ have the values 9.0 and 4.0 Hz, respectively (Fig. 2). The protons H_γ give a sharp singlet with the chemical shift $\nu_\gamma = 7.89\tau$.

From the NMR spectrum of the reaction mixture after reaction of the compound *I*f with acetone (see Experimental) it was found that the reaction produces the isomers *II*f and *III*f in the ratio 3 : 2 (Fig. 1b). The measured sample of 1-(4-bromophenyl)-4-acetyl-1,4-dihydropyridine contained 20% of the 1,2-isomer *III*d, whereas 1-(4-tolyl)-4-acetyl-1,4-dihydropyridine was free from the 1,2-isomer *III*a.

Although the reaction solutions of the products from the pyridinium salts *Ia*–*d* contained, after a certain time, practically only the 4-isomers, it was not possible to obtain the latter as pure crystalline solids. Partial concentration of methanolic solutions of the 4-methyl and 4-bromo derivatives caused partial separation of crystalline isomers *Iia* and *Iid*, however, the both substances melted within a considerable temperature range (about 20°C), and attempts of purification *via* crystallization failed. Both the isolated solids and solutions gradually turned dark, and electronic spectra of their methanolic solutions showed a new intensive band at λ_{\max} 420–430 nm. Similar behaviour was observed by Kröhnke and coworkers^{2,3}; in the case of the reaction products from 2,6-dichlorobenzyl- and styrylpyridinium salts with acetone they found that the oxidation produced the compounds type *VI*.

Reaction of 1-Arylpyridinium Salts with Cyclohexanone

Again the reaction of the compounds *I* with cyclohexanone can produce two isomers *IV* and *V* (Scheme 2). From the reaction solutions of the salts *Ia* resp. *Id* with cyclohexanone in methanolic sodium methoxide pale yellow crystals separated melting

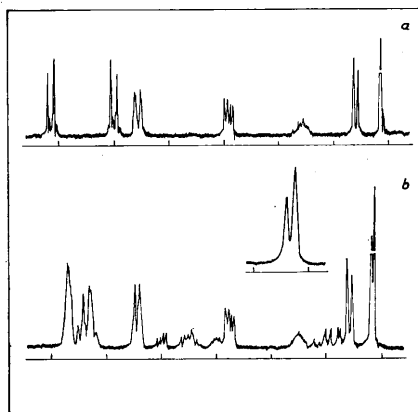


FIG. 1

¹H-NMR Spectrum *a* of 1-(4-Nitrophenyl)-4-acetyl-1,4-dihydropyridine (*IIg*) in CD₂Cl₂ and *b* Spectrum of Mixture of 1-(3-Nitrophenyl)-4-acetyl-1,4-dihydropyridine (*IIg*) and 1-(3-Nitrophenyl)-2-acetyl-1,2-dihydropyridine (*IIIg*) in CCl₄

Scales in *a* and *b* from left to right 2, 3, 4, 5, 6, 7, 8 τ . The peaks in detail scale 7,75 and 8,0 τ .

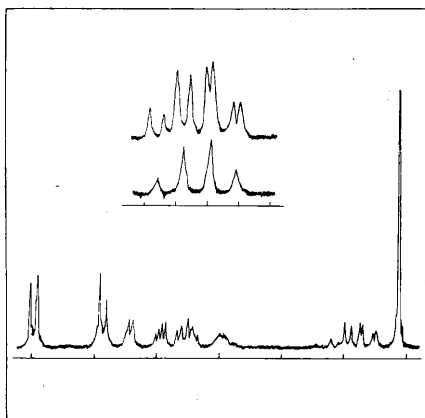
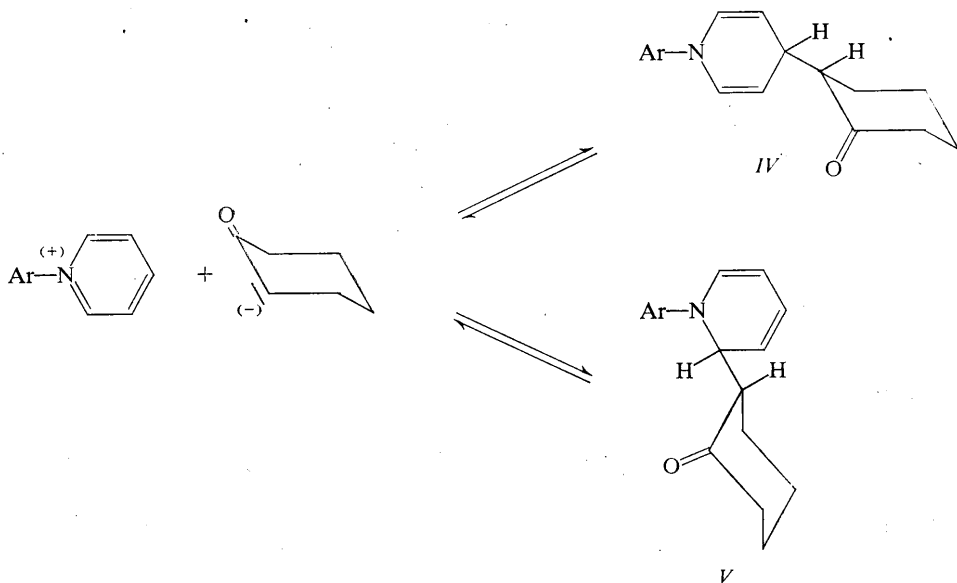


