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A Kinetic Study of Cyclodehydration of β-(*p*-Toluidino)acrolein. III[1]

Shinzo Tamura and Reiko Todoriki (née Imamura)

School of Pharmaceutical Science, Toho University[2]

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The reversible sulfonation at the α-position of β-(*p*-chloroanilino)acrolein (V) in sulfuric acid at various concentrations was studied kinetically. The rate constants of cyclodehydration of β-(*p*-toluidino)acrolein (I) with reversible sulfonation at the α-position were evaluated by non-linear least-squares analysis using the rate constants of the reversible sulfonation of V as approximate initial values for those of I.

The rate constant k_1 of cyclodehydration of I is related to Hammett's acidity function H_0 as expressed by the equation $\log k_1 + H_0 = -13.97$.

The rate of cyclodehydration of I is one-fortieth of that of 4-(*p*-toluidino)-3-penten-2-one (VIII) in sulfuric acid at 25°.

Keywords——kinetic study; cyclodehydration; reversible sulfonation; β-(*p*-chloroanilino)acrolein; β-(*p*-toluidino)acrolein; 6-methylquinoline; 3-(*p*-chloroanilino)-1-oxo-2-propene-2-sulfonic acid

In the previous paper[3] we reported a kinetic study on the cyclodehydration of β-(*p*-toluidino)acrolein (I) in sulfuric acid. A reversible sulfonation of I to form 3-(*p*-toluidino)-1-oxo-2-propene-2-sulfonic acid (III) proceeded in parallel with the cyclodehydration to give 6-methylquinoline (II) (Chart 1).

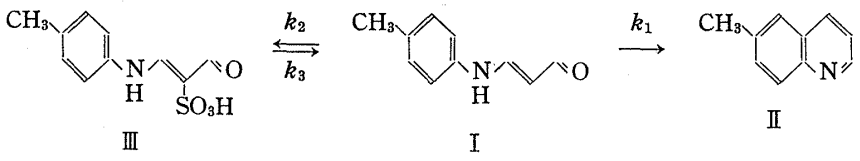


Chart 1

In 83% sulfuric acid, formation of II from I was negligible and III was completely hydrolyzed to form I within 24 hr. In the kinetic runs, the proportion of II in each reaction solution was evaluated by the least-squares method based on the optical densities at 241, 242, 332 and 333 nm of the solution at 24 hr after the dilution of the reaction solution with 50% sulfuric acid to 83% sulfuric acid. The proportions of I and III in reaction solution, however, could not be estimated owing to the similarity of their ultraviolet absorption (UV) spectra, and to the slow conformational isomerization of III in sulfuric acid.

The rate equations for the formation of II are represented by equations 1 and 2,

$$y_S = 1 + \frac{1}{2\sqrt{\alpha^2-\beta}}(r_2 e^{r_1 t} - r_1 e^{r_2 t}) \quad (1)$$

$$y_M = 1 + \frac{k_1(r_1+k_3)}{2r_1\sqrt{\alpha^2-\beta}} e^{r_1 t} - \frac{k_1(r_2+k_3)}{2r_2\sqrt{\alpha^2-\beta}} e^{r_2 t} \quad (2)$$

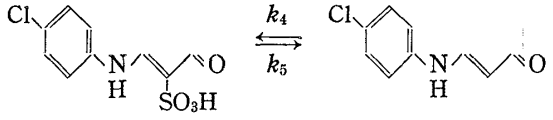
where y_S is the proportion of II when the starting material was the sodium salt of III (IV), and y_M is the proportion of II when the starting material was I, and

1) Part II: S. Tamura and R. Todoriki, *Chem. Pharm. Bull.*, **28**, 3395 (1980).
2) Location: *2-2-1, Miyama, Funabashi, 274, Japan.*
3) S. Tamura, R. Imamura, and K. Ito, *Chem. Pharm. Bull.*, **26**, 930 (1978).

$$2\alpha = k_1 + k_2 + k_3,\ \beta = k_1k_3$$
$$r_1 = -\alpha + \sqrt{\alpha^2-\beta},\ r_2 = -\alpha - \sqrt{\alpha^2-\beta}.$$

However, the non-linear least-squares method afforded rather unsatisfactory results.[3] This was because the proportion of I in the reaction solution could not be evaluated,[3] and because the approximate starting value of each rate constant used in the non-linear least-squares method was presumably unsuitable.

