

KINETICS AND MECHANISM OF HYDROLYSIS OF SUBSTITUTED N-(5-METHYLSALICYLIDENE)ANILINES IN ACIDITY RANGE $H_0 -4$ TO 4.5

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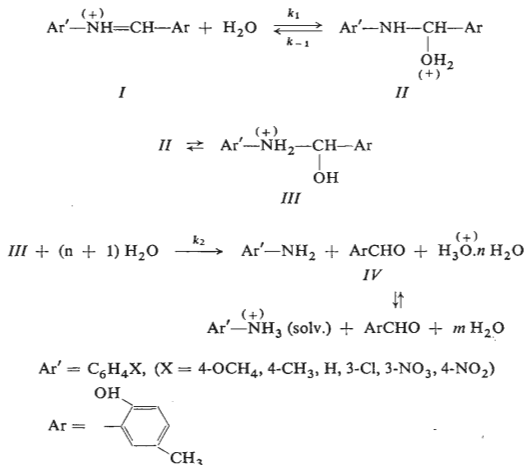
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In diluted sulphuric acid the dependence of logarithms of experimental rate constants of hydrolysis of six N-(5-methylsalicylidene)aniline derivatives on pH is linear with a slope 1.60. The value of the Hammett reaction constant ρ is 2.85. The water-catalyzed decomposition of the protonated carbinolamine is rate-determining for all the derivatives in this medium. In acetate and chloroacetate buffers the basic buffer components are also kinetically significant besides water, and the formation of the protonated carbinolamine gradually becomes rate-determining with the derivatives having substituents with positive σ constant values. From the pH dependence of the $\log k_{\text{exp}}$ values determined by the stopped-flow method the pK_a values of the protonated Schiff's bases have been determined and correlated with the σ^0 constants.

In the foregoing papers^{1,2} the pH dependence of the hydrolysis rate of salicylideneanilines was measured in the pH range 5–13. At a pH < 7 the protonated Schiff's base reacted with water, and the reaction rate constant was proportional to the proton concentration. At a pH > 9 the neutral Schiff's base reacted with the hydroxyl ion. The dependence of $\log k_{\text{exp}}$ on the Hammett σ constants showed a break in the both cases which was explained by a change of the rate-determining step. The formation and decomposition of the intermediate was rate-limiting in the case of substituents with positive and negative σ constant values, respectively. At a pH < 5 the hydrolysis proceeds so fast that its rate cannot be measured by usual kinetic methods. Reeves³ measured the hydrolysis rate of *p*-trimethylammoniumbenzylidene-*p'*-hydroxyaniline chloride in this range up to pH 1. He found that the rate was proportional to the proton concentration up to pH about 3; further the rate increased more slowly than $[H^+]$ and at a pH < 2 it was practically pH-independent, as the greater part of the Schiff's base was protonated. In stronger acids the hydrolysis of Schiff's bases again becomes inasmuch slow that it can be measured by conventional kinetic methods, and the rate rapidly decreases with increasing acid concentration. In media of 7-11M- H_2SO_4 the logarithm of the hydrolysis rate constant of *p*-chlorobenzylideneaniline⁴ depends linearly on H_0 , the slope being 1.24. Such a course is characteristic for the reactions in which water molecules act both as nucleophilic agents and proton-transfer agents at the same time. The dependence suggests that the splitting of the intermediate III is rate-limiting, proton and aniline being split off simultaneously (Scheme 1).

In this work the hydrolysis of substituted N-(5-methylsalicylidene)anilines has been measured in the range of pH 4.5 to $H_0 -4$. The aim of the work was: a) to determine the influence of substituents on the hydrolysis rate in diluted sulphuric acid media



SCHEME 1

where all the Schiff's base was present in the protonated form, and the decomposition of the intermediate was rate-limiting for all the derivatives. *b*) To determine the overall dependence of the hydrolysis rate on the acid concentration and to try to find when the change of the rate-limiting step took place. *c*) To determine, from the kinetic dependence, the pK_a values of the protonated forms which cannot be measured directly due to their short half-lives.

EXPERIMENTAL

The salicylideneaniline derivatives described in our previous papers^{1,2} were used for kinetic measurements. The measurements were carried out in aqueous-alcoholic media (22% by vol. ethanol) in acetate and chloroacetate buffers, in diluted hydrochloric acid (pH range 1.51–0.10) and diluted sulphuric acid (H_0 range –1.2 to –4.1) at the temperature of 22°C. Constant ionic strength was maintained by addition of potassium chloride up to pH 1.18, whereas at higher acidities the ionic strength increased.