FIG. 2

¹H-NMR Spectrum of 1-(4-Nitrophenyl)-2-acetyl-1,2-dihydropyridine (*IIIg*) in CCl₄ and Its Part after Spin Decoupling from H₂

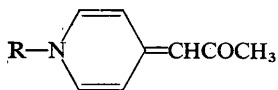
Upper scale: 6.75, 7.0, 7.25 and 7.5 τ , lower scale 2, 3, 4, 5, 6, 7, 8 τ .

within several degrees. From their electronic and NMR spectra (measured immediately after isolation of the products) it was found that they are practically pure isomers *IVa* and *IVd*. As it was the case with the products *IIa* and *IId*, the crystals turned dark after a time, and their recrystallization resulted in lowering of their melting points.



SCHEME 2

A more detailed analysis of the spectrum was carried out in the case of 1-(4-bromophenyl)-4-(2-cyclohexanonyl)-1,4-dihydropyridine (*IVd*). The spectrum contains, besides the absorptions of the aromatic protons, four multiplets with integral intensities 2 : 2 : 1 : 9 belonging to the protons $H_{2,6}$, H_3 , H_4 and protons of cyclohexanonyl group. Positions of the multiplets of the protons of dihydropyridine ring correspond roughly to those of the acetyl derivative *IIId*. However, the multiplets are much more complex, which is due to the presence of the asymmetric carbon atom in the cyclohexanonyl residue^{8,9}. The best interpretation can be given for formation of the multi-

*VI*

plet of H_4 proton ($\nu_4 = 6.33\tau$). The broadened quartet, after spin decoupling from the protons $H_{2,6}$, was simplified to a quartet formed by interaction with the protons $H_{3,5}$ and H_α with the same coupling constants (3.5 Hz). The coupling constants $J_{2,4} = J_{4,6} \approx 1$ Hz. The interpretation of the quartet formation was confirmed by formation of a triplet after spin decoupling from H_α . From the considerably extended doublet between 3.5 and 3.7 τ corresponding to the protons $H_{2,6}$ the coupling constants $J_{2,3} = J_{5,6} \approx 8$ Hz can be estimated. This value is practically the same as that for the acetyl derivatives *II*. The multiplet between 5.25 and 5.55 τ belongs to the protons H_3 and H_5 . After spin decoupling from both the protons $H_{2,6}$ and the proton H_4 , again complex multiplet were obtained, which proves the non-equivalence of the protons H_3 and H_5 . From the spectra after spin decoupling it was possible to estimate the value of difference in chemical shifts of the protons H_3 and H_5 , $\Delta\nu \approx 9$ Hz.

In contrast to the reaction with acetone, the electronic spectra of the reaction solutions measured under the conditions of a large rate of formation of the product showed no changes indicating isomerization. It means that either the isomers *V* are formed in small quantities (less than about 5%), or they are rapidly transformed into the isomer *IV*. One of the reasons can be in the greater volume of cyclohexanone anion and hence also greater sterical requirements in addition to the position 2 (compared with the reaction of acetone).

The reactions of pyridinium salts with cyclohexanone proceed at sufficient rates even with relatively low cyclohexanone concentrations so that, in contrast to reactions with acetone where the absorbances of acetone itself were about 2 or higher in the range of absorptions of the products, it was possible to follow the kinetics of formation of the reaction products by direct spectral method. The time dependence of $\log(A_\infty - A_t)$ was linear in the whole studied range (at least 80% of the reaction). This fact confirms that the extent of isomerization is so small that it cannot be proved from kinetic data.