β-(p-Chloroanilino)acrolein (V) does not undergo cyclodehydration in sulfuric acid.[4] Thus, kinetic examination of the reversible sulfonation of V was attempted in order to estimate better starting values for the non-linear least-squares method on the assumption that the effect of a substituent of the aromatic ring on the rate of the reversible sulfonation at the α-position of β-arylaminoacroleins is insignificant. For this purpose, 3-(p-chloroanilino)-1-oxo-2-propene-2-sulfonic acid (VI) and its sodium salt (VII) were prepared by the same method used for the preparation of III and IV.[3]



VI V

Chart 2

The measurement of the extinction coefficients of III in sulfuric acid of various concentrations was difficult owing to the slow conformational isomerization of III in the solution. We previously reported that the decrease in optical density at 340 nm of a solution of III in 100% sulfuric acid is attributable to the slow conformational isomerization of III.[3] However, the decrease in optical density is mainly due to the sulfonation of the benzene ring of III in sulfuric acid.[1]

The evidence for the conformational isomerization of III was obtained from the ^{13}C nuclear magnetic resonance spectrum (CMR spectrum) of III in 100% sulfuric acid-d_2. Immediately after dissolution, the signals of the 1- and 3-position of III were observed at δ 179.54 and 158.44 ppm, respectively. In addition to these signals, other signals of the 1- and 3-position of III began to appear at δ 176.54 and 153.41 ppm on standing. The latter signals increased with time, suggesting that III existed in one conformational form in the crystalline state and that another conformational form developed in solution. The conformational isomerization virtually reached equilibrium in about an hour (Fig. 1, Table I).[5]

Similar conformational isomerization was observed in the CMR spectrum of VI in 100% sulfuric acid-d_2, *i.e.*, the signals of the 1- and 3-position of VI were observed at δ 180.03 and 159.74 ppm immediately after dissolution and other signals of the same positions of another conformer appeared at δ 177.80 and 154.62 ppm on standing. The rate of conformational isomerization of VI was slightly faster than that of III so that the isomerization was virtually complete within 45 min.

The UV spectra of V in 79.7% sulfuric acid and of VI in 96.0% sulfuric acid are shown in Fig. 2. The latter spectrum was measured immediately after dissolution. The optical density at 329 nm of the solution of V decreased on standing in sulfuric acid, while that of VI, which was initially lower than that of V in an equimolar solution, increased on standing. The optical densities became equal within experimental error after prolonged standing.

The kinetic examinations of the sulfonation of V and of the hydrolysis of VI were carried

4) S. Tamura and E. Yabe, *Chem. Pharm. Bull.*, **22**, 2982 (1974).
5) The benzene ring of III does not undergo sulfonation at higher concentrations of substrate such as that used for measurement of CMR spectra.[1]

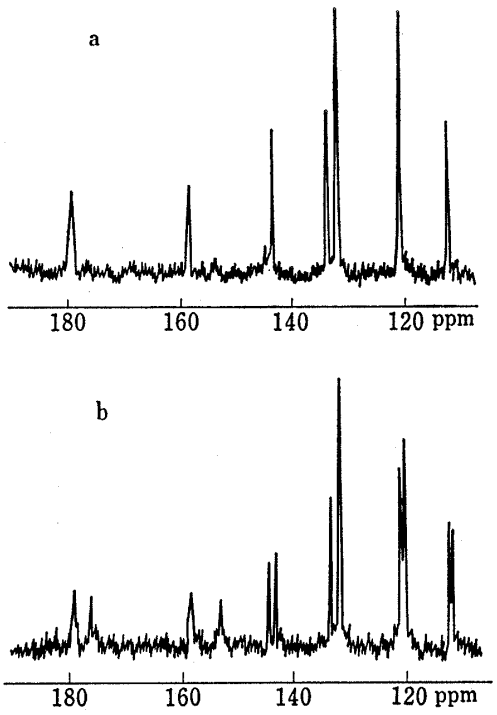


Fig. 1. CMR Spectra (Complete Decoupling) of III in 100% D_2SO_4 (Containing some H_2SO_4)

a, Immediately after dissolution.
b, 122 min after standing at 31°.

