The mechanisms of hydrolysis of alkyl *N*-alkylthioncarbamate esters at 100 °C[1]

Eduardo Humeres, Maria de Nazaré M. Sanchez, Conceição M.L. Lobato, Nito A. Debacher, and Eduardo P. de Souza

Abstract: The hydrolysis of ethyl *N*-ethylthioncarbamate (ETE) at 100 °C was studied in the range of 7 mol/L HCl to 4 mol/L NaOH. The pH–rate profile showed that the hydrolysis occurred through specific acid catalysis at pH < 2, spontaneous hydrolysis at pH 2–6.5, and specific basic catalysis at pH > 6.5. The Hammett acidity plot and the excess acidity plot against X were linear. The Bunnett–Olsen plot gave a negative slope indicating that the conjugate acid was less hydrated than the neutral substrate. It was concluded that the acid hydrolysis occurred by an A1 mechanism. The neutral species hydrolyzed with general base catalysis shown by the Brønsted plot with $\beta = 0.48 \pm 0.04$. Water acted as a general base catalyst with (pseudo-)first-order rate constant, $k_N = 3.06 \times 10^{-7}$ s^{-1}. At pH > 6.5 the rate constants increased, reaching a plateau at high basicity. The basic hydrolysis rate constant of ethyl *N*,*N*-diethylthioncarbamate, which must react by a $B_{Ac}2$ mechanism, increased linearly at 1–3 mol/L NaOH with a second-order rate constant, $k_2 = 2.3 \times 10^{-4}$ (mol/L)$^{-1}$ s^{-1}, which was 10 times slower than that expected for ETE. Experiments of ETE in 0.6 mol/L NaOH with an excess of ethylamine led to the formation of diethyl thiourea, presenting strong evidence that the basic hydrolysis occurred by the E1cb mechanism. In the rate-determining step, the E1cb mechanism involved the elimination of ethoxide ion from the thioncarbamate anion, producing an isothiocyanate intermediate that decomposed rapidly to form ethylamine, ethanol, and COS.

Key words: alkylthioncarbamate esters, ethyl *N*-ethylthioncarbamate, ethyl *N*,*N*-diethylthioncarbamate, hydrolysis, mechanism.

Résumé : Opérant à 100 °C, dans des milieux allant du HCl à 7 mol/L au NaOH à 4 mol/L, on a étudié la réaction d'hydrolyse du *N*-éthylthionecarbamate d'éthyle (ETE). Le profile de la vitesse en fonction du pH montre que l'hydrolyse se produit par le biais d'une catalyse acide spécifique à des pH inférieurs à 2, par une hydrolyse spontanée à des pH allant de 2 à 6,5 et par une hydrolyse par catalyse basique à des pH supérieurs à 6,5. La courbe d'acidité de Hammett et la courbe d'excès d'acidité en fonction de X sont linéaires. La courbe de Bunnett–Olsen donne une pente négative qui indique que l'acide conjugué est moins hydraté que le substrat neutre. On en conclut que l'hydrolyse acide se produit par un mécanisme A1. L'espère neutre s'hydrolyse par une catalyse générale basique mise en évidence par la courbe de Brønsted avec une valeur de $\beta = 0{,}48 \pm 0{,}04$. L'eau agit comme catalyseur basique général avec une constante de vitesse de (pseudo-)premier ordre, $k_N = 3{,}06 \times 10^{-7}$ s^{-1}. À des pH supérieurs à 6,5, les constantes de vitesse augmentent pour atteindre un plateau aux pH élevés. Pour l'hydrolyse basique du *N*,*N*-diéthylthionecarbamate d'éthyle, qui doit obligatoirement réagir par un mécanisme $B_{Ac}2$, la constante de vitesse augmente d'une façon linéaire dans le NaOH à des concentrations allant de 1 à 3 mol/L et la constante de vitesse du deuxième ordre, $k_2 = 2{,}3 \times 10^{-4}$ (mol/L)$^{-1}$ s^{-1}, est 10 fois plus lente que celle attendue pour l'ETE. Des expériences avec l'ETE dans du NaOH à 0,6 mol/L, en présence d'un excès d'éthylamine, conduit à la formation de diéthylthiourée, ce qui suggère fortement que l'hydrolyse basique se produit par un mécanisme E1cb. Dans l'étape cinétiquement déterminante, le mécanisme E1cb implique l'élimination de l'ion éthylate à partir de l'anion thionecarbamate avec formation d'un intermédiaire isothiocyanate qui se décompose rapidement pour former de l'éthylamine, de l'éthanol et du COS.

