[Chem. Pharm. Bull. 27(8)1919—1922(1979)]

UDC 547.775.03.04 : 541.515.04

Kinetic Studies on the Decomposition of the 4-Diethylaminoantipyrine Cation Radical in Aqueous Acetonitrile Solutions

HIROTERU SAYO

Faculty of Pharmaceutical Sciences, Kobe-Gakuin University[1)]

(Received December 22, 1978)

4-Diethylaminoantipyrine cation radical (II) was generated by the anodic oxidation of 4-diethylaminoantipyrine (I) in acetonitrile containing 0.1 M $NaClO_4$ at a glassy-carbon anode, and the rate of disappearance of II in aqueous acetonitrile solutions was measured by spectrophotometry. In aqueous acetonitrile solutions of pH 7.4 and 10.4, II decayed in a first-order manner, and the first-order rate constant obtained increased with increasing concentration of the buffers and hydroxyl ions and with decreasing concentration of $NaClO_4$ added. On the other hand, in a solution containing 0.1 M $HClO_4$, II decayed in a second-order manner. The second-order rate constant obtained was independent of the ionic strength of the solution and decreased with increasing concentration of acetonitrile. A mechanism for the decomposition of II is suggested.

Keywords——4-diethylaminoantipyrine; 4-diethylaminoantipyrine cation radical; disproportionation of cation radical; decomposition of 4-diethylaminoantipyrine cation radical; anodic oxidation of 4-diethylaminoantipyrine; kinetics of decomposition of cation radical

We previously reported on the anodic oxidation of 4-diethylaminoantipyrine (I) at a glassy-carbon electrode in acetonitrile.[2)] The first step in the anodic oxidation of I was a quasi-reversible one-electron transfer to form the blue-violet cation radical of I (II). In the absence of oxygen, II decayed in a first-order manner with a rate constant of *ca.* 3×10^{-5} sec^{-1}, whereas in the presence of oxygen, II decayed in a second-order manner with a rate constant of *ca.* 0.7 M^{-1} sec^{-1}.

To obtain more detailed information on the stability and decomposition of II, kinetic studies on the disappearance of II in aqueous acetonitrile solutions were attempted. Chemical[3)] and enzymatic[4)] oxidations of aminopyrine have been studied extensively by many workers, and the aminopyrine cation radical was proposed as an intermediate and studied in some detail. However, no study has been made on II.

Results

Kinetics of Decomposition of 4-Diethylaminoantipyrine Cation Radical (II)

A 2 mM solution of I in acetonitrile containing 0.1 M sodium perchlorate was subjected to electrolysis for 1—4 min at a glassy-carbon anode at 0.45 V.[5)] An aliquot of the resulting blue-violet solution was mixed with an appropriate amount of buffer, and the change of absorbance (A) of the mixture with time was measured at 590 nm.[2)] The concentration of II was estimated from the number of coulombs consumed in the electrolysis, assuming that

---

1) Location: *Ikawadani-cho, Tarumi-ku, Kobe 673, Japan.*
2) H. Sayo and M. Masui, *Chem. Pharm. Bull.* (Tokyo), **24**, 2137 (1976).
3) W. Awe and R. Buerhop, *Arch. Pharm.*, **293**, 462 (1960); W. Awe, E. Stoy-Geilich, R. Buerhop, and H. Bammel, *Arzneim. Forsch.*, **10**, 796 (1960); F. Pechtold, *ibid.*, **14**, 258 (1964).
4) B.N. La Du, L. Gaudette, N. Trousof, and B.B. Brodie, *J. Biol. Chem.*, **214**, 741 (1955); B.W. Griffin, *FEBS Lett.*, **74**, 139 (1977); B.W. Griffin and P.L. Ting, *Biochemistry* **17**, 2206 (1978); *idem, FEBS Lett.*, **89**, 196 (1978).
5) All potentials were measured against a saturated calomel electrode.