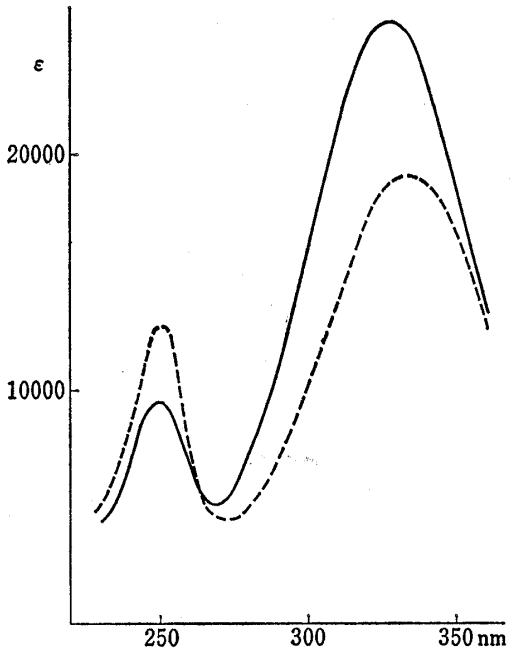


Fig. 2. UV Spectra of V in 79.7% H_2SO_4 and of VI in 96.0% H_2SO_4

———, V.
– – – – –, VI.

TABLE I. Change of the Signal Height in the CMR Spectrum of III in 100% D_2SO_4 (Containing some H_2SO_4) at 31°

Time (min)[a]	7	25	41	56	71	90	106	122
1-Position[b]	0.15	0.23	0.42	0.30	0.45	0.48	0.45	0.48
3-Position[c]	0.20	0.29	0.34	0.32	0.41	0.44	0.43	0.46

a) The starting time of accumulation after dissolution.
b) The values of signal heights at 176.53 ppm divided by the sum of those at 176.53 and 179.54 ppm.
c) The values of signal heights at 153.41 ppm divided by the sum of those at 153.41 and 158.44 ppm.
0.4 g of IV was dissolved in 4 g of 100 % D_2SO_4 (containing so me H_2SO_4) under ice-cooling. The accumulation time was 909 seconds for each measurement. Tetramethylsilane was used as an external standard.

out in sulfuric acid of various concentrations at 25°. Assuming both sulfonation and the reverse reaction to be of first order, the rate equations can be expressed as equations 3 and 4,

$$\ln(\varepsilon_0^{M}-\varepsilon_e) - \ln(\varepsilon-\varepsilon_e) = \frac{k_4}{x_e}t \tag{3}$$

$$\ln(\varepsilon_e-\varepsilon_0^{S}) - \ln(\varepsilon_e-\varepsilon) = \frac{k_5}{1-x_e}t \tag{4}$$

where ε^{M} and ε^{S} represent the extinction coefficients of conformationally equilibrium solutions of V and VI, ε_e is that of the equilibrium mixture of V and VI, ε is that of the reaction solution at time t, x_e is the proportion of VI at equilibrium, and k_4 and k_5 are the rate constants of sulfonation and of the reverse reaction, respectively.

As stated in the preceding section, the value of ε^{S} could not be measured because of the slow conformational isomerization and of the progress of the hydrolysis reaction. The values of ε_0^{M}, ε_0^{S}, k_4/x_e and $k_5/(1-x_e)$ were estimated by the least-squares method using the values of

Table II. Rate Constants of Sulfonation of V and Hydrolysis of VI in Sulfuric Acid at 25°

Concentration of H_2SO_4 (%)	10^5k_4 (sec^{-1})	10^5k_5 (sec^{-1})	k_4/k_5	$K^{a)}$
89.4	0.95	8.35	0.11	0.28
90.0	2.94	8.34	0.35	0.32
90.9	6.06	8.21	0.74	0.64
92.0	6.39	9.37	0.68	0.63
92.9	8.45	7.53	1.12	1.04
93.8	10.23	8.76	1.17	1.15

a) K is the equilibrium constant of reversible sulfonation of V calculated from the values of ε_0^M, ε_0^S and ε_e.

