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A Kinetic Study of Cyclodehydration of β-Arylaminocrotonaldehyde Derivatives

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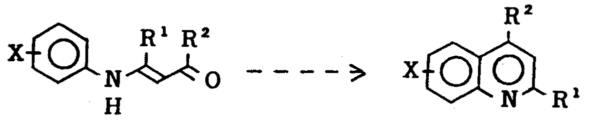
Cyclodehydration of β-arylaminocrotonaldehydes (**1**) was studied kinetically in comparison with those of β-(*p*-toluidino)acrolein (**2a**) and 4-(*p*-toluidino)-3-penten-2-one (**3a**).

The rate constants k_1 of cyclodehydration of **1** were not consistent with the Zucker–Hammett hypothesis, *i.e.*, $\log k_1$ was related linearly to $-H_0$, but the slopes were between 1.28 and 1.36. Bunnett-Olsen plots for $\log k_1$ were linear. Statistically corrected values of $\log k_{\mathrm{r}}^{0}/K_{\mathrm{SH^+}}$ were applied to Jaffé's four-parameter Hammett equation. The reaction constant for the site of the aromatic ring at which cyclodehydration takes place was evaluated to be -8.54, and that for the oxobutenylamino group was evaluated to be $+0.72$.

The effect of substituents on the aromatic ring upon the reactivity is discussed.

Keywords——kinetic study; cyclodehydration; Combes reaction; β-arylaminocrotonaldehyde; quinaldine derivative; Zucker–Hammett hypothesis; Bunnett–Olsen plot; four-parameter Hammett equation

In previous papers we reported the cyclodehydration reactions of β-arylaminoacrolein (**2**)[1] and β-arylaminocrotonaldehyde (**1**)[2] in sulfuric acid solution to give quinoline derivatives (Combes reaction). β-(*p*-Chloroanilino)crotonaldehyde (**1d**) was cyclodehydrated to give 6-chloroquinaldine in quantitative yield[2] on treatment with sulfuric acid while β-(*p*-chloroanilino)acrolein (**2d**)[1] and 4-(*p*-chloroanilino)-3-penten-2-one (**3d**)[3] gave no quinolines under the same conditions. β-Arylaminocrotonaldehydes (**1**) are more reactive in cyclodehydration than the derivatives of **2** and of 4-arylamino-3-penten-2-one (**3**).



	1	2	3		a	b	c	d
R¹:	CH_3	H	CH_3	X:	*p*-CH_3	H	*m*-Cl	*p*-Cl
R²:	H	H	CH_3					

Chart 1

In this paper we wish to report a kinetic study of the cyclodehydration of β-arylaminocrotonaldehydes. The effect of substituents on the aromatic ring upon the cyclodehydration was elucidated; this could not be done in the cases of **2** and **3** derivatives owing to their limited susceptibility to the reaction. The kinetic study covered β-(*p*-toluidino)- (**1a**), β-anilino- (**1b**), β-(*m*-chloroanilino)- (**1c**) and β-(*p*-chloroanilino)crotonaldehyde (**1d**).

Experimental

The ultraviolet (UV) absorption spectra were measured with a Hitachi spectrometer, model 139.

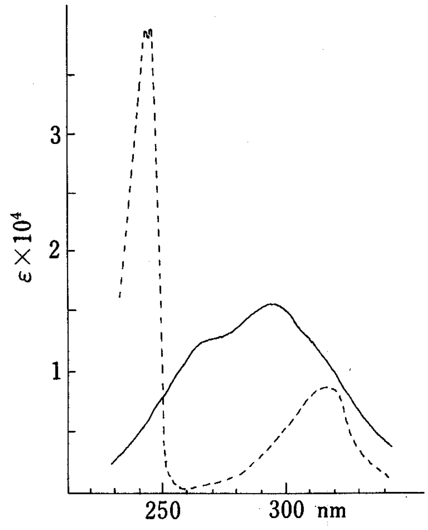


Fig. 1. UV Spectra of **1a** and 2,6-Dimethylquinoline in Sulfuric Acid

——, **1a** in 63.1% H_2SO_4; ------, 2,6-dimethylquinoline in 75.3% H_2SO_4.