The measurements in diluted sulphuric acid media were carried out with a spectrophotometer Unicam SP 800 in 4 cm cells at such a wavelength that the difference between the extinction of the protonated Schiff's base and that of the reaction products was maximum. Each derivative was measured at 3–5 various sulphuric acid concentrations. The rate constants were calculated from Eq. (1) by means of a computer. The measurements in

$$\log(E - E_\infty) = -k_{\text{exp}}t + \text{const.} \quad (1)$$

acetate and chloroacetate buffers and in diluted hydrochloric acid were carried out by the stopped-flow method using a Durrum Stopped-Flow Spectrophotometer Model D-110. The reaction half-life $\tau_{1/2}$ was read directly from the screen of the apparatus. Three to four measurements were carried out for each derivative and pH, and the rate constant was calculated from the average value of the half-life ($k = 0.693/\bar{\tau}_{1/2}$). Solutions of the Schiff's bases in absolute ethanol were prepared immediately before measurements and were diluted with water to give 44% by vol. ethanol. A small amount of phosphate buffer of pH 8 was added to this solution, as the Schiff's bases decomposed most slowly in stock solutions of this pH, and they also did not hydrolyze so quickly in the stock solution syringe of the apparatus by action of the small amounts of acids diffused from the mixing chamber into the syringe. During the proper measurement this solution was mixed with an equal volume of aqueous buffer in the mixing chamber. The ethanol concentration in the reaction medium was 22% by vol., that of the Schiff's bases was about $1-2 \cdot 10^{-5}$ mol/l. The sulphuric acid concentration was determined by titration with sodium hydroxide using the Tashiro indicator. The pH of the solutions was measured with a pH-meter Type 4 (Radiometer, Copenhagen).

RESULTS AND DISCUSSION

Fig. 1 gives the dependence of $\log k_{exp}$ on pH event. H_0^* for all the six 3'- and 4'-substituted N-(5-methylsalicylidene)-anilines. It can be seen that the dependence $\log k_{exp}$ vs H_0 is linear with the slope 1.60 for all the derivatives in the H_0 range -2 to -4 . This dependence resembles that found by Jencks for hydrolysis of *p*-chlorobenzylideneaniline⁴. The values of $\log k_{exp}$ found at $H_0 -3.0$ were correlated with the Hammett σ constants (Eq. (2)). 4'-Nitroderivative reacts faster than it should react accord-

$$\log k = -(3.25 \pm 0.05) + (2.84 \pm 0.12)\sigma \quad (2)$$

ing to Eq. (2). The calculated value of σ constant is 0.99. The linear dependence found in correlating $\log k_{exp}$ with σ constants, as well as the same value of the slope of the dependence $\log k_{exp}$ vs H_0 for all the derivatives measured, and magnitude of this slope confirm that there is the same rate-limiting step, viz. the decomposition of the intermediate into the products, in all the cases.

In the pH range 4.5–0 the rate constants first of all increase linearly with increasing proton concentration, further the increase in rate gradually diminishes, and at last the rate becomes pH-independent. At a pH about 0 the reaction rate again decreases due to decreasing water activity. The main reason of the change of the linear dependence into the pH-independence is that practically all the Schiff's base changes into the respective protonated form with increasing proton concentration. However,

* Although we worked with aqueous-ethanolic media, we used the H_0 function of the water-sulphuric acid system⁵, because our aim was merely a comparison of the reactivities of individual derivatives. For the mentioned system the H_0 function is far more elaborated and, hence, more accurate and more used than other acidity functions. In addition to it, it is not quite clear to us which type of indicator would correspond to the system protonated Schiff's base — activated complex.

the overall kinetic course does not depend only on concentration of the protonated form, and it is more complicated, because the base catalysis is also significant here and, in addition to it, a change in the rate-limiting step takes place in the case of substituents having positive σ values. The influence of base catalysis is especially striking with 4'-methoxy- and 4'-methyl derivatives, where there is a perceptible decrease of the rate constant in the pH range 2.5–1.7 due to the decreasing chloroacetate concentration. Therefore, we followed the influence of concentration of this base on the hydrolysis rate of the 4'-methoxy derivative at a constant pH (2.55), and thus we made ourselves sure that the decrease of the hydrolysis rate is really caused by the decrease of chloroacetate ions concentration and not by a pH change. The hydrolysis rate increases with increasing base concentration, and the increase is gradually smaller at higher concentrations. A tenfold increase in chloroacetate concentration (from 0.01M to 0.1M) caused a 67% increase of the rate constant. The catalytic influence of chloroacetate is caused by its kinetic participation (besides water) in the decomposition of the intermediate *III* into products. The reason of the abovementioned

