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Kinetics of Hydrolyses of Insecticides: Cartap Hydrochloride and Nereistoxin

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Cartap hydrochloride, 1,3-bis(carbamoylthio)-2-N,N-dimethylaminopropane hydrochloride (I), an insecticide, hydrolyzes to 1,3-dimercapto-2-N,N-dimethylaminopropane (II) which are oxidized to nereistoxin, 4-N,N-dimethylamino-1,2-dithiolane (III). The hydrolysis was a base-catalyzed pseudo-first-order reaction, of which the rate constants were measured by a pH stat method and polarography in pH 4—12 at 0° and 25°. For example, the half-life ($t_{1/2}$) at pH 7 was 10 min at 25°. III was so stable that no degradation was observed after 24 hr at 100° in pH 1—4 and that $t_{1/2}$ at pH 7 was to be 2.4 years at 25°. However the disulfide (III) hydrolyzes to 2-N,N-dimethylamino-3-mercaptopropanesulfenic acid (IV) at pOH 1.1 with $t_{1/2}$ 2.2 hr at 100°. The isomer of I, 2,3-bis(carbamoylthio)-N,N-dimethylpropylamine hydrochloride (VII), hydrolyzes 10 times as rapid as I.

Keywords——base-catalyzed hydrolysis; 1,2-dithiolane; insecticide; kinetics; pH stat; polarography; thiolcarbamate

Stabilities of insecticides, cartap hydrochloride, 1,3-bis(carbamoylthio)-2-N,N-dimethylaminopropane hydrochloride (I),[2a,d] and nereistoxin, 4-N,N-dimethylamino-1,2-dithiolane (III),[2b,c] in aqueous solutions were investigated to elucidate the pharmaco-kinetic nature. It has been revealed in this paper that I converts easily to III, which is very stable to further hydrolysis. In addition, stability of 2,3-bis(carbamoylthio)-N,N-dimethylpropylamine hydrochloride (VII), the isomer of I, has been also studied in comparison with that of I.

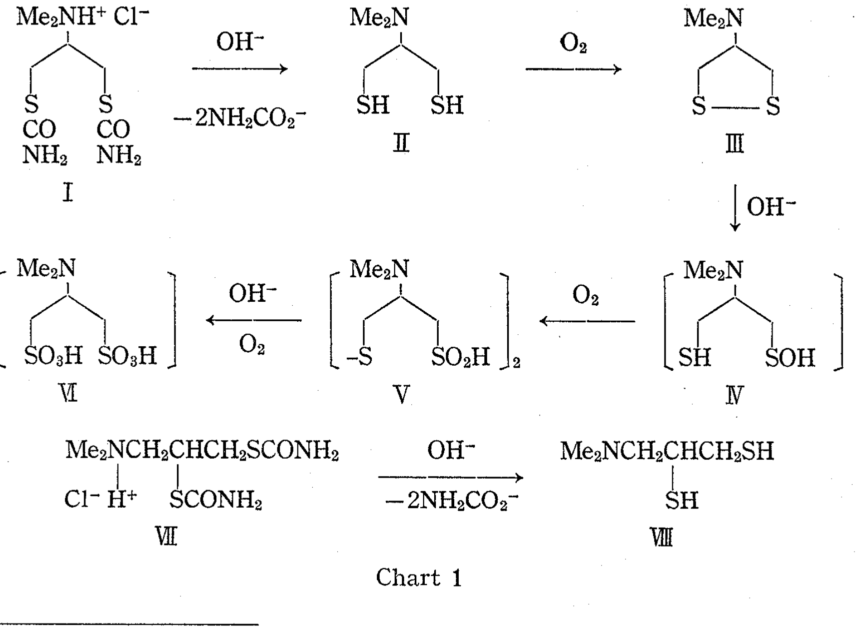

Chart 1

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[2] *a*) K. Konishi, *Agr. Biol. Chem.*, 32, 689, 119 (1968); *b*) H. Hagiwara, M. Numata, K. Konishi, and Y. Oka, *Chem. Pharm. Bull.* (Tokyo), 13, 253 (1965); *c*) M. Numata and H. Hagiwara, *ibid.*, **16**, 311 (1968); *d*) H. Hirano, M. Sakai, and M. Numata, *Takeda Kenkyusho Nempo*, **28**, 272 (1969).