Mots clés : alkylthionecarbamates d'esters, *N*-éthylthionecarbamate d'éthyle, *N*,*N*-diéthylthionecarbamate d'éthyle, hydrolyse, mécanisme.

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Introduction

The reaction of carbon dioxide and carbon disulfide with alkoxides, halides, and amines produces derivatives that are important pesticides (eq. [1]) (1). Carbamic acid acid esters (**1**, X = O) are widely used as insecticides because of their ability to inhibit the enzyme acetylcholinesterase. Thioncarbamic esters (**1**, X = S) are used as fungicides and bactericides (2), nematocides (3), collectors in flotation (4), and in a variety of industrial applications (5). The formation of the highly stable thioncarbamate group has been used to immobilize enzymes in a cellulose matrix (eq. [1], R = cellulose, R″ = enzyme) (6).

The biological activity depends on the C=X group (X = O, S) because of the different properties of the oxo and sulfo groups. The carbonyl can stabilize α-carbocations better than sulfur, but this capacity is inverted for carbanions. The thiocarbonyl is a powerful electron-withdrawing group because sulfur can easily accept electrons.

There is a duality of mechanisms for the basic hydrolysis of carbamates and thioncarbamate esters depending on the availability of a proton on the nitrogen atom of the ester. Mechanism $B_{Ac}2$ applies if there is no proton on the nitrogen (*N*,*N*-disubstituted nitrogen), but if the nitrogen contains a proton, mechanism E1cb might apply, although not necessarily. All aryl esters follow this pattern. Alkyl carbamates apparently follow the $B_{Ac}2$ mechanism. However, no information exists about the mechanisms involved in the hydrolysis of alkyl thioncarbamate esters.

In this work, we studied the hydrolysis (at 100 °C) of ethyl *N*-ethylthioncarbamate in the range of 7 mol/L of HCl to 4 mol/L of NaOH, to obtain an insight into the mechanisms involved.

Experimental

Materials

Reagents were all of analytical grade and were used without further purification. Distilled water was deionized and deoxygenated by boiling and cooling under nitrogen. Ethylamine was distilled (bp 18 °C), condensed in a trap cooled with liquid nitrogen, and bubbled into water to obtain a 2 mol/L solution. UV spectra and kinetics were obtained using a Cary 219 spectrophotometer. All compounds were identified by ^{1}H NMR and IR spectra.

Ethyl *O*-ethylxanthate (EXE)

Potassium *O*-ethylxanthate (EXK) was obtained using the classical procedure (7), adding 60 mL of carbon disulfide to a cooled solution of 56 g (1 mol) potassium hydroxide in 200 mL of ethanol. The product was recrystallyzed twice in ethanol; λ_{max} (ethanol) 301 nm. Ethyl *O*-ethylxanthate was obtained after refluxing a solution of EXK (32 g, 0.2 mol) and ethyl bromide (21.8 g, 0.2 mol) for 4 h in 50 mL of ethanol. The product was washed with water, dried over anhydrous sodium sulfate, and distilled under vacuum: bp 35 °C at 1 mmHg (lit. value (8) bp 78 °C at 18 mmHg) (1 mmHg = 133.322 4 Pa); λ_{max} (water) 283 nm.

Ethyl *N*-ethylthioncarbamate (ETE)

Ethyl *O*-ethylxanthate (13.3 g, 0.1 mol) was dissolved in 10 mL of ethanol, and an aqueous solution of ethylamine (0.11 mol) at pH 11 was added with cooling, allowing the solution to react for 24 h at 10 °C under constant stirring. The ethanol was eliminated under vacuum in a rotatory evaporator and the product was washed with water, dried over anhydrous sodium sulfate, and distilled under vacuum: bp 74 °C at 1 mmHg (lit. value (9) bp 78 °C at 3 mmHg); λ_{max} (water) 242 nm.