TABLE I. Rate Constants of Cyclodehydration of **1** in Sulfuric Acid at 25 °C

H_2SO_4 (%)	H_0 [a]	$H_0+\log[H_2SO_4]$ [a]	Rate constants 10^5k_1 (s^{-1}) **1a**	**1b**	**1c**	**1d**
68.2	−5.53	−4.51	0.597			
69.2	−5.69	−4.64	0.871			
70.1	−5.83	−4.78	1.44			
71.0	−5.98	−4.90	2.26	0.285		
72.2	−6.16	−5.08	3.69	0.468		
73.0	−6.30	−5.16	5.63	0.711		
73.9	−6.44	−5.34	8.89	1.12		
75.3	−6.68	−5.56	16.6	2.09	0.551	
76.2	−6.82	−5.74	27.6	3.29	0.892	
77.2	−6.98	−5.86		5.79	1.48	
78.2	−7.16	−6.03		9.14	2.28	
78.9	−7.28	−6.14		14.4	3.52	
80.1	−7.48			25.9	6.45	
81.0	−7.62				10.6	
82.2	−7.82				20.4	
83.2	−8.00				35.0	0.154
84.0	−8.11					0.207
85.4	−8.33					0.382
85.9	−8.44					0.567
87.0	−8.57					0.910
88.0	−8.71					1.45
88.9	−8.86					2.28
90.2	−9.04					3.76
91.0	−9.16					5.38
91.8	−9.28					7.12

a) J. F. Bunnett, "Investigation of Rates and Mechanisms of Reactions. Part I," 3rd ed., John Wiley and Sons, Inc., New York, 1974, p. 446.

Compounds **1a**—**d** were prepared according to the preceding paper.[2] The kinetic runs were carried out in 3×10^{-5} M H_2SO_4 solution at 25 °C. The UV spectra of **1a** and of 2,6-dimethylquinoline in H_2SO_4 are shown in Fig. 1. The optical densities of the reaction solution of **1a** were measured at 242, 245, 292 and 293 nm, and the concentrations of **1a** and of 2,6-dimethylquinoline were calculated by the least-squares method. An isosbestic point was observed at 250 nm. Cyclodehydration of **1c** gave a mixture of 5-chloro- and 7-chloroquinaldines in a ratio of 11 : 89.[2] Extinction coefficients of chloroquinaldines used for evaluation of the concentration of each component in the reaction solution of **1c** were those of the mixture in the above-mentioned ratio. The wavelengths (nm) at which the