Experimental

Samples——Nereistoxin (III) hydrogen oxalate, I and VII were offered from Dr. K. Konishi and Mr. M. Numata[2] in our company.

Polarography——A Pen-recording polarograph, Yanaco's model PA 2, was used to obtain current-potential or current-time curves. A dropping mercury electrode with $m=1.45$ mg sec^{-1}, $\tau=4.78$ sec and $k_c=1.66$ and a normal calomel electrode as an external reference electrode were used. Polarograms were measured in a thermostat at 25±0.1° or in an ice-water bath at 0—1° after bubbling nitrogen. Buffer solution (0.08 M) used were acetate at pH 4—6, phosphate at pH 6.8—7.5 and pH 11—12, and borate at pH 8—10.5.

Automatic Measurement of Rapid Hydrolyses of I and VII by Current-Time Curve——Current-time ($i-t$) curves at -0.2——0.3 V were automatically recorded to follow the rapid hydrolyses of I and VII to 1,3-dimercapto-2-N,N-dimethylaminopropane (II) and 2,3-dimercapto-N,N-dimethylpropylamine (VIII), respectively. For example, 0.1 ml of 40 mM I was added to 10 ml of buffer under bubbling nitrogen, which was stopped after 10 sec to record the $i-t$ curve.

pH Stat Method[3] for Rate Determination of Hydrolyses of I and VII——An aqueous solution of I or VII (0.01 M, 10 ml) was titrated with 1 N NaOH in a jacket cell thermostated at 25±0.1° or 0—1° on a Radiometer's Titrigraph model SBR2C. A time course of consumption of alkali to maintain a certain pH was automatically recorded to follow the formation of acid substances in the hydrolyses of I and VII.

Results and Discussion

Polarography and pH Stat Method for Kinetic Study

Polarographic behavior of I—VIII was studied as following. The thiolcarbamates (I, VII) gave no polarographic wave in the acid solutions. It has been previously reported[4] that the dithiol (II), the reduction product of III, gives anodic waves due to a formation of mercaptide accompanied with adsorption waves (i_a) and that the total wave height (i_d) is proportional to the concentration lower than 0.5 mM to give diffusion current constant (k_D) of 3.7 μA mM^{-1} mg$^{-2/3}$ sec$^{1/2}$. The hydrolyzate of I in the alkaline solution was identified to be II by the polarographic nature (Fig. 1c). The hydrolyzate of VII was safely predicted to be VIII by the polarographic behavior similar to those of II. The pH dependence of the half wave potentials ($E_{1/2}$) of 2 steps for 0.1 mM VIII was given by the equations, $E_{1/2}=-0.24-0.065$ pH and $E_{1/2}=-0.08-0.056$ pH at 25°. The total wave height (i_d) was proportional to the concentration (0.1—0.4 mM) to give k_D 3.2 at 25° and 1.7 at 0°. The height of the first adsorption wave (i_a) approached to a limit on increasing the concentration (0.1—1 mM).

It has been also reported[4] that III gives a reduction wave of the disulfide to the dithiol (II) accompanied with an adsorption wave. The oxidation of II to III by air was followed by a change of the anodic wave to the reduction wave. The anodic waves of VIII (the hydrolyzate of VII) changed to reduction waves similar to those of III after aeration. The oxidized product of VIII seems to be the dimeric or polymeric disulfides since the wave height ($k_D=2.8$) is smaller than those of VII ($k_D=3.2$) and III ($k_D=3.7$).