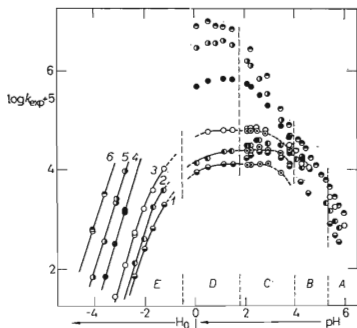


FIG. 1

Dependence of Hydrolysis Rate of N-(5-Methylsalicylidene)-anilines on pH resp. H_0 in Media of Acetate Buffers (A², B), Chloroacetate Buffers (C), Diluted Hydrochloric Acid (D), and Diluted Sulphuric Acid (E)

Curves 1 4'-OCH₃, 2 4'-CH₃, 3 unsubstituted, 4 3'-Cl, 5 3'-NO₂, 6 4'-NO₂ derivatives. The rate constants are given in s⁻¹.

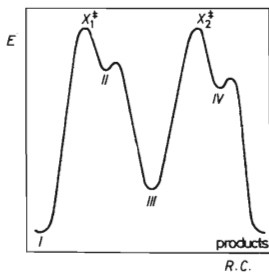


FIG. 2

Rough Dependence of Energy on Reaction Coordinate during Hydrolysis of Salicylidene-anilines in Acid Medium

tioned decrease of the slope of the dependence of rate constant on chloroacetate concentration consists in the fact that, at higher decomposition rates of the intermediate into products, the antecedent step *viz.* the formation of the intermediate by the reaction of the protonated Schiff's base with water begins to be significant kinetically, too. In the case of the derivatives having substituents with higher positive σ values the formation of the intermediate is more significant kinetically at this pH and, in accord to this, we have found a much smaller influence of the base in the case of the 3'-nitro derivative. In the region of pH about 1, when all the Schiff's bases are predominantly protonated and the water activity is not yet practically changed, the rate constants were correlated with the Hammett σ constants. 4'-Methoxy-, 4'-methyl- and the unsubstituted derivatives lie on a line having almost the same slope $\rho = 2.80$ as that of the hydrolysis in sulphuric acid, but the 3'-chloro, 3'-nitro and 4'-nitroderivatives deviate gradually more and more. The break encountered here is similar to that of the hydrolysis in acetate buffer (pH 5.5)², the difference being in that here the break (suggesting the change of the rate-limiting step) is situated between the 3'-chloro and 3'-nitro derivatives. The shift of the break towards the substituents of higher positive σ values is caused by that in acetate buffer the decomposition of the intermediate into products is catalyzed by acetate ion, so that it proceeds faster than its decomposition into starting substances (the break is near the unsubstituted derivative), whereas in the medium containing water as the only base the decomposition into products becomes slower than the reverse reaction. Further increase of acid concentrations brings about a decrease of water activity which is manifested in a further retardation of decomposition of the intermediate, so that the latter gradually becomes rate-limiting even in the case of 3'- and 4'-nitro derivatives. With 3'-nitro derivative this change apparently begins already at pH 0, because here a perceptible decrease of the hydrolysis rate takes place, whereas with the 4'-nitroderivative the rate is still pH-independent.

The pK_a determination of the protonated Schiff's bases is impossible by direct measurement, because their half-lives are within several seconds and several hundredths of a second. In such a case the most convenient way of pK_a determination is that from the dependence of $\log k_{exp}$ vs pH. In our case this is complicated by that the rate constants depend not only on $[H^+]$ but also on the base concentration, so that there is not any linear dependence between the concentration of the protonated form and the rate constants measured. In order to eliminate the influence of base as far as possible, we estimated the rate constants of base-noncatalyzed hydrolysis on the basis of several measurements of the dependence of $\log k_{exp}$ on the base concentration (in Fig. 1 they are marked with crosses). From the dependence of the $\log k_{exp}$ thus obtained on pH the pK_a values were obtained and correlated with σ^0 constants (Eq. (3)), which gave a far better correlation similarly to dissociation of neutral Schiff's bases¹. The value of ρ constant is practically the same as that for the dissociation of neutral Schiff's bases¹, although in this case the protona-

$$pK_a = (3.48 \pm 0.06) - (2.08 \pm 0.13) \sigma^0 \quad (3)$$

tion takes place at nitrogen, whereas in the previous case it took place at oxygen. During the

proton dissociation from neutral Schiff's base both the O—H bond and the intramolecular hydrogen bond to nitrogen are split simultaneously, the both processes being influenced by substituent in the same sense. The influence of substituent on the splitting of the hydrogen bond is relatively large, nitrogen atom being much closer to the substituent than the oxygen atom. During the dissociation of the protonated Schiff's base, on the contrary, the splitting of N—H bond is accompanied by simultaneous formation of intramolecular hydrogen bond, the influences of a substituent on the both processes being opposite. The splitting or formation of the hydrogen bond causes an increase of the absolute value of ρ constant in the first case, whereas it causes a decrease in the second case.