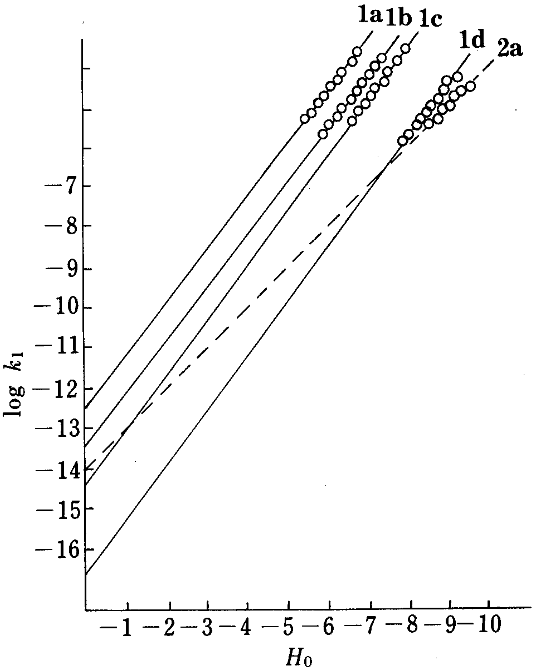


Fig. 2. Zucker–Hammett Plots for Cyclodehydration of **1a**—**d** and **2a**

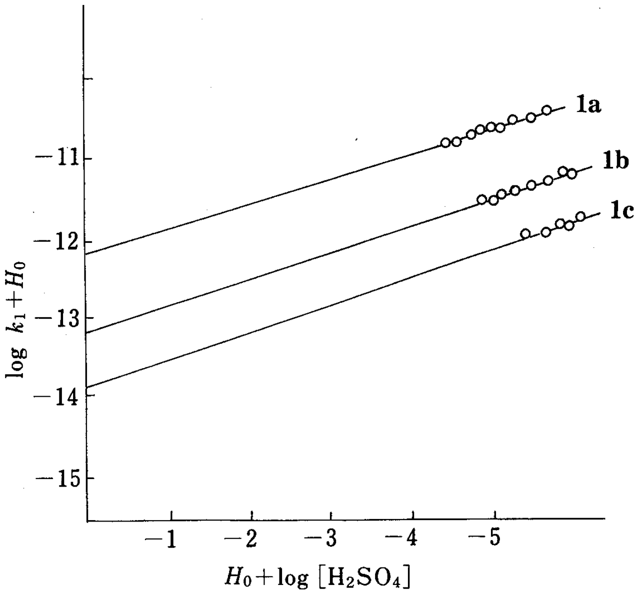


Fig. 3. Bunnett–Olsen Plots for Cyclodehydration of **1a**—**c**

optical densities of each reaction solution were measured for the least-squares method were as follows: **1b**, 237, 240, 287 and 288; **1c**, 241, 244, 287 and 288; **1d**, 242, 243, 290 and 291. The wavelengths (nm) at which the isosbestic points of the reaction solutions were observed were as follows: **1b**, 245; **1c**, 251; **1d**, 251.

Results

First-order rate constants were obtained in all the media studied, and the results are shown in Table I.

Cyclodehydrations of **2a**[4)] and **3a**[5,6)] were consistent with the Zucker–Hammett hypothesis, $\log k_1 + H_0 = \text{constant}$, and values of -14.02 and -12.51 were obtained for the Zucker–Hammett constants for **2a**[4,7)] and for **3a**,[6−9)] respectively. The rate of cyclodehydration of **3a** is thirty times faster than that of **2a** in sulfuric acid of the same concentration.

In the present study, the rate constants of cyclodehydration of **1** were linearly related to $-H_0$, but the slopes exceeded unity. The relations were as follows: **1a**, $\log k_1 + 1.28\ H_0 = -12.34$; **1b**, $\log k_1 + 1.30\ H_0 = -13.36$; **1c**, $\log k_1 + 1.36\ H_0 = -14.35$; **1d**, $\log k_1 + 1.34\ H_0 = -16.52$.

The rates of cyclodehydration of **1** increase with increasing concentration of sulfuric acid used to a greater extent than those of **2a** and **3a** (Fig. 2). Quantitative comparison of the rates of cyclodehydration of **1** and of **2** or **3** can not be made because of the different dependences of the rates on sulfuric acid concentration.

Bunnett–Olsen plots[10)] (Eq. 1) for the rate constants of cyclodehydration of **1** in sulfuric acid (below 80%) were linear.

$$\log k_1 + H_0 = \phi\,(H_0 + \log [H_2SO_4]) + \log k_r^0 / K_{SH^+} \tag{1}$$

where K_{SH^+} is the dissociation constant of the protonated substrate and k_r^0 is the rate coefficient for the protonated substrate. The values of ϕ and $\log k_r^0/K_{SH^+}$ obtained were as follows: **1a**, -0.304, -12.13; **1b**, -0.321, -13.12; **1c**, -0.335, -13.80 (Fig. 3).

The coefficient ϕ is the sum of ϕ_e and ϕ_r. The former ϕ value for dissociation of protonated substrates can be regarded as a proportionality constant between the number of water molecules released in the proton transfer process, $SH^+ + B \rightleftharpoons S + BH^+$, and the number of water molecules released when a base B is protonated, where S is the substrate and B is a base that obeys the H_0 function. The latter ϕ value for the reaction can be regarded as a proportionality constant between the hydration change in the rate-determining step and the hydration change on protonation of B.[10,11] The ϕ value for a base should be identical, therefore, with those for other bases of the same system.

The ϕ values for dissociation of amides used to construct the H_A function[12] lie between $+0.42$ and $+0.55$, and those for dissociation of tertiary aromatic amines used to construct the H_0''' function[13] lie between -0.33 and -0.48.[14] The $\log k_r^0/K_{SH^+}$ values for **1a**, **1b** and **1c** were recalculated using an average value of ϕ, -0.320, to obtain values of -12.21 (**1a**), -13.11 (**1b**) and -13.71 (**1c**). The Bunnett–Olsen plot for the cyclodehydration of **1d** could not be prepared because the rates were too low to evaluate in sulfuric acid at concentrations below 80%. In 82.3% sulfuric acid (Table I), the rate of cyclodehydration of **1d** was only 0.00437 times that of **1c**. The $\log k_r^0/K_{SH^+}$ value for **1d** was estimated to be -16.07.