The polarography and current-time curve (Fig. 1a) are useful for the rate determination of hydrolyses of I and VII because these are automatic, rapid and precise.

Another appropriate method for the kinetic study is the pH stat method. On a potentiometric titration of I with alkali, the ammonium salt (I) was immediately neutralized to give apparent pK_1 7.65 at 0° and the thiolcarbamate hydrolyzed successively to the dithiol (II) and 2 moles of carbamic acid, which consumed 4 eq. alkali to reach pH 11. The hydrolyzate (II) was oxidized to III, which was extracted with ether and determined as a base of pK 7.2. Carbamate in the aqueous layer was fairly stable at pH>5 but carbamic acid decomposed to carbonic acid and ammonium salt by strong acid. The former product was detected as a

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[3] Y. Asahi, M. Numata, and E. Mizuta, *Chem. Pharm. Bull.* (Tokyo), **21**, 112 (1973).

[4] *a*) Y. Asahi, K. Terada, and M. Ishio, *Rev. Polarography* (Kyoto), **14**, 382 (1967); *b*) K. Nishi, R. Owaki, and N. Tan, *Takeda Kenkyusho Nempo*, **27**, 47 (1968).

volatile acid of pK 6.3 and 10.3 and the latter as a non-volatile conjugated acid of pK 9.3 by potentiometric titration. Therefore the rates of hydrolyses of I and VII can be followed by the volume-time curve (Fig. 1b).

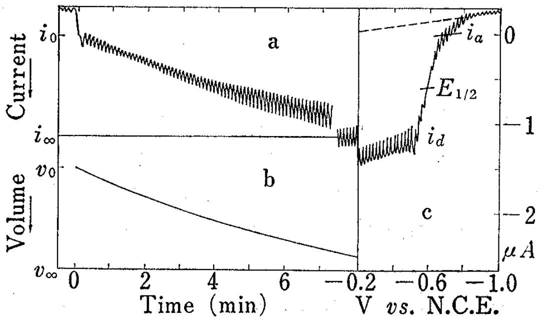

Fig. 1. Current-Time Curve (a) and Volume-Time Curve (b) in the Course of Hydrolysis of Cartap Hydrochloride (I) and Polarogram (c) of the Hydrolyzate (II) at pH 8 and 25°

a) A tenth ml of 40 mM I was added to 10 ml of borate buffer. Current at −0.25 V was recorded.
b) One N NaOH was added to 10 ml of 0.01 M I.
c) Final solution of (a) after 1 hr.

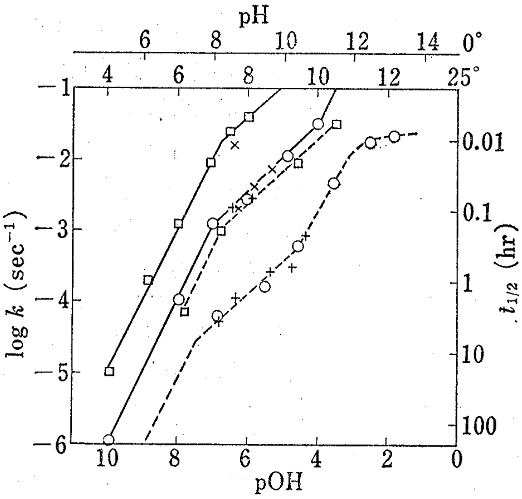

Fig. 2. pH Profiles of Rate Constants (k: sec^{-1}) and Half-lives ($t_{1/2}$: hr) of Hydrolyses of Thiolcarbamates

I (○+) and VII (□×) at 25° (——) or 0° (------) measured by polarography (○□) or pH stat (+×).

