REACTIONS OF THIOUREA WITH CHLORO- AND BROMOACETIC ACIDS

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The reaction of chloroacetic acid with thiourea represents an S_N2 substitution of chlorine by sulphur atom and is about two orders of magnitude slower than that of bromoacetic acid. Chloroacetate ion reacts slower than chloroacetic acid by only about 30%. The acid catalyzed splitting off of hydroxyl group from the formed tetrahedral intermediate is rate-limiting in the cyclization of the S-carboxylatomethyleneisothiouronium salt, formation of the intermediate being rate-limiting below pH 2.

Reactions of substituted thioureas with chloroacetic acid derivatives giving substituted 2-imino-4-thiazolidinones are described in the review[1]. Most papers cited aim at syntheses of substances with potential biological activity. Though the reaction proceeds in two steps, its intermediate (thiouronium salt) was only isolated in few cases[2,4]. Kinetics of formation and subsequent cyclization of the thiouronium salt was not described in literature. The present paper deals with kinetics of reactions of chloro(II)- and bromoacetic acid (*III*) with thiourea giving S-carboxylatomethyleneisothiouronium salts and its cyclization to 2-imino-4-thiazolidinone.

EXPERIMENTAL

Reagents

Bromoacetic acid (*III*) was prepared by bromination of acetic acid according to ref.[5]. The S-carboxylatomethyleneisothiouronium salt (*IV*) was prepared by mixing of equal volumes of 2M solutions of thiourea (*I*), chloroacetic acid (*II*) and sodium acetate. The solution was left to stand overnight at room temperature. The separated solid was filtered off, washed with water and methanol, and dried in a dessiccator over phosphorus pentoxide. Yield 90%, m.p. 235°C (decomp.). For $C_3H_6N_2O_2S$ (134·1) calculated: 26·86% C, 4·50% H; found: 27·10% C, 4·64% H. 2-Imino-4-thiazolidinone (*V*) was prepared by reaction of thiourea with ethyl chloroacetate in ethanol[6]. The first and the second dissociation constants of the substance *IV* were measured spectrophotometrically[7] in dilute hydrochloric acid solutions at 250 nm ($pK_{a_1} = 2·30$) and in borax buffers at 245 nm ($pK_{a_2} = 9·54$) at the ionic strength $I = 0·5$ at 25°C.

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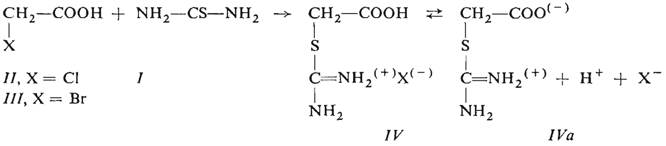
Kinetic Measurements

Formation of thiouronium salt IV: *a*) By reaction of thiourea with bromoacetic acid. 1 ml 0·5 or 1M thiourea was added to 19 ml aqueous solution of the acid *III* (0·1 to 0·25M) containing 2 ml 1M-HCl. 0·1 ml samples were withdrawn at suitable time intervals, and, after dilution with 25 ml water the absorbance decrease was measured at 240 nm. *b*) By reaction of thiourea with chloroacetic acid. In a thermostatted flask (25°C) 100 ml 2M acid *II* was mixed with 100 (or 200) ml water and 200 (or 100) ml 2M thiourea. The mixture was divided into 40 ml samples. At suitable time intervals (20 min to 1 h) the individual samples were treated with 20 ml 2M sodium acetate, and the separated product was filtered off, washed with water, dried and weighed. *c*) By reaction of thiourea with sodium chloroacetate. In a thermostatted flask 100 ml 2M chloroacetic acid was mixed with 100 ml 2M sodium acetate and 200 ml 2M thiourea. The mixture was divided into 400 ml samples and at 1 h intervals the separated product was filtered off, washed with water and weighed.

Cyclization of thiouronium salt IV. Fresh aqueous thiouronium salt IV solution (1 ml about $2 \cdot 10^{-4}$M) was added into 1 ml temperated buffer solution or dilute hydrochloric acid (ionic strength adjusted at $I = 1 \cdot 0$ by addition of potassium chloride) in a quartz cell. The absorbance increase was followed at 250 nm at 25°C using a VSU-2P apparatus (Zeiss, Jena). Spectrum of the mixture after the finished reaction was identical in all cases with that of solution of the ketone *V* of the same concentration in the same solvent.