From the Hammett correlations of pK_a (Eq. (3)) and proper hydrolysis of the protonated Schiff's bases (Eq. (2)) it follows that σ^o and σ constants must be used, respectively. In the previous reports^{1,2} $\log k_{rel}$ values were correlated with normal σ constants. The k_{rel} is a product of the reciprocal of the acid-base equilibrium constant and the proper reaction rate constant. As there were different σ constants in the two steps, the correlation gave a distorted picture especially in those cases where the difference between σ and σ^o was greater (4'-methoxy and 4'-methyl derivatives). The real difference between the ρ constants of the both parts of the correlation (in one part decomposition of the intermediate is rate-limiting, whereas in the other one the formation of the intermediate is rate-limiting) is substantially smaller ($\Delta\rho$ about 1–1.5) than it follows from the figures given^{1,2}. This is similar (though to a lesser extent) to the correlation of rate constants of the derivatives showing $-M$ effect, where the influence of a substituent on the antecedent equilibrium is expressed by its σ resp. σ^o constant, whereas its mesomeric effect must be taken into account for the proper reaction².

The overall energy profile of the hydrolysis of Schiff's bases is given in Fig. 2 (for numbers see Scheme 1). In acetate buffers and diluted hydrochloric acid media the energies of the both activated complexes X_1^\ddagger and X_2^\ddagger are comparable, and the rate-limiting step depends on the nature of the substituent. In sulphuric acid medium, where the water activity considerably decreases, the energy of the activated complex X_2^\ddagger increases and the respective step becomes rate-limiting. The transformation of the intermediate *II* into *III* is energetically advantageous, as the proton is transferred from the positively charged oxygen atom to nitrogen atom. The hydroxyl group and the substituted aniline molecule are the nucleophilic agent and leaving group, respectively, during formation of the activated complex X_2^\ddagger from the intermediate *III*, whereas ArNH-group and a water molecule play the respective parts in formation of X_1^\ddagger from *II*. Therefore, the formation of X_2^\ddagger will have greater energy demands than that of X_1^\ddagger , and thus it can be anticipated that the absolute value of the ρ constant will be far greater in this case. Approximate values of the reaction constants can be estimated by the following analysis. The ρ value measured in diluted sulphuric acid (2.84) represents the influence of substituent during formation of the activated complex X_2^\ddagger from the protonated Schiff's base. The hydrolyses of Schiff's bases, carrying substituents with positive σ values, in acetate buffers follow the rela-

tion $k_{\text{exp}} = k_1/K_a$ (ref.²). The experimental ρ value is -0.15 , the ρ value of the dissociation of the protonated Schiff's bases is 2.08 ; hence $\rho_1 = 1.93$. On going from *II* to *III* the protonation takes place at nitrogen atom and, therefore, the influence of a substituent in the neighbouring benzene nucleus will be similar to that during protonation of aniline derivatives. The absolute value of ρ constant will be about 3 . There remains the ρ value to be estimated for formation of the intermediate *III* from the protonated Schiff's base *I*. As a partial shift of the π bond $\text{—NH}=\text{CH—}^{(+)}$ towards the nitrogen atom takes place in the protonated base, the overall positive charge at nitrogen is smaller than in the intermediate *III* and, thus, the substituents having a positive σ value will hinder the process $I \rightarrow III$. The value about -0.5 seems to be most acceptable. By using the mentioned values we obtain $\rho_{-1} = -0.57$. The absolute value of ρ_{-1} is comparatively small, as this step has low energy demands and the influence of substituents will be slight; the value of ρ_{-1} is negative, because a positive charge is formed at the nitrogen atom. A considerably high calculated value of $\rho_2 = 3.34$ for the rate constants of the transformation of the intermediate *III* into products is caused by two factors: a) the configuration of the activated complex X_2^\ddagger is more shifted towards the products (in the reverse step an acid-catalyzed addition of aniline to carbonyl group takes place which has low energy demands), so that the ρ_2 value is only slightly less than the ρ value of the equilibrium reaction $III \rightleftharpoons IV$ would be. b) The influence of a substituent in the aniline nucleus on the complete formation resp. splitting of an N—C bond is substantially higher than that during the formation or splitting of an N—H bond^{6,7}, which is expressed quantitatively by higher values of the Hammett ρ constants.

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