Hydrolysis of Cartap Hydrochloride (I)

Hydrolysis of I to II and carbamate was followed by the methods mentioned above. Rate constants (k) of the pseudo-first-order reaction were calculated by Eq. 1 or 2, where i_0, i_∞, i_t, and v express initial current, final current, current at a certain period (t sec), and volume of alkali, respectively.

$$k = \frac{2.3}{t} \log \frac{i_\infty - i_0}{i_\infty - i_t} \qquad \text{Eq. 1}$$

$$k = \frac{2.3}{t} \log \frac{v_\infty - v_0}{v_\infty - v_t} \qquad \text{Eq. 2}$$

Both methods gave nearly the same results under the same conditions to justify the methods and the prediction of the first-order reaction kinetics with respect to I.

pH profiles of the rate constants at 25° and 0° are shown in Fig. 2. The rate constant was proportional to the concentration of hydroxyl ion (OH^-) at pOH 3—4 and 7—10. The amino group of I (pK_1 7.65) exists mainly as a free base (I′) at pOH 3—4 and as a cation (I) at pOH 7—10. Therefore the hydrolysis is considered to be a secondorder reaction between OH^- and I at pOH 7—10 or I′ at pOH 3—4. At pOH 4—7, both species (I and I′) coexist and hydrolyze concurrently. In strongly alkaline solutions, the carbamoylthio group in I will ionize to an enolate form (I″) since dissociation constants (pK) of the related compounds have been given as follows: acetamide (15.1),5a) hydroxyisobutyramide (13.16),5a) phenyldithiocarbamate (14.6)5b) and O-isopropyl-N-methylthionocarbamate (11.56).5c) It may be explained by postulating the enolate form (I″) that the rate constants at 0° become to be independent of (OH^-) at pOH below 2. These relationships between the overall rate constant (k) and $(OH)^-$ are expressed by Eq. 3, where k_1 and k_2 are catalytic constants

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5) *a*) R.O. Gould and H.M. Sutton, *J. Chem. Soc.* (A), **1970**, 1185; *b*) F. Takami, S. Wakahara, and T. Maeda, *Tetrahedron Lett.*, **1971**, 2645; *c*) A.K. Livshits, A.V. Glembotskii, and S.M. Gurvich, *Tsvet. Metal.*, **41**, 19 (1968) [*C.A.*, **69**, 80926*u* (1968)].

of OH⁻ for the cation (I) and the base (I′), respectively, k_3 is rate constant for the anion (I″), and K_1 and K_2 are dissociation constants of the amine and the enol, respectively.

$$k=\frac{k_1(\mathrm{OH}^-)}{1+K_1/(\mathrm{H}^+)}+\frac{k_2(\mathrm{OH}^-)}{[1+(\mathrm{H}^+)/K_1][1+K_2/(\mathrm{H}^+)]}+\frac{k_3}{1+(\mathrm{H}^+)/K_2} \qquad \text{Eq. 3}$$

The equation 3 is reduced into Eq. 4 under the specific conditions.

$$\begin{aligned} k &= k_1(\mathrm{OH}^-) && \text{at } (\mathrm{H}^+) \gg K_1 \gg K_2 \\ k &= k_2(\mathrm{OH}^-) && \text{at } K_1 \gg (\mathrm{H}^+) \gg K_2 \\ k &= k_3 && \text{at } K_1 \gg K_2 \gg (\mathrm{H}^+) \end{aligned} \qquad \text{Eq. 4}$$

The observed rate constants(k) fitted well in the simulation curves (Fig. 2) if the parameters were assumed to be $k_1=1\times10^4\,\mathrm{M}^{-1}\,\mathrm{sec}^{-1}$, $k_2=2.8\times10^2\,\mathrm{M}^{-1}\,\mathrm{sec}^{-1}$ and $K_1=2\times10^{-8}$ at 25°, and $k_1=1\times10^3\,\mathrm{M}^{-1}\,\mathrm{sec}^{-1}$, $k_2=2\times10\,\mathrm{M}^{-1}\,\mathrm{sec}^{-1}$, $k_3=7\times10^{-3}\,\mathrm{sec}^{-1}$, $K_1=2\times10^{-8}$ and $K_2=1\times10^{-12}$ at 0°. The dissociation constant (K_1) estimated kinetically was close to that ($K_1=2.2\times10^{-8}$) measured by potentiometric titration.

