KINETICS OF REVERSIBLE REACTION OF N-ARYLPYRIDINIUM SALTS WITH METHOXIDE IONS IN METHANOL AND METHANOL–DIMETHYL SULPHOXIDE MIXTURES

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With the use of the stopped flow method rate constants have been measured of the conversion of 1-aryl-2-methoxy-1,2-dihydropyridines into N-arylpyridinium and methoxide ions in the mixture methanol–dimethyl sulphoxide. The dependence of these reaction rate constants on dimethyl sulphoxide concentration has been determined. From the rate constants found and from the known equilibrium constant of this reaction the rate constants of formation of 1,2-dihydropyridines have been calculated. The rate constant of the reverse reaction of 1-(4-nitrophenyl)-2-methoxy-1,2-dihydropyridine measured in methanol increases linearly with acetic acid concentration, and it is independent of sodium acetate concentration.

In previous work we measured the equilibrium constants of the reactions of N-phenyl-pyridinium salts having substituents in 3- or 4-position of phenyl nucleus with methoxide ion in methanol (reaction (A)). Formation of the adducts II was so fast in all the cases that it could not be measured even by the stopped flow method. The aim of the present work was the determination of the rate constants k_{-1} of the reverse reaction and calculation of the rate constants k_1 of formation of the adducts II from the k_{-1} values and the equilibrium constants found previously[1].

EXPERIMENTAL

Reagents. N-(3- resp. 4-Substituted phenyl)pyridinium salts $Ia-g$ ($Ia = $ 4-CH$_3$, $Ib = $ 3-CH$_3$, $Ic = $ H, $Id = $ 4-Br, $Ie = $ 3-Cl, $If = $ 3-NO$_2$, $Ig = $ 4-NO$_2$) were prepared by the method described previously[2]. Dimethyl sulphoxide (commercial reagent, Lachema) was refluxed with calcium oxide for several hours and distilled. For kinetic measurements the middle fraction was used, and it was kept over molecular sieves. The other reagents were commercial products of p.a. purity grade.

Kinetic measurements were carried out by the stopped flow method with the use of a Durrum Stopped Flow Spectrophotometer Model D 110 at 25°C. Solutions of the adducts $IIa-g$ were prepared by mixing 5.10^{-3}M methanolic solutions of the pyridinium salts $Ia-g$ with 0·2 to $1·0.10^{-2}$M sodium methoxide in methanol resp. methanol–dimethyl sulphoxide mixture immediately before the proper measurements. The final concentration of the compounds II was $2 . 10^{-4}$M. The second syringe of the spectrophotometer was filled with $0·25-1·2 . 10^{-2}$M solution of acetic

acid in methanol resp. methanol–dimethyl sulphoxide mixture. The final acetic acid concentration was $0.25-1 \cdot 10^{-3}$M. In the case of the compound *IIg* higher concentrations of acetic acid resp. acetic acid–sodium acetate mixtures were used, too. After mixing the absorbance decrease was measured at 325 nm resp. 385 nm (compound *IIg*). The reaction half-life was read directly from the screen of the oscilloscope. Each measurement was repeated three or four times. The differences in the values measured were maximum $\pm 5\%$ (derivative *IIa*), except for the reactions of *IIf* and *IIg* in methanol with the highest concentration of acetic acid where the differences increased up to $\pm 10\%$. The rate constants were computed from the relation $k_{-1} = 0.693 : \tau_{1/2}$. The equilibrium constant of formation of the product *IIa* in the 1 : 1 (by vol.) mixture methanol–dimethyl sulphoxide was determined in the same way as it is given in the report[1].

RESULTS AND DISCUSSION

The reaction of the pyridinium salts *Ia*$-g$ with methoxide ion leading to formation of the products *II* is reversible (Eq. (A)). The rate constant of the formation of the equilibrium mixture is a sum of the rate constant of formation of the product, $k_1[\text{CH}_3\text{O}^-]$, and that of its decomposition, k_{-1}. If in the reaction mixture containing the compound *II* the methoxide ion present is neutralized with acetic acid, the value $k_1[\text{CH}_3\text{O}^-]$ decreases compared with k_{-1} to such an extent that the rate of formation of the product becomes negligible. The product *II* is converted almost completely into the starting pyridinium salt, and the experimentally found reaction rate constant is equal to k_{-1}. This constant must always be smaller (and hence the reaction half-life must be greater) than the rate constant obtained by measuring the reaction rate after mixing the pyridinium salt solution with methoxide ion solution. In spite of that, in pure methanolic medium we succeeded to determine the k_{-1} values only for 3- and 4-nitro derivatives (*IIf* and *IIg*). Half-lives of the reverse reactions of the other products *II* were less than 0.5 millisecond. Increasing dimethyl sulphoxide concentration in the reaction mixture results in a rate decrease of the reverse reaction (Table I). In the 1 : 1 (by vol.) methanol–dimethyl sulphoxide it was possible to measure k_{-1} for all the other derivatives (Table II). The dependence $\log k_{-1}$ vs σ^0 constants is linear (Eq. (1)).