The studied reactions proceed in two steps. A rapid antecedent equilibrium between cyclohexanone and methoxide ion produces cyclohexanone anion which adds to the pyridine ring in the following rate-limiting step. The formation of the products is reversible, hence the measured rate constant represents a sum of the constants k_1 (involving the cyclohexanone anion concentration, Eq. (2)) and k_{-1} (of the reverse reaction). Therefore, the reverse reaction rates were measured separately, and the values k_1 were calculated from the rate constants found.

The reverse reaction rate depends on the concentration and structure of the product and on medium. In all the cases the time dependence of $\log(A_t - A_\infty)$ was linear (at least 80% of the reaction). Logarithms of the rate constants k_{-1} (Table I) correlate with σ^0 constants (except for the 4-nitro derivative) according to Eq. (1). For the 4-nitro derivative the value $\sigma = 1.18$ was calculated which is only slightly smaller than the $\sigma_{p-NO_2}^-$ value given in the literature¹⁰.

$$\log k_{-1} = -(1.48 \pm 0.05) \sigma^0 - (2.04 \pm 0.02); \quad r = 0.9986. \quad (1)$$

The value of ρ constant is practically the same as that for the reverse reaction of the reaction products with cyanide⁶ and methoxide ions¹¹, in spite of that these nucleophiles are considerably different in structure and reactivity, and in the case of methoxide the splitting proceeds at a different position.

The rate of formation of the dihydropyridine *IV* (and the derivative *V* formed in a small amount) depends on the concentration of the pyridinium salt and cyclohexanone anion and hence on concentrations of methoxide ion and cyclohexanone, and it is defined by Eq. (2). As the *K* value of the antecedent equilibrium is not

$$\vec{v} = k_1[I] = k_2[I_{\text{eff}}][\text{C}_6\text{H}_9\text{O}^-] = k_3[I_{\text{eff}}][\text{CH}_3\text{O}^-][\text{C}_6\text{H}_{10}\text{O}]. \quad (2)$$

known, it is impossible to determine the concentration of cyclohexanone anion; therefore, the rate constants $k_3 = k_2K$ (Table II) were calculated. $[I_{\text{eff}}]$ stands for

TABLE I

Chemical Shifts (τ) and Coupling Constants (Hz) of Protons in Substituted 1-Phenyl-4-acetyl-1,4-dihydropyridines Type *II*

Compound	H _{2,6}	H _{3,5}	H ₄	H _{α}	H _{γ}	J _{2,3}	J _{3,4}	J _{4,α}
<i>IIa</i>	3.79	5.53	6.51	7.54	7.95	8.3	4.0	6.3
<i>IIc</i>	3.78	5.44	6.55	7.54	7.95	8.2	3.9	6.3
<i>IIe</i>	3.58	5.29	6.56	7.49	7.93	8.0	3.8	6.3
<i>IIg</i>	3.46	5.11	6.45	7.49	7.94	8.0	3.8	6.3

TABLE II

Values of Rate Constants k_3 ($l^2 \text{ mol}^{-2} \text{ s}^{-1}$) and k_{-1} (s^{-1}) for Reactions of Compounds *I* with Cyclohexanone

Derivative	k_3	$k_{-1} \cdot 10^3$
<i>Ia</i>	3.10	16.6
<i>Ib</i>	—	11.7
<i>Ic</i>	3.72	8.9
<i>Id</i>	7.96	2.7
<i>Ie</i>	10.77	1.7
<i>If</i>	17.85	0.35
<i>Ig</i>	38.00	0.042

TABLE III

Effect of Dimethyl Sulphoxide (DMSO) Concentration on the Rate Constants k_3 ($l^2 \text{ mol}^{-2} \text{ s}^{-1}$), k_2 ($l \text{ mol}^{-1} \text{ s}^{-1}$) and k_{-1} (s^{-1})

% DMSO (by vol.)	k_3 (IVa)	$10^3 k_{-1}$ (IVc)	$10k_2$ (VIIIc)	$10^3 k_{-1}$ (VIIIc)	k_{-1} (VIIb) ^a
0	3.10	8.93	1.02	1.26	886
10	—	4.36	1.45	0.95	420
20	9.64	2.14	2.15	0.75	182
30	—	1.05	3.20	0.66	86.2
40	90.6	0.645	4.49	0.54	42.0
45	—	0.511	5.74	0.51	24.7
50	461	0.321	7.18	0.49	15.8

^a Ref.¹¹ gives $k_2 = 2.82 \cdot 10^4$ in methanol, $3.16 \cdot 10^5$ in 50% DMSO.

real concentration of the pyridinium salt *I* at the given methoxide ion concentration which is, in the case of the derivatives *Id–g*, substantially lower than the analytical concentration* due to the reaction with CH_3O^- .