Table I. Data on the Decay of the 4-Diethylaminoantipyrine Cation Radical (II) in Aqueous Acetonitrile Solution measured by Spectrophotometry at 25°

Buffer	Buffer conc. (M)	Acetonitrile (v/v, %)	pH	Ionic strength	$10^4 k_1$ (sec^{-1})	k_2 ($\mathrm{M}^{-1}\,\mathrm{sec}^{-1}$)
Borate	0.06	40	10.4	0.2	37	
	0.03	40	10.4	0.2	30	
	0.015	40	10.4	0.2	23	
	0.03	40	10.4	0.1	42	
Phosphate	0.06	40	7.4	0.2	17	
	0.03	40	7.4	0.2	7.8	
	0.015	40	7.4	0.2	4.5	
	0.03	40	7.4	0.1	15	
Acetate	0.03	40	5.5	0.2	1.3	1.8
$HClO_4$	0.1	40		0.2		2.7
	0.1	40		0.3		2.7
	0.1	40		0.4		2.7
	0.1	20		0.2		4.0
	0.1	60		0.2		2.0
	0.1	80		0.2		1.5

Initial concentration of II: 7×10^{-5}—3×10^{-4} M.

the coulometric n-value (number of Faradays passed per mol of I) was one. As described in the previous paper,[2] the rate of disappearance of II in acetonitrile is very slow, so no correction for decomposition of II during the electrolysis is necessary.

The results are summarized in Table I. The kinetic measurements were carried out both with and without deoxygenation. Contrary to the case of the decomposition of II in acetonitrile, the presence of oxygen in aqueous acetonitrile solutions had no effect on the rate of disappearance of II. In aqueous acetonitrile solutions of pH 7.4 and 10.4,[6] plots of log A against time were linear up to 90% decay, characterizing the disappearance of II as a first-order process. The first-order rate constant obtained from the above plots, k_1, was constant in the concentration range of II between 7×10^{-5} and 3×10^{-4} M. The value of k_1 increased with increasing concentration of the buffers and hydroxyl ions, and decreased with increase in the ionic strength of the solution (Fig. 1).

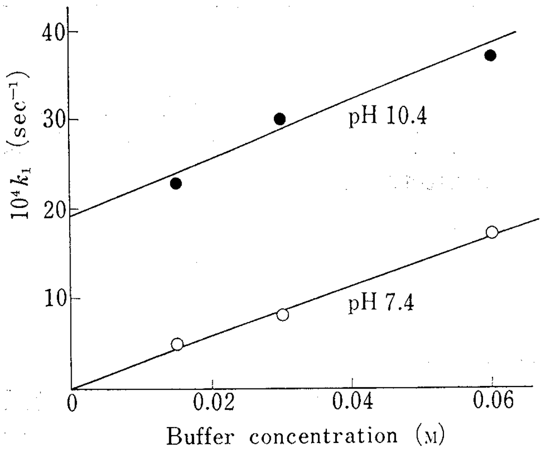


Fig. 1. Dependence of the First-order Rate Constant on the Concentration of Buffer at 25°

Ionic strength 0.2.

In aqueous acetonitrile solutions containing 0.1 M $HClO_4$, plots of 1/A against time were linear up to 70% decay, characterizing the disappearance of II as a second-order process. The second-order rate constant obtained from the above plots, k_2, was independent of the ionic strength of the solution and decreased with increasing concentration of acetonitrile.

In aqueous acetonitrile solution of pH 5.5 the rate of disappearance of II appeared to occur by competitive first- and second-order rate processes. The first- and second-order rate constants, k_1 and k_2, were obtained from the intercept and the slope of plots of $(dc/dt)/c$ against c, where c is the concentration of II.

---

[6] In this paer, the author will use the notation "pH" even for aqueous acetonitrile solutions, and pH-meter readings are given without correction.