Ethyl *N*,*N*-diethylthioncarbamate (DETE)

A solution of 10 g (75 mmol) of EXE and 6 g (82 mmol) of diethylamine in 200 mL of ethanol was allowed to react at room temperature. The reaction was followed via UV spectrophotometry by the disappearance of the band at 283 nm because of EXE and the appearance of the band at 245 nm because of DETE. The product was distilled under vacuum: bp 85 °C at 1 mmHg; λ_{max} (water) 245 nm.

1,3-Diethyl thiourea (DETU) (10)

Ethyl isothiocyanate (4.5 g of a 90% aqueous solution) was slowly added to 8.7 g of a 70% aqueous solution of ethylamine. The reaction was exothermic and the mixture was cooled in an ice bath. The water was evaporated at 60 °C, and the crystals were recrystallized twice in dried ethanol; mp 77.1 °C (lit. value (11, 12) mp 72–78 °C); λ_{max} (methanol) 210 and 234 nm.

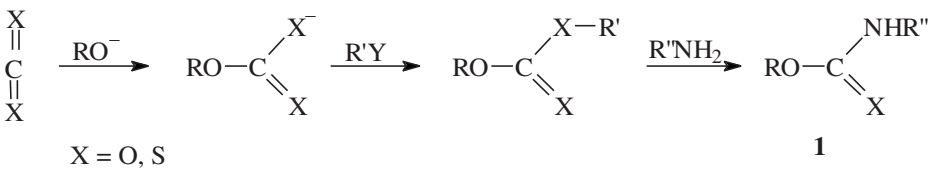
Reverse base dissociation constant of ethyl *N*-ethylthioncarbamate ($-pK_b$)

The dissociation constant was obtained at 25 °C from a series of measurements of the absorbance at 242 nm of a ca. 10^{-5} mol/L solution of the substrate, in the range of H_- = 10–15. The initial solution was 0.01 mol/L NaOH and known volumes of a 8 mol/L NaOH solution were added, correcting the absorbance for the dilution and the absorbance of the base. The UV spectra in the range of pH 7 to 2.7 mol/L NaOH, μ = 5 (NaCl) showed a single isosbestic point at 228 nm. Inversion of the basicity after the titration showed that the dissociation at 25 °C was reversible, with no noticeable reaction. The value of $-pK_b = 13.6 = pK_2$ (see the following) was calculated from the inflection point of the plot of the corrected absorbance vs. H_- for NaOH (Fig. 1) (13).

Correction of pH and pK_a with temperature

The pH of the solutions was measured at 25 °C and corrected to 100 °C as described elsewhere (14). The same

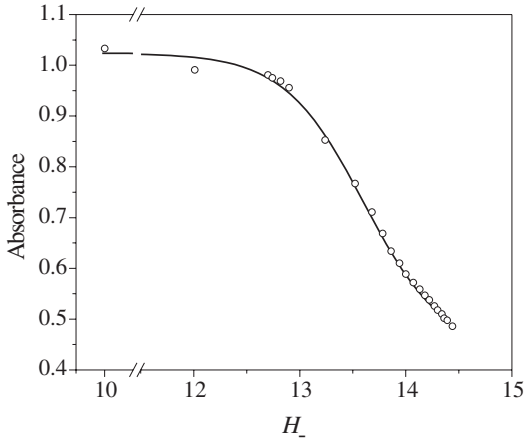
[1]



X = O, S

1

Fig. 1. Titration curve of ETE at 25 °C.



method was followed to calculate the pK_as of the buffers at 100 °C.

Kinetics

Kinetics were studied at 100 °C in distilled deoxygenated water in the range of H_o = –2.4 to 4 mol/L NaOH. The kinetic solution (50 mL) had a final concentration of ca. 10^{-4} mol/L; samples of 3 mL were placed in sealed glass ampoules and immersed in a thermostat at 100 °C. The samples were collected at different times and quenched in a Dewar bath with salted ice. The kinetics were followed spectrophotometrically at 25 °C by the disappearance of ETE at 242 nm or at 230 nm for the basic hydrolysis. The disappearance of DETE was followed at 245 nm. All runs were followed for at least three half-lives and the ln ΔA vs. time plots produced straight lines that were considered when $r \geq 0.99$. The pH of unbuffered runs was controlled at the end of the experiment and showed no change.