$\log k_3$ correlate with σ^0 constants according to Eq. (3), the only exception being again the 4-nitro derivative.

$$\log k_3 = (0.97 \pm 0.07) \sigma^0 + (0.61 \pm 0.03); \quad r = 0.9918. \quad (3)$$

Influence of medium on the rates of reactions of 1-arylpyridinium salts with nucleophiles. Products of addition of carbanions on the pyridinium salts are far more stable than the reaction products of the compounds *I* with methoxide ions. Reverse reactions of 1-aryl-2-methoxy-1,2-dihydropyridines¹¹ *VII* proceed faster by 6 to 7 orders of magnitude than those of the compounds *IV*. Splitting off of cyanide ion from 1-aryl-4-cyano-1,4-dihydropyridines *VIII* proceeds several times more slowly than that of cyclohexanone anion, in spite of cyanide ion being a weaker base by at least 6 to 7 orders of magnitude. Solvation of nucleophile before (resp. after) the reaction and in the transition state has a great influence on the rates of these reactions. Therefore, we determined and compared the changes in the reaction rates caused by a changed solvation ability of medium during gradual substitution of methanol by dimethyl sulphoxide (Table III). The increase in k_3 resulting from a change to 50% (by vol.) dimethyl sulphoxide is by more than one order of magnitude greater.

* Real concentrations of *Id* to *Ig* were calculated from methoxide ion concentration and equilibrium constants of formation⁷ of the compounds *VIIId–g* (for $[\text{CH}_3\text{O}^-] = 0.1 \text{ mol/l}$ corresponding to the ionic strength 0.1).

ter than the increase in k_2 of the reaction with methoxide and cyanide ions. This is largely caused by that the change of k_3 value involves the influence of medium on the equilibrium constant of the reaction of cyclohexanone with methoxide ion, too. From the analogy of the influence of medium on the equilibrium constant of the reaction of CH_3O^- with dimethyl malonate¹² it is possible to estimate that K increases about 20 to 30 times; it means that the change of k_2 of the reaction with cyclohexanone anion is similar to that of the reaction with cyanide and methoxide ions. In general it can be stated that the difference between solvation of the nucleophile and that of the activated complex is similar in the reactions with all the three nucleophiles. A great difference is observed, however, in the rate constants of the reverse reaction, where the overall decrease in k_{-1} of the reaction of the compound *VIII* is lower by more than one order of magnitude than that of the reverse reactions of the adducts *IV* and *VII*. Obviously the main reason is in the impossibility of formation of hydrogen bond between methanol molecules and electron pair at the carbon atom of the cyanide ion being formed in the transition complex. Therefore, the reverse reaction of the compound *VIII* in methanol is seven times slower than that of the adduct *IVc*. In 50% (by vol.) dimethyl sulphoxide, where the solvation by methanol is less significant, the splitting of the adduct *IVc* is slower (Table III).

Acid catalysis of the reverse reaction of 1-(4-tolyl)-4-acetyl-1,4-dihydropyridine (IIa). The influence of acids on the reverse reaction of the product *IIa* was studied in the medium of acetate and chloroacetate buffers. Influence of concentration and composition of acetate buffer on the reaction rate was negligible. In chloroacetate buffers the reaction rate increased linearly with increasing concentration of chloroacetic acid but was independent of ratio of the acid to its anion. It means that the reaction is catalyzed by chloroacetic acid and not by the proton (up to the maximum proton concentration of 10^{-7} mol/l calculated from the published value of $\text{p}K_a$ of chloroacetic acid in methanol¹³). The experimental rate constants are defined by relation (4).

$$k = (4.58 \pm 0.36) \cdot 10^{-2} [\text{ClCH}_2\text{CO}_2\text{H}] + (1.78 \pm 0.47) \cdot 10^{-3}; \quad r = 0.9794. \quad (4)$$

The value $1.78 \cdot 10^{-3} \text{ s}^{-1}$ is practically the same as that found in diluted acetate buffers ($1.75 \cdot 10^{-3} \text{ s}^{-1}$) and represents the value of the non-catalyzed reaction rate constant.

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