ε_e and ε; the latter was measured at an hour or more after the initiation of the reaction. k_4, k_5 and x_e were evaluated from equations 3 and 4 by using the values of ε_0^M and ε_0^S estimated by the above-mentioned method (Table II).

The rate constant k_5 in 79.7% sulfuric acid was evaluated by a similar method. The optical densities of the 79.7% sulfuric acid solution of VI were measured at 329, 331, 375 and 380 nm at selected intervals at 25°. Hydrolysis of VI in 79.7% sulfuric acid is a practically irreversible first-order reaction. The ε_0^S values of VI at the given wavelength were evaluated by the least-squares method from rate equation 5,

$$\ln|\varepsilon_0^M-\varepsilon_0^S| - \ln|\varepsilon_0^M-\varepsilon| = k_5t \quad (5)$$

where ε_0^M is the extinction coefficient of V in 79.7% sulfuric acid solution, and ε is that of the reaction solution at time t. The concentrations of V and VI in the reaction solution were evaluated by the least-squares method, and a good straight line was obtained by plotting $\ln a/(a-x)$ against time, where a is the initial concentration of VI, and x is the concentration of VI at time t. k_5 was evaluated as 3.06×10^{-5} sec^{-1}. The rate constant k_3 of the hydrolysis reaction of III in 79.7% sulfuric acid at 25° was evaluated as 2.93×10^{-5} sec^{-1} by the same method. This k_3 value is very similar to the value of k_5 in 79.7% sulfuric acid, and this supports the assumption that the effect of an aromatic ring substituent on the rates of the reversible sulfonation is insignificant.

Table III. Rate Constants of Cyclodehydration and Reversible Sulfonation of I in Sulfuric Acid at 25°

Concentration of H_2SO_4 (%)	H_0	10^5k_1 (sec^{-1})	10^5k_2 (sec^{-1})	10^5k_3 (sec^{-1})	$\log k_1+H_0$
88.2	−8.64	0.538	4.73	7.32	−13.91
89.0	−8.80	0.602	3.03	7.75	−14.02
90.1	−8.96	1.04	5.72	9.06	−13.94
91.2	−9.13	1.56	7.02	9.47	−13.94
91.9	−9.28	2.28	7.56	9.50	−13.92
93.1	−9.45	2.96	10.1	11.5	−13.98
94.0	−9.69	3.90	11.3	10.4	−14.10

The approximate starting value of k_1 was estimated to be 4.13×10^{-6} sec^{-1} at 25° on the assumption that I and III were nearly in equilibrium at the beginning of the cyclodehydration reaction, and were in a molar ratio of I : III = 1 : 0.28 (Table II). The approximate starting values of k_1 in sulfuric acid of various concentrations were estimated on the assumption that the sum of $\log k_1$ and Hammett's acidity function H_0 is constant.[3)]

The non-linear least-squares method for the evaluation of k_1, k_2 and k_3 gave satisfactory results using the above-mentioned values of k_1 as approximate starting values of k_1, and the