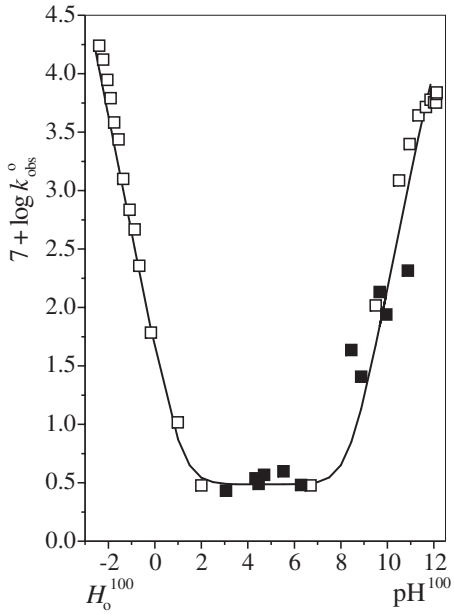
For the kinetics under strong basic conditions, the rate constants were also calculated by the Guggenheim method (15) because of a precipitate of sulfur that interfered with the absorbance readings. The rate constants for the slowest kinetics were obtained from initial rates.

Product analysis

The products of the hydrolysis of ETE were characterized in a preparative run at 2.5 mol/L NaOH and 100 °C, allowing a 50 min reaction. A sample was extracted with chloroform, and ethylamine was identified as a product by GLC. Another sample was extracted with cyclohexane, and ethanol was also identified as a product by GLC.

To trap the isothiocyanate intermediate, a preparative run of the hydrolysis of ETE in the presence of ethylamine was carried out. An aqueous solution of 4.5 mmol/L ETE, 0.6 mol/L NaOH, and 3 mol/L ethylamine was refluxed for 30 min, and after cooling, it was neutralized with HCl. The products were extracted with chloroform, concentrated in a rotatory evaporator, dried over anhydrous sodium sulphate, and then analyzed by TLC (silica gel, MeOH). A single spot was found with R_f 0.75, the same as an authentic sample of 1,3-diethyl thiourea. This result was confirmed by UV spectra.

Fig. 2. pH–rate profile of the hydrolysis of ETE at 100 °C. Unbuffered (□) and values extrapolated to zero buffer concentration (■).



Activation parameters

Activation parameters were calculated from the rate constants in the temperature range of 90–110 °C by least-squares fitting to the Eyring equation.

Results and discussion

pH–rate profile of ETE

The pH–rate profile was obtained at 100 °C in the range of H_o = –2.4 to pH 12 (Fig. 2). The values of k^o_{obs} were obtained in the absence of buffer or extrapolated to zero buffer concentration, and the pH was corrected for the temperature as has been previously described (14).

In the acid range of pH < 2, HCl was used and the H_o values obtained at 25 °C from the excess acidity X, and the HCl acid molarity (C_{H^+}) was corrected at 100 °C for the change of the excess acidity X with temperature (eqs. [2] and [3]) (16).

[2] $$-H_o = X + \log C_{H^+}$$

[3] $$X_T = X_{25^\circ}\left(\frac{298.15}{T}\right)$$

At pH > 10, H_- was calculated from

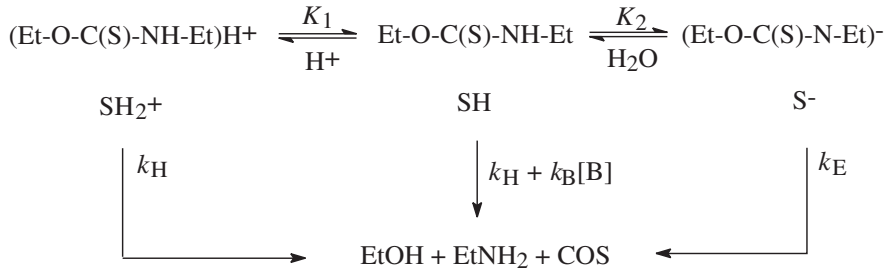
[4] $$H_- = pK_w^{100} + \log[OH^-]$$

where pK_w^{100} = 12.26 (14*b*, 17).

In the 0.05–1.0 mol/L NaOH range at 25 °C, these values are less than 0.1% different from those obtained from the acidity function using thioacetamide as an indicator (13).