A reaction mechanism of the hydrolysis is proposed as Chart 2. The carbon atom of the carbamoylthio group ($\mathrm{SCONH_2}$) in I and I′ may be attacked by OH⁻ to form a labile intermediate anion (Ia), which cleaves spontaneously into the thiol (II) and carbamic acid. The cation (I) is more unstable to OH⁻ than the base (I′) probably because the electrophilic nature of $\mathrm{SCONH_2}$ may be enhanced by the positive charge in I. The reactivity of two groups in 1,3-position of I seems to be equal and independent of each other since Eq. 1 and 2 are valid in the full course of hydrolysis. The C–S bond of the enolate (I″) cleaves spontaneously in a similar manner as that of the anion (Ia).

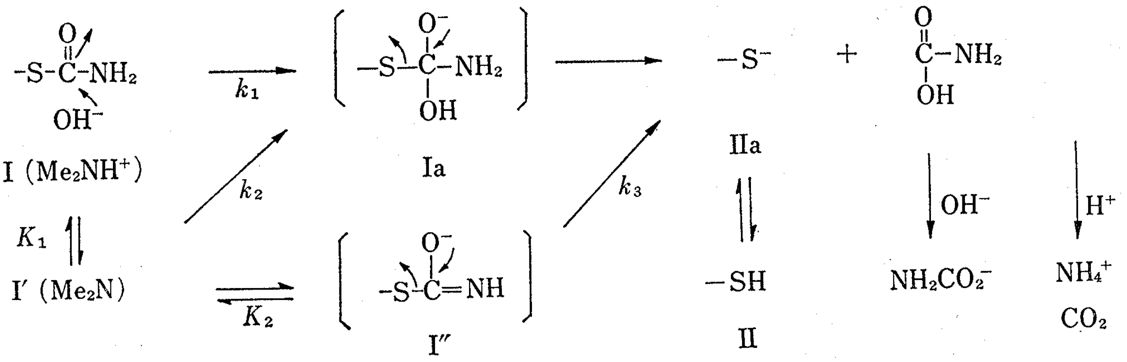

Chart 2

Activation energy (E_a) of the hydrolysis was estimated to be 20 kcal mol⁻¹ from the temperature dependence of the rate constants at pOH 7 according to the Arrhenius equation. Half-lives ($t_{1/2}$) of I in aqueous solutions under selected conditions were predicted from the results mentioned above as shown in Table I.

Table I. Half-life ($t_{1/2}$) of Cartap Hydrochloride (I) predicted from the pH and Temperature Dependence of Rate Constant

pH	0°	15°	25°	35°
4	1800 day	950 hr	190 hr	32 hr
5	180 day	95 hr	19 hr	3.2 hr
6	18 day	9.5 hr	1.9 hr	19 min
7	43 hr	57 min	11 min	1.9 min
8	4.3 hr	18 min	3.5 min	0.6 min
9	1.4 hr	5.7 min	1.1 min	0.2 min
10	0.43 hr	1.8 min	0.35 min	0.06 min

It is concluded that this insecticide (I) is fairly stable in acid solutions but rapidly converted to the other insecticides (II and III) in neutral or alkaline solutions. It has been previously noticed[6] that I reacts rapidly with an SH reagent, 5,5′-dithio-bis(2-nitrobenzoic acid), in an alkaline solution. This fact also supports the hydrolysis of I to II.

Hydrolysis of the Isomer (VII)

Stability of VII was examined in a similar manner as that of I. Hydrolysis of VII results in 2,3-dimercapto-N,N-dimethylpropylamine (VIII). This reaction is considered to be a successive pseudo-first-order reaction catalyzed by OH^- ion. pH profiles of the initial rate constants (Fig. 2) are parallel with those of I although VII is 10 times as unstable as I. Activation energy of the hydrolysis of VII, E_a 21 kcal mol^{-1}, is close to that of I. The reaction mechanism for VII seems to resemble that for I although an electron withdrawing effect of the adjacent carbamoylthio groups in VII may facilitate the alkaline hydrolysis more than those in I.