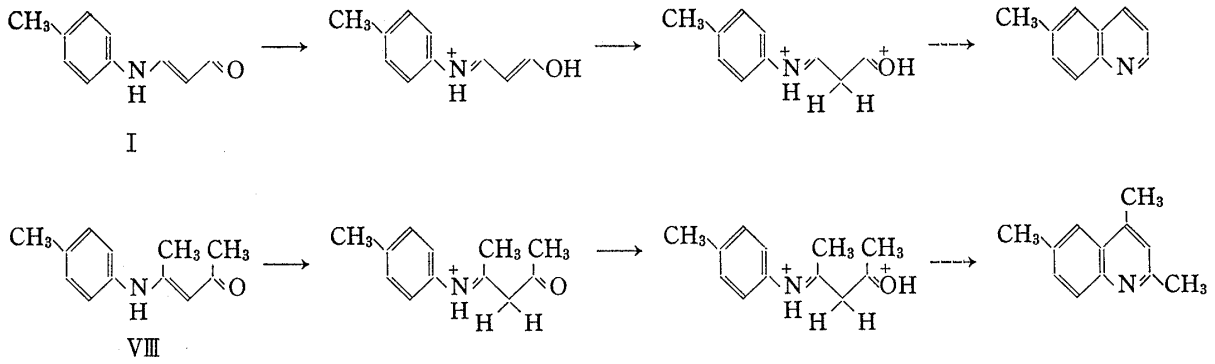


Chart 3

values of k_4 and k_5 as approximate starting values of k_2 and k_3, respectively. The detailed procedure of calculation is described in the appendix. The results are shown in Table III. The rate constant k_1 is related to H_0 as follows: $\log k_1 + H_0 = -13.97$.

The rate constant k of cyclodehydration of 4-(*p*-toluidino)-3-penten-2-one (VIII) in sulfuric acid was found to be related to H_0 as follows: $\log k + H_0 = -12.36$ at 25°.[3]

We have previously attributed the difference of reactivity in the cyclodehydrations of I and VIII to the position at which protonation takes place[3] (Chart 3). In the present study, the difference of reactivity between I and VIII was evaluated quantitatively. The rate of cyclodehydration of VIII is forty times higher than that of I in sulfuric acid at every concentration examined at 25°.

Experimental

The UV spectra were measured on a Hitachi spectrophotometer, model 139, and the proton magnetic resonance (PMR) spectrum was recorded on a JNM-PMX 60 NMR spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d).

Materials——Compounds I and V were prepared according to a previous paper.[6] The melting points of I and V were 122° and 160.5°, respectively. Compound III was prepared according to a previous paper.[3]

Preparation of VII——Compound V (0.55 g, 0.003 mol) was dissolved in a mixture of 5.0 g of 99.4% H_2SO_4 and 3.0 g of 10% oleum under ice-cooling. The reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was then poured onto 8 g of ice under ice-cooling, and the precipitate was collected and washed successively with AcOH and ether to afford 0.56 g (71%) of VI as a pale yellow crystalline mass. The crystalline mass was dissolved in 25 ml of 1% aqueous Na_2CO_3. A pale yellow crystalline mass precipitated immediately from the solution. The precipitate was collected and washed with cold H_2O, affording 0.53 g (62%) of VII. It darkened at 227°. PMR (CD_3SOCD_3, δ): 10.18 ppm (1H, d, $J=13$ Hz, NH), 9.20 ppm (1H, s, 1-position) and 7.88 ppm (1H, d, $J=13$ Hz, 3-position). *Anal.* Calcd for $C_9H_7NNaO_4SCl$: C, 38.11; H, 2.49; N, 4.96. Found: C, 38.42; H, 2.41; N, 5.47.

Acknowledgement The authors are indebted to Mr. K. Aoki, Analytica Corporation, for measurements of CMR spectra.

Appendix The non-linear least-squares method was carried out on the assumption that the approximate equations 6 and 7 are valid.

$$y_S - y_S^{calcd} = \frac{\delta y_S}{\delta k_1}\Delta k_1 + \frac{\delta y_S}{\delta k_2}\Delta k_2 + \frac{\delta y_S}{\delta k_3}\Delta k_3 \quad (6)$$

$$y_M - y_M^{calcd} = \frac{\delta y_M}{\delta k_1}\Delta k_1 + \frac{\delta y_M}{\delta k_2}\Delta k_2 + \frac{\delta y_M}{\delta k_3}\Delta k_3 \quad (7)$$

where y_s^{calcd} is the value of the right-hand side of equation 1 when the initial approximate values of each rate constant (k'_1, k'_2 and k'_3) and the time t were applied, $\delta y_S/\delta k_1$ is the partial derivative of y_S with respect to k_1 when the values of k'_1, k'_2, k'_3 and t were applied, and $\Delta k_1 = k_1 - k'_1$. Δk_1, Δk_2 and Δk_3 were evaluated by a

6) S. Tamura and E. Yabe, *Chem. Pharm. Bull.*, **21**, 2105 (1973).

linear least-squares method at various concentrations of sulfuric acid. The value of $k'_1+\Delta k_1$ was used as an initial approximate value for subsequent non-linear least-squares calculation. The calculation was repeated until the value of $\sum(y_S-y_S^{calcd})^2+\sum(y_M-y_M^{calcd})^2$ no longer decreased. The differences of experimental y_S and y_S^{calcd}, as well as that of experimental y_M and y_M^{calcd}, both with the finally obtained value of each rate constant, were less than ± 0.013 (Table IV).