The profile was divided into three regions. At pH < 2, $\log k^o_{obs}$ increases with acid concentration by a specific acid catalysis mechanism. In the range of pH 2–6.5, the rate constants were independent of the pH. A specific basic hydroly-

Scheme 1. Kinetic scheme of the hydrolysis of ETE.



sis occurred at pH > 6.5, and the rate constants reached a plateau in the region of pH > 12. The pH–rate profile can be described according to Scheme 1 by eq. [5].

$$[5] \qquad k^{o}_{obs} = k_H \frac{a_{H^+}}{K_1 K'} + \frac{k_N}{K'} + \frac{k_E K_2 [OH^-]}{K_w K'}$$

where

$$K' = \frac{a_{H^+}}{K_1} + 1 + \frac{K_2}{a_{H^+}} \text{ and } a_{H^+} = h_o \text{ when pH} < 2.$$

In Scheme 1, K_1 and K_2 are the acid and reverse base dissociation constants of species SH_2^+ and SH, respectively, k_H is the specific acid hydrolysis rate constant, and k_N and k_E are the rate constants of spontaneous and basic hydrolysis, respectively. Equation [5] assumes that the basic hydrolysis occurs by the E1cb mechanism as will be discussed in the following.

Acid hydrolysis

At HCl concentrations higher than 1 mol/L, the terms due to spontaneous and basic hydrolysis in eq. [5] are very small compared to those of acid hydrolysis because

$$k_H \frac{a_{H^+}}{K_1 K'} >> \frac{k_N}{K'} + \frac{k_E K_2 [OH^-]}{K_w K'}$$

and eq. [5] becomes

$$[6] \qquad k^{o}_{obs} = \frac{k_H h_o}{h_o + K_1}$$

and, when the ester is predominantly protonated, $k^{o}_{obs} = k_H$ at that acidity range.

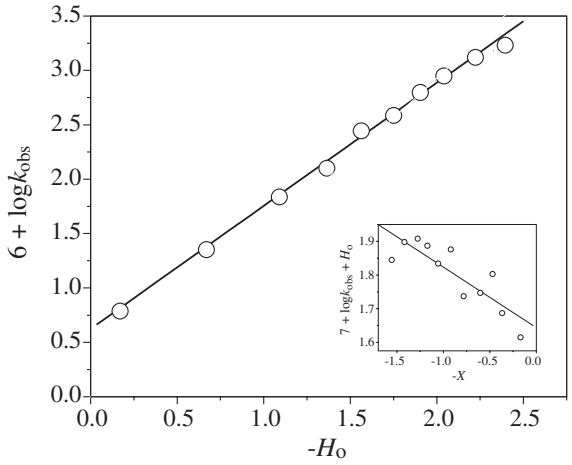
Several plots showed that the acid hydrolysis occurred by the A1 mechanism. The Hammett plot of $\log k_{obs}$ vs. $-H_o$ (Fig. 3) was linear with a slope of 1.14 (r = 0.999), close to the unity value expected by the Zucker–Hammett hypothesis for this mechanism (18).

The pH–rate profile suggests that in the of 1–7 mol/L HCl concentration range, the substrate is unprotonated, and the relevant rate equation is eq. [7] (19)

$$[7] \qquad \log k^{o}_{obs} - \log C_{H^+} = \log \frac{k_o}{k_1} + m^{\ddagger} m^* X$$

where k_o is the medium-independent specific acid catalysis rate constant. The excess acidity assumption is that the term containing the activity coefficient of the transition state $f_{\ddagger}$ is linearly related to the activity coefficient ratio containing the conjugate acid SH_2^+ (20), and that this is linear in X (eq. [8]).

Fig. 3. Hammett plot for the acid hydrolysis of ETE at 100 °C. Insert: Bunnett–Olsen plot.



$$[8] \qquad \log \frac{f_{SH} f_{H^+}}{f_{\ddagger}} = m^{\ddagger} \log \frac{f_{SH} f_{H^+}}{f_{SH_2^+}} = m^{\ddagger} m^* X$$

The excess acidity slope value (m^*) is associated with solvation differences between SH and SH_2^+ (21). For A1 reactions, $m^{\ddagger} > 1$ and the excess acidity plots are linear for A1 mechanisms, while these plots are curved for A2 mechanisms.