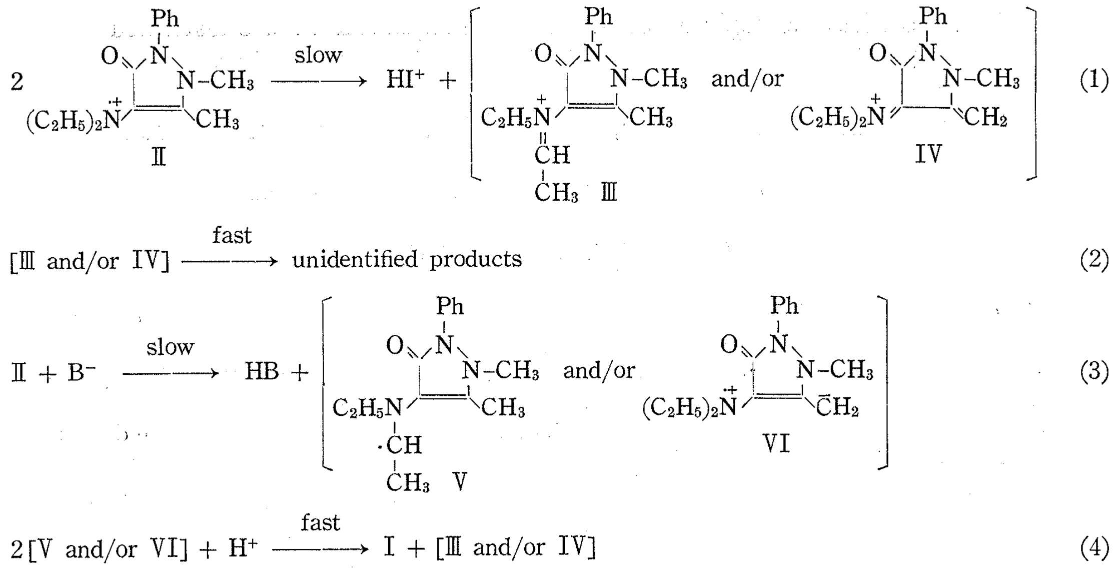
Product Identification

Large-scale controlled potential electrolysis of I in acetonitrile (10 mM, 100 ml) at 0.45 V gave an n-value of 0.94±0.1. The resulting blue-violet solution was mixed with an equal amount of 0.1 M phosphate buffer (pH 6.8). The blue-violet color faded slowly, and the solution finally turned yellow. The yellow solution was made alkaline by addition of sodium hydroxide solution and extracted with chloroform. Concentration of the extract gave a yellow residue, which was extracted with hexane, and concentration of the hexane extract by evaporation gave I (67%). A similar experiment carried out with 0.2 M $HClO_4$ instead of phosphate buffer gave I (24%).

Discussion

The finding that the rate of disappearance of II in aqueous acetonitrile containing 0.1 M $HClO_4$ is second-order in II suggests that disproportionation of II is a major process in its decomposition. However, the salt effect observed did not support the above mechanism, because a positive salt effect should be observed for a reaction between two positively charged molecules. This discrepancy remains to be explained. The solvent effect observed on the disappearance of II is modest. This indicates that the rate-limiting step in the disproportionation of II is hydrogen atom transfer rather than electron transfer followed by proton transfer.[7]

In aqueous acetonitrile buffers of pH 7.4 and 10.4 the rate of disappearance of II is first-order in II and increases with increasing concentrations of the buffers and hydroxyl ions. This indicates that the buffer anions and hydroxyl ions accelerate proton loss from II in the rate-determining step. A plot of k_1 against the buffer concentration at pH 7.4 is approximately linear and passes near the origin, whereas that at pH 10.4 has a definite intercept (Fig. 1). This indicates that catalysis by hydroxyl ions is significant at pH 10.4. The negative salt effect observed supported the above mechanism.



Ph=phenyl, B^-=buffer anion or hydroxyl ion

Chart 1

The following schemes are suggested for the decomposition of II. In aqueous acetonitrile buffers of higher pH, reaction 3 becomes faster than reaction 1, and the rate of disappearance of II obeys pseudo-first-order kinetics.