$$\log k_{-1} = (1.90 \pm 0.05)\,\sigma^0 + (2.51 \pm 0.02) ; \quad r = 0.9985 \tag{1}$$

$$k_{\text{exp}} = k_1 + k_{\text{HA}}[\text{HA}] \tag{2}$$

$$I \qquad\qquad\qquad\qquad II$$
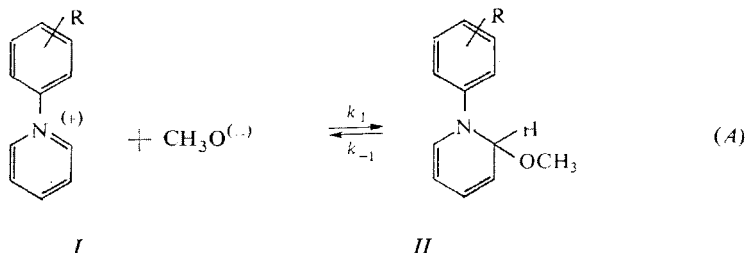
The ϱ value 1·9 is similar to that found for decomposition of 1-aryl-4-cyano-1,4-dihydro-pyridines[3] in spite of that the splitting off of cyanide ion is a reaction slower by seven orders of magnitude. In the case of the 4-nitro derivative *IIg* the acid catalysis of the reverse reaction has been studied in methanol. The value k_{-1} increases linearly with

TABLE I

Dependence of Rate Constants k_{-1} (s^{-1}) of Derivatives *IIe,f* on Content of Dimethyl Sulphoxide (DMSO) in Methanol at 25°C

% DMSO	k_{-1}		R^a
(by vol.)	*IIe*	*IIf*	
0	—	870	—
10	—	420	—
20	770	182	4·23
30	308	86·6	3·55
40	128	42·0	3·06
45	86·6	24·8	3·49
50	57·8	15·8	3·66

^{a} R ratio of the rate constants k_{-1} of the derivatives *IIe* and *IIf*.

TABLE II

Values of k_{-1} (s^{-1}), k_1 $(l\,mol^{-1}\,s^{-1})$ and K $(l\,mol^{-1})$ of Derivatives *Ia—g* in Methanol at 25°C

Compound	$k_{-1}{}^a$	K^b	$k_{-1} . 10^{-4,c}$	$k_1 . 10^{-4,d}$
Ia^e	602	0·85	3·3	2·8
Ib	408	—	2·2	—
Ic	330	1·7	1·8	3·1
Id^f	96	17·0	0·53	9·0
Ie	57·8	40·8	0·32	13·0
If	15·8	389	0·086	33·0
Ig	—	2 570	0·019	48·0

^{a} In mixture methanol–dimethyl sulphoxide 1 : 1 (by vol.); ^{b} ref.[1]; ^{c} the method of calculation of the values *Ia—e* see the text; ^{d} calculated from the relation $k_1 = k_{-1}K$; ^{e} values for 1 : 1 (by vol.) mixture methanol–dimethyl sulphoxide: $K = (5·25 \pm 0·30) . 10^2\,l\,mol^{-1}$; $k_1 = 3·16 . 10^5\,l\,mol^{-1}\,s^{-1}$; ^{f} the values for ethanol: $K = 5·1 . 10^3\,l\,mol^{-1}$; $k_{-1} = 4·1 . 10^2\,s^{-1}$; $k_1 = 2·1 . 10^6\,l\,mol^{-1}\,s^{-1}$.

increasing acetic acid concentration, and it is independent of the sodium acetate concentration. It means that the reaction is catalyzed by acetic acid, and that the proton concentration has no influence on its rate under the reaction conditions used. The dependence k_{exp} vs acetic acid concentration can be expressed by Eq. (2), where k_{HA} is the rate constant of the acetic acid-catalyzed reverse reaction, its value being 3220 ± 71, i.e. 17 times greater than the rate constant k_{-1} of the non-catalyzed reaction. As the final acetic acid concentrations in the reaction mixture for k_{-1} determinations were $0.25 - 1.0 \cdot 10^{-3}$M, the rate constants measured at the highest acetic acid concentration are higher by about 2% due to catalysis by acetic acid.

As it can be seen in Table I the ratio of the rate constants k_{-1} of 3-nitro and 3-chloro derivatives is independent (within experimental error) of the reaction medium. Thus it is possible to estimate the k_{-1} values of other derivatives in methanol from the k_{-1} values found in 1 : 1 (by vol.) methanol–dimethyl sulphoxide mixture and from that of 3-nitro derivative measured in methanol. From the values thus obtained and from the known values of equilibrium constants the rate constants of formation of the products II were calculated according to the relation $k_1 = k_{-1}K$ (Table II).

The equilibrium constant value of formation of the product IIa in the 1 : 1 (by vol.) methanol–dimethyl sulphoxide mixture is about $600 \times$ greater than that in methanol. This increase in K is due to an about tenfold increase in k_1 and more than fiftyfold decrease in k_{-1}. The influence of medium on the reaction (A) is similar to that of the formation of Meisenheimer complexes[4-6].

The situation in reactions of pyridinium salts with methoxide ion is complicated by that there react two ions carrying opposite charges. Dielectric constant of dimethyl sulphoxide is greater than that of methanol, and bulky organic anions are more strongly solvated by dimethyl sulphoxide than by methanol[6]. Both these factors should make the reaction more difficult. In fact, the increase in k_1 is similar to that found in formation of Meisenheimer complexes. Solvation of the split off CH_3O^- groups by methanol molecules plays an important role in the reverse reaction. In the case of the reaction (A) (in contrast to Meisenheimer complexes) this process is accompanied by formation and separation of opposite charges. Solvation of the methoxide ion being formed facilitates this process, and this can be one of the reasons of the large decrease of k_{-1} of this reaction when the dimethyl sulphoxide concentration is increasing.

As expected, the reaction rate constant of Id with ethoxide ion in ethanol is about 20 times greater than that with methoxide ion in methanol, and, on the contrary, the reverse reaction is about 10 times slower. The formation of the adduct is influenced by both lower dielectric constant of ethanol (reaction of two oppositely charged ions) and higher nucleophility of ethoxide ion, whereas in the reverse reaction the latter effect is obviously decisive.

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