The linearity of the excess acidity plot against X of the hydrolysis of ETE in HCl is shown in Fig. 4, where $m^{\ddagger} m^*$ = 1.18, $\log (k_o/K_1)$ = –5.36, and r = 0.996.

We do not know the value of m^* for ETE, but the Bunnett–Olsen plot gave $\phi_{\ddagger}$ = –0.18 (r = 0.854) from eq. [9] for unprotonated substrates (Fig. 3, insert) (22).

$$[9] \qquad \log k^{o}_{obs} + H_o = \left(\log \frac{k_o}{K_1} \right) + \phi_{\ddagger} (H_o + \log C_{H^+})$$

Although the correlation coefficient is lower, the negative slope indicates that SH_2^+, whose structure should be closer to the transition state, is less hydrated than SH as expected for the A1 mechanism. We note that for HCl, $H_o + \log C_{H^+} = -X$, and eq. [9] is equivalent to eq. [7], where $m^{\ddagger} m^* = 1 - \phi_{\ddagger}$, and the value of $\log (k_o/K_1) = -5.36$ is the same as that found in the excess acidity plot.

In Table 1, it can be observed that the activation parameters for the acid hydrolysis at 2.5 mol/L HCl, $\Delta G^{\ddagger} = \Delta H^{\ddagger}$, because $\Delta S^{\ddagger}$ (–1.6 ± 2.2 cal mol^{-1} K^{-1}, 1 cal = 4.184 J) is

Table 1. Activation parameters for the hydrolysis of ETE at 100 °C.

Hydrolysis	Concentration	$\Delta G^{\ddagger}$ (kcal mol^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})
Acid	HCl (2.5 mol/L)	29.5±1.7	28.9±0.9	–1.6±2.2
Water catalysis	pH 5.5	32.8±2.9	22.6±1.4	–27.4±3.8
Basic	NaOH (2.5 mol/L)	26.2±1.6	14.0±0.6	–34.5±1.5
Basic (DETE)	NaOH (2.0 mol/L)	27.7±1.8	21.3±.0.9	–17.2±2.5

Note: Standard state: 1 mol/L, 100 °C.

Fig. 4. Excess acidity plot against X of the hydrolysis of ETE in HCl at 100 °C.

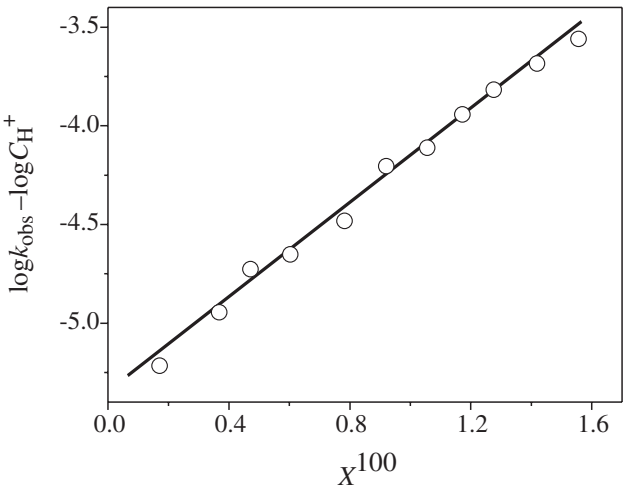
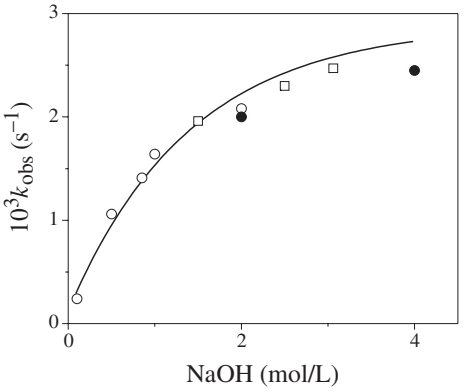


Fig. 5. Basic hydrolysis of ETE at 100 °C. Average from values calculated from the Guggenheim method and assuming absorbance = 0 at t_∞ (○); calculated from the Guggenheim method (□); average calculated from the Guggenheim method at 4 μ (NaCl) (●).



close to zero considering the standard deviation. This value is characteristic of an A1 mechanism (23).