Discussion

The rate of cyclodehydration of **1c** to give 7-chloroquinaldine is 0.89 times the observed rate. The rate constants of **1a**, **1b** and **1d** are halved in order to compare them with that of formation of 7-chloroquinaldine. The symbol $\log k$ represents the recalculated $\log k_r^0/K_{SH^+}$ value for each substrate.

In the cyclodehydration of **1d**, the chlorine substituent affects the nucleophilic reactivity at the *m*-position, at which the cyclodehydration takes place. At the same time, the chlorine affects the basicity of the side chain and electrophilic reactivity of the formyl group as a substituent at the *p*-position.

Fersht and Kirby[15] employed Jaffé's four-parameter Hammett equation[16] (Eq. 2) in order to evaluate the substituent effect on the hydrolysis of substituted acetylsalicylic acids, in which the ionized carboxyl group acted as a general base catalyst. Hegarty, Frost and Cremin[17] employed the same equation for analysis of the hydrolysis of *N*-(*o*-carboxyphenyl)-carbamate, in which isatoic anhydride is formed as an intermediate.

$$\log k = \rho_1\sigma_1 + \rho_2\sigma_2 + \log k_0 \qquad (2)$$

Let the reaction constant ρ_1 correspond to the nucleophilic reactivity at the *m*-position to the chlorine substituent in **1d**, Brown and Okamoto's electrophilic substituent constant,[18] σ^+, should be used for σ_1. The reaction constant ρ_2 corresponds to the basicity of the side chain at the *p*-position in **1d**. The nucleophilic substituent constant, σ^-, should be used for ρ_2. However, the ρ^- values for electron-releasing substituents do not differ from the original σ values for dissociation of aromatic amines.[19]

The least-squares method for Eq. 2[20] gave the following parameter values: $\rho_1^+ = -8.54$; $\rho_2 = +0.72$; $\log k_0 = -13.14$. The correlation coefficient was 0.993. Experimental and calculated $\log k$ values for each substrate were as follows: **1a**, -12.51, -12.70; **1b**, -13.41, -13.14; **1c**, -13.76, -13.84; **1d**, -16.37, -16.38.

The ρ_1^+ value, -8.54, is comparable to those of other electrophilic aromatic substitution reactions, *e.g.*, halogenation in acetic acid ($\rho^+ = -11.35$) and nitration in nitromethane or acetic anhydride ($\rho^+ = -6.53$).[18] The ρ_2 reaction constant reflects two different factors. One corresponds to protonation of the monoprotonated substrate,[21] and electron-withdrawing substituents are expected to shift ρ_2 toward a negative value. The diprotonated species is a cross conjugation hybrid (a and b in Chart 2), and the other factor corresponds to the electrophilic reactivity of the protonated formyl group. Electron-withdrawing substituents are expected to enhance the reactivity through hyperconjugation (b) to shift ρ_2 toward a positive

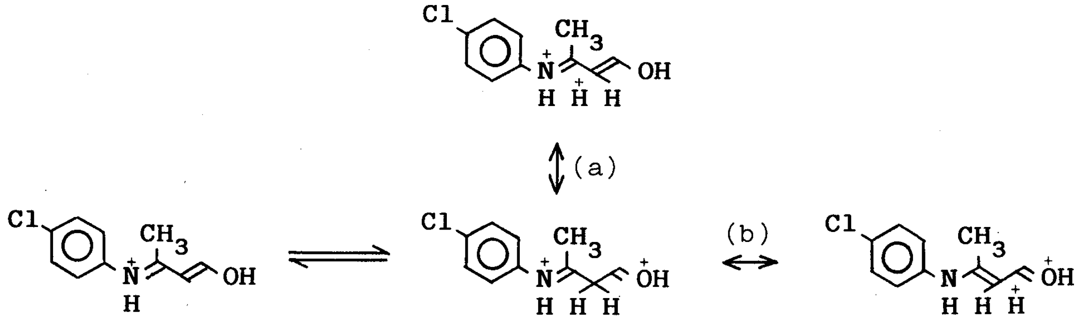


Chart 2

value. The ρ_2 value obtained, $+0.72$, suggests that the latter effect predominates over the former to a small extent.

Sulfuric acid in the Combes reaction should be replaced by other cyclodehydrating agents for wider application because ρ_1^+, a dominant factor in cyclodehydration, has a large negative value. We have already reported a synthetic approach to quinoline derivatives from β-arylamino-α,β-unsaturated carbonyl compounds in the presence of aluminum halides.[1,22]

References and Notes

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