Hydrolysis of Nereistoxin (III)

Stabilities of III must be examined since I converts easily to III in aqueous solutions. Residual III was determined by polarography and absorbance at 318 nm after 0.5 mM III in buffer solutions at pH 1—13 was treated at 100° in ampoules. No change was observed after the treatment at pH 1—4 for 24 hr. In an alkaline solution of pOH 1.1, however, the reduction wave of III diminished whereas absorbance at 270 nm probably due to a linear disulfide increased. When the reaction mixture was subjected to thin–layer chromatography, the main product gave a spot at *Rf* 0.15 on a silica gel plate HF_{254} developed with methanol. This fact suggests a hydrophilic nature of the substance.

Generally disulfides (RSSR′) are hydrolyzed[7] by alkali to the corresponding thiol (RSH) and sulfenic acid (R′SOH), which are oxidized to disulfide (RSSR), sulfinic acid ($R'SO_2H$) and sulfonic acid ($R'SO_3H$). It is safely predicted that III will be hydrolyzed by alkali to 2-N,N-dimethylamino-3-mercaptopropanesulfenic acid (IV), which will be oxidized to 3,3′-dithio-bis-(2,2-N,N-dimethylaminopropanesulfinic acid) (V) and 2-N,N-dimethylaminopropane-1,3-disulfonic acid (VI).

The hydrolysis of III was again revealed to be a pseudo-first-order reaction since linear relationship between logarithm of the residual concentration of III and time was observed in 0.08 N sodium hydroxide at 100° for 1—3 hr. The rate constant (*k*) was proportional to the concentration (OH^-) in pOH 1.1—1.7 at 100°, which suggested a base-catalyzed reaction.

TABLE II. Half-life ($t_{1/2}$) of Nereistoxin (0.5 mM) in Aqueous Solutions

Temp. (°C)	pOH at t°	pH at 25°	Medium	$t_{1/2}$
100	1.1	12.9	0.08 N NaOH	2.2 hr
	1.7	12.3	0.02 N NaOH	7.9 hr
	3.3	10.0	0.08 M borate	20 hr
	5.3	7.0	0.08 M phosphate	26 hr
	8.2	4.1	0.08 M acetate	>100[a] hr
	11.2	1.1	0.08 M HCl	>100[a] hr
50	1.1	12.9	0.08 N NaOH	29 hr
47	6.4	7.0	0.08 M phosphate	95 day
25	7.0	7.0	0.08 M phosphate	880[b] day

a) No change after 24 hr.
b) Estimated by extrapolation.

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[6] K. Nishi, I. Kodo, and N. Tan, *Takeda Kenkyusho Ho*, **29**, 231 (1970).
[7] Y. Asahi and K. Shinozaki, *Takeda Kenkyusho Ho*, **30**, 233 (1971).

The activation energy (E_a=12.3 kcal mol^{-1}) and the activation entropy ($\Delta S^{\ne}=-41$ e.u.) were estimated from the temperature dependence of the second-order rate constant, $k/(\mathrm{OH}^-)$. The negatively large activation entropy may suggest such a transition state as a complex of the disulfide and OH^- ($\overset{|}{\mathrm{S}}-\overset{|}{\mathrm{S}}\cdots\mathrm{OH}^-$) with a restricted freedom.

In neutral and weakly alkaline solutions (pOH 3.3—5.3 at 100°), the rates of hydrolysis were almost independent of OH^- to postulate a water-catalyzed reaction. Half-life ($t_{1/2}$) in a practical condition (pH 7, 25°) was estimated to be 2.4 years by extrapolating the temperature dependence curve of the rates.

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