---

[7] M. Mohammad and E.M. Kosower, *J. Am. Chem. Soc.*, **93**, 2709 (1971); P.D. Wildes, N.N. Lichtin, and M.Z. Hoffman, *ibid.*, **97**, 2288 (1975).

At present only I has been identified as a product, and the yield of I at pH 7.4 was larger than that expected for reaction 3 alone (50%). This suggests that products of the decomposition of II can reduce II to I, as a large concentration of II was used for the product determination. Further studies are necessary on this.

Experimental

Materials——4-Diethylaminoantipyrine was prepared as described previously.[2] The buffers used in this study were prepared from: $HClO_4$, HOAc–NaOAc (pH 5.5), NaH_2PO_4–Na_2HPO_4 (pH 7.4), and $Na_2B_4O_7$ (pH 10.4). The pH values of the aqueous acetonitrile solutions were determined with a Hitachi-Horiba M-7 pH meter after kinetic measurements. The ionic strength of the solutions was adjusted by addition of $NaClO_4$. Acetonitrile and sodium perchlorate were purified as described previously.[8]

Apparatus——A Hokuto Denko HA-101 potentiostat, HF-102 coulometer, and a Riken Denshi SP-J5V recorder were used for controlled potential electrolysis. Electrolysis was carried out as described previously.[8] A Hitachi 101 spectrophotometer equipped with a thermostatically controlled cell compartment was used for spectrophotometric measurements.

Kinetic Measurements——All reactions were carried out at 25±0.1°. I (10 mg) was subjected to electrolysis in acetonitrile (20 ml) containing 0.1 M $NaClO_4$ at 0.45 V for 2 min. Dissolved oxygen was removed by passing nitrogen through the solution. From the electricity consumed (0.891 coulombs) the concentration of II generated was calculated to be 0.463 mM. An aliquot of the resulting blue-violet solution (1—4 ml) was mixed with an appropriate amount of buffer (4—1 ml) in a standard spectrophotometric cell of 1.0 cm light path. The change of absorbance with time was measured at 590 nm.

---

[8] H. Sayo and M. Masui, *J. Chem. Soc. Perkin II*, 1973, 1640.

[Chem. Pharm. Bull. 27(8)1922—1926(1979)]

UDC 547.759.3.04 : 542.951.04

Studies on Psychotropic Agents. IV.[1] Alkylation of 2-Substituted 2,3,4,5-Tetrahydro-1H-pyrido[4,3-*b*]indole Derivatives

YASUTAKA NAGAI, AKIRA IRIE, HITOSHI UNO, and SHINSAKU MINAMI

Research Laboratory, Dainippon Pharmaceutical Co., Ltd.[2]

(Received January 5, 1979)

The alkylation of 2-substituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles (**1**) with sodium amide and alkyl halide in non-polar solvents proceeded most smoothly when the substituent in the 2 position was a benzyl group, and gave 5-alkyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]indoles (**2**) and 5-alkyl-tetrahydropyrido[4,3-*b*]indoles (**3**). The ratio of **2** to **3** depended on the halide employed. The tetrahydropyrimido[1,6-*a*]indole derivatives (**5**) with a 3-(*p*-fluorobenzoyl)propyl group in the 2 position were also prepared.

Keywords——2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole derivative; 1,2,3,4-tetrahydropyrimido[1,6-*a*]indole derivative; alkylation; rearrangement; butyrophenone derivative

It has been reported that the alkylation of 2-substituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole derivatives (I) with sodium amide and dialkylaminoalkyl halide gives 5-(dialkylaminoalkyl) derivatives (II)[3,4] but that the reaction of the 2-methyl derivative (Ia) with

---

[1] Part III: Y. Nagai, H. Uno, and S. Umemoto, *Chem. Pharm. Bull.* (Tokyo), 27, 1159 (1979).

[2] Location: *33-94, Enokicho, Suita, Osaka.*

[3] U. Hörlein, *Chem. Ber.*, **87**, 463 (1954).

[4] R.G.W. Spickett, *J. Med. Chem.*, **9**, 436 (1966).