Table IV. Experimental and Calculated Values of the Proportions of II (y_S and y_M) in Sulfuric Acid at 25°

Time (min)	y_S		y_M	
	Found	Calcd	Found	Calcd
88.2% H_2SO_4				
365	0.0436	0.0447	0.0836	0.0836
720	0.1046	0.1062	0.1474	0.1452
1460	0.2290	0.2249	0.2637	0.2589
1800	0.2824	0.2740	0.3037	0.3058
2190	0.3266	0.3265	0.3352	0.3561
2980	0.4140	0.4216	0.4469	0.4470
3630	0.4867	0.4897	0.5091	0.5121
4390	0.5533	0.5592	0.5699	0.5785
90.1% H_2SO_4				
200	0.0410	0.0391	0.0851	0.0938
420	0.1053	0.1092	0.1687	0.1686
640	0.1770	0.1784	0.2383	0.2345
840	0.2384	0.2372	0.2938	0.2894
1420	0.3886	0.3852	0.4343	0.4273
1680	0.4449	0.4419	0.4801	0.4801
1930	0.4910	0.4915	0.5256	0.5262
2100	0.5207	0.5226	0.5537	0.5553
91.9% H_2SO_4				
130	0.0391	0.0418	0.1369	0.1317
240	0.0993	0.1038	0.2038	0.2072
360	0.1667	0.1743	0.2764	0.2755
480	0.2438	0.2414	0.3303	0.3360
720	0.3704	0.3609	0.4419	0.4411
960	0.4742	0.4618	0.5366	0.5294
1200	0.5567	0.5468	0.6073	0.6037
1440	0.6164	0.6184	0.6705	0.6663
94.0% H_2SO_4				
90	0.0430	0.0389	0.1569	0.1507
160	0.0916	0.0932	0.2316	0.2245
250	0.1611	0.1677	0.2953	0.2988
340	0.2364	0.2393	0.3548	0.3620
480	0.3405	0.3399	0.4442	0.4473
640	0.4413	0.4391	0.5307	0.5305
800	0.5288	0.5234	0.6001	0.6011
960	0.5958	0.5951	0.6560	0.6611
89.0% H_2SO_4				
240	0.0272	0.0298	0.0673	0.0718
480	0.0815	0.0814	0.1295	0.1295
720	0.1384	0.1347	0.1827	0.1818
880	0.1750	0.1692	0.2169	0.2147
1480	0.2916	0.2872	0.3309	0.3263
1925	0.3690	0.3638	0.4005	0.3987
2160	0.4049	0.4008	0.4437	0.4338
2920	0.5099	0.5066	0.5361	0.5337
91.2% H_2SO_4				
180	0.0473	0.0489	0.1154	0.1210
360	0.1257	0.1270	0.2044	0.2040
540	0.2052	0.2034	0.2753	0.2753
720	0.2746	0.2739	0.3394	0.3397
1360	0.4797	0.4779	0.5274	0.5253
1620	0.5445	0.5434	0.5867	0.5849
1870	0.5937	0.5987	0.6316	0.6351
2080	0.6357	0.6398	0.6696	0.6725
93.1% H_2SO_4				
90	0.0363	0.0322	0.1287	0.1204
190	0.0954	0.1022	0.2057	0.2082
280	0.1631	0.1679	0.2674	0.2721
360	0.2225	0.2241	0.3177	0.3228
560	0.3501	0.3499	0.4300	0.4333
720	0.4404	0.4359	0.5188	0.5083
840	0.5006	0.4929	0.5552	0.5580
1060	0.5817	0.5828	0.6257	0.6363