RESULTS AND DISCUSSION

The first reaction step, formation of *IV*, is an S_N2 substitution of halogen by sulphur (Eq. (*A*)). At pH above 2·5 the inner salt *IVa* is formed predominantly which is slightly soluble in water and, hence, separates even from very dilute solutions. At low pH values (mineral acid media) the main product is *IV* which is much more soluble and crystallizes from more concentrated solutions.



$$\begin{array}{l} CH_2\text{—}COOH \\ | \\ X \end{array} + NH_2\text{—}CS\text{—}NH_2 \rightarrow \begin{array}{l} CH_2\text{—}COOH \\ | \\ S \\ | \\ C{=}NH_2^{(+)}X^{(-)} \\ | \\ NH_2 \end{array} \rightleftarrows \begin{array}{l} CH_2\text{—}COO^{(-)} \\ | \\ S \\ | \\ C{=}NH_2^{(+)} \\ | \\ NH_2 \end{array} + H^+ + X^- \qquad (A)$$

II, X = Cl
III, X = Br
I
IV
IVa

The reaction of thiourea with bromoacetic acid (*III*) was carried out in a 4 to 10 fold excess of the acid *III** and in the presence of hydrochloric acid, so that the salt *IV* was the primary product. The reaction was followed spectroscopically from thiourea absorbance decrease. The dependence $\log(A_t - A_\infty)$ *vs* time was linear up to at least 80% conversion. Then the absorbance decrease began to be somewhat slower than it should have been according to pseudomonomolecular reaction, because the cation *IV* undergoes cyclization to some extent (reaction (*B*)). The observed rate

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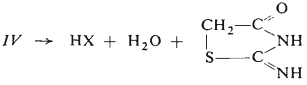
* For the four-fold excess the rate constants were also calculated according to equation of the 2nd order reaction, and the differences found were within experimental error.

constants were directly proportional to concentration of the acid *III*. The calculated rate constant was $k_2 = k_{obs}/[III] = (1{\cdot}07 \pm 0{\cdot}10) . 10^{-2}\ l\ mol^{-1}\ s^{-1}$.



V (*B*)

The reaction of thiourea with chloroacetic acid (*II*) was followed under two different conditions: first with pure acid *II* and next with predominant chloroacetate anion (addition of sodium acetate). In the both cases the reaction course was followed gravimetrically by the amount of the separated inner salt *IVa*, as no suitable spectral or titrimetric analytical method could be found. The reaction was carried out both with equimolar ratio and with excess acid *II* (or its anion). The rate constants were calculated from Eqs (*1*) and (*2*).

$$k_2 t = 1/[I]_t - 1/[I]_0\,, \quad \text{where} \quad [I]_t = [I]_0 - [IV]_t \tag{1}$$

$$k_2 t = ([I]_0 - [II]_{0,\text{anal}})^{-1} . 2{\cdot}3 \log ([I]_t/[II]_{t,\text{anal}}) + \text{const.}\,, \quad \text{where} \quad [II]_{t,\text{anal}} = [II]_{0,\text{anal}} - [IVa]_t\,. \tag{2}$$

The reactions with the acid *II* (both equimolecular and excess *II*) produce mixture of *IV* and *IVa* cyclizing slowly to *V*. As the product *V* is far more soluble, it remains in solution, and the weighed yields of the product were gradually lower than they should have been according to kinetic relations. The dependence concentration *vs* time was linear up to 30–40% conversion only. The calculated value of the 2nd order constant $k_2 = (1{\cdot}3 \pm 0{\cdot}1) . 10^{-4}\ l\ mol^{-1}\ s^{-1}$. The reaction of thiourea with chloroacetate ion produces the inner salt *IVa* which is immediately separated from the reaction mixture. Therefore, the cyclization does not practically occur. The dependence concentration *vs* time was linear up to at least 70% conversion. The calculated constant $k_2 = (0{\cdot}98 \pm 0{\cdot}05) . 10^{-4}\ l\ mol^{-1}\ s^{-1}$.

Bromoacetic acid (*III*) reacts with thiourea (*I*) faster than chloroacetic acid (*II*) by almost 2 orders of magnitude. This difference reflects the reactivity difference between chloride and bromide leaving groups in S_N2 reaction with a reactive nucleophile[8]. Thiourea (*I*) reacts 100 times faster with bromoacetic acid (*III*) than with bromomethane,* though substitution of hydrogen by COOH group increases sterical interactions between nucleophile and substrate decreasing thus the reaction rate[11].

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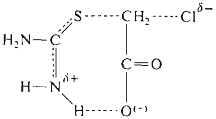
* The rate constant of the reaction of bromomethane with thiourea ($k_2 = 0{\cdot}93 . 10^{-4}\ l . mol^{-1}\ s^{-1}$) was calculated from that of hydrolysis of bromomethane[9] at 25°C ($k_1 = 4{\cdot}07 . 10^{-7}\ s^{-1}$) and relation $\log (k/k_0) = n$, where $n = 4{\cdot}1$ for thiourea[10].

A likely reason of the large reactivity increase (as compared with bromomethane) lies in the activating effect of the carbonyl group (partial bond formation between the attacking nucleophile and the electrophilic carbonyl carbon atom)[12], resembling but smaller than that in *e.g.* substitution of 1-chloro-2-propanone[13]. It is, however, surprising to find chloroacetate ion to be highly reactive (only 30% less than the non-dissociated acid), which cannot be explained in the same way, as electrophilicity of the carbon atom is strongly diminished in the anion. A possible explanation of the enhanced reactivity in this case can be in formation of intramolecular hydrogen bond between negatively charged oxygen of the carboxyl group and the hydrogen of imino group carrying partial positive charge.



VI

The cyclization of the compound *IV* (Eq. (*B*)) was measured in dilute hydrochloric acid solution and chloroacetate buffers. The cyclization rate increases with increasing buffer concentration, but the change is relatively low, and, therefore, the rate constant for catalysis by buffer was not calculated, and the rate constants measured in chloroacetate buffers were extrapolated to zero buffer concentration. The dependence log *k* *vs* pH is given in Fig. 1. The cyclization mechanism (Scheme 1) is similar

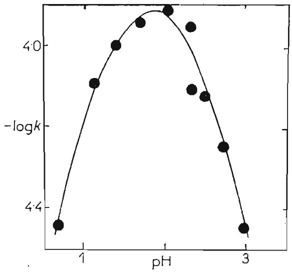
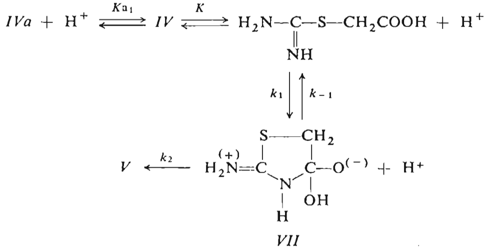


FIG. 1

Dependence of Rate of Cyclization Reaction (*IV* + *IVa*) → *V* on pH in Aqueous Solutions at 25°C

The full line represents the theoretical dependence calculated from Eq. (*3*).



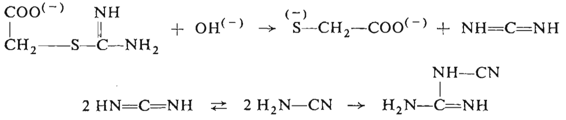
SCHEME I

to that of the acid-catalyzed cyclization of S-ethoxycarbonylmethyleneisothiouronium chloride[14], and k_{obs} is defined by kinetic equation (*3*).

$$v = k_{obs}([IV] + [IVa]) = k_1 k_2 K[H^+]([IV] + [IVa])/(k_{-1} + k_2[H^+]) \,.\, (K_{a_1} + [H^+]) \qquad (3)$$

The theoretical dependence in Fig. 1 (full line) was calculated from Eq. (*3*) and the values $k_2/k_1 = 25$, $k_1K = 9{\cdot}0 \,.\, 10^{-6}$ found by comparison of the calculated values k_{obs} with the experimental ones.

At pH above 3 it is $K_{a_1} \gg [H^+]$; $k_{-1} \gg k_2[H^+]$ and $k_{obs} = k_1 k_2 K[H^+]/k_{-1} \,.\, K_{a_1}$; k_{obs} decreases with decreasing proton concentration. The rate is directly proportional to $[H^+]$, and transformation of the intermediate *VII* into the product *V* (k_2) is the rate-limiting step. At pH below 1 it is $K_{a_1} \ll [H^+]$; $k_1 \ll k_2[H^+]$, and $k_{obs} = k_1K/[H^+]$; k_{obs} is inversely proportional to $[H^+]$, and formation of the intermediate *VII* (k_1) is the rate-limiting step. The dissociation constant K_{a_2} (dissociation of the proton from nitrogen of the compound *IVa*) equals $10^{-9 \cdot 54}$. From analogy with values of the dissociation constants of succinic acid[15] it can be presumed that $K \sim 10^{-9}$ and $k_1 \sim 10^4$. At pH above 10 spectral changes again are observed, they are, however, due to another reaction. In this medium the compound *IV* exists predominantly in the form of anion ($pK_{a_2} = 9{\cdot}54$) which decomposes on reaction with hydroxide into mercaptoacetate anion and cyanamide giving dicyandiamide[16]. Mechanism of this reaction (*C*) obviously is the same as that of decomposition of S-alkylisothioureas[17].



$$\begin{array}{l}\overset{\displaystyle COO^{(-)}}{\overset{|}{CH_2}}\text{——}S\text{—}\underset{}{\overset{\overset{\displaystyle NH}{\|}}{C}}\text{—}NH_2 + OH^{(-)} \rightarrow \overset{(-)}{S}\text{—}CH_2\text{—}COO^{(-)} + NH{=}C{=}NH \\ 2\,HN{=}C{=}NH \rightleftarrows 2\,H_2N\text{—}CN \rightarrow H_2N\text{—}\overset{\overset{\displaystyle NH\text{—}CN}{|}}{C}{=}NH\end{array} \qquad (C)$$

The rate constant of the reaction (*C*) increased linearly with OH^- concentration. The calculated constant $k_2 = 5 \pm 2$ l mol^{-1} s^{-1} is 2–3 times greater than that of the reaction of S-ethylisothiourea with hydroxide determined in the same way.

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