The conjugate acid SH_2^+ should be preferentially N-protonated to produce ethylamine by breaking the N—C bond, and an ethyl thionformyl cation (S=C$^+$-OEt), which hydrolyzes rapidly to produce COS and ethanol.

Basic hydrolysis

At pH > 6.5, the pH–rate profile of ETE presented an increase of the rate constants that reached a plateau at high basicity (Fig. 5).

At high basicity, $K' = 1 + \dfrac{K_2}{a_{H^+}}$

because $1 + \dfrac{K_2}{a_{H^+}} >> \dfrac{a_{H^+}}{K_1}$.

Also $k^{o}_{obs} >> k_N$ and $\dfrac{k_E K_2[OH^-]}{K_w K'} >> k_H \dfrac{a_{H^+}}{K_1 K'} + \dfrac{k_N}{K'}$.

Therefore,

$$[10] \qquad k^{o}_{obs} = \frac{k_E K_2[OH^-]}{K_w + K_2[OH^-]} = \frac{k_E K_2}{a_{H^+} + K_2}$$

The reciprocal plot of $1/k^{o}_{obs}$ vs. $1/[OH^-]$ was linear (r = 0.999) and allowed the calculation of $k_E = 3.79 \times 10^{-3}$ s^{-1} and $pK_2 = -pK_b = 12.43$. At 25 °C the experimental value of pK_2 was 13.6. The difference of 1.2 pK units with temperature is about the same as that found for the *N*-aryl thioncarbamate series (24).

Equation [5] assumed that the specific basic catalysis occurs through the E1cb mechanism, but it is also possible that it occurs by a $B_{Ac}2$ mechanism as shown in Scheme 2. Both have been observed for carbamate esters (25, 26).

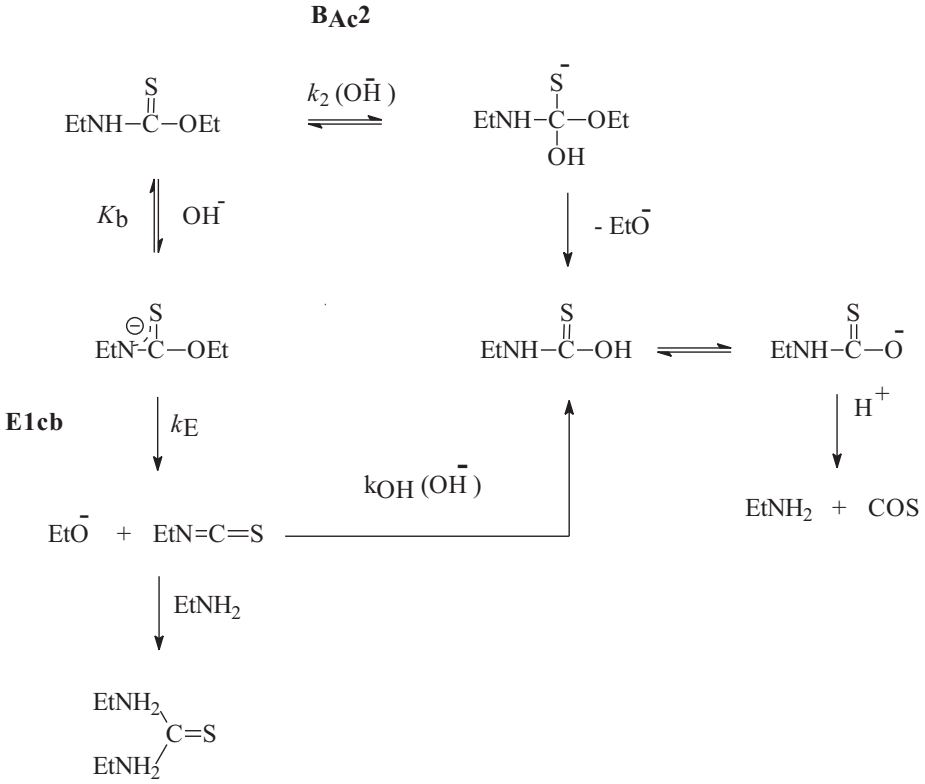
The E1cb mechanism eliminates ethoxide ion from the thioncarbamate anion in the rate-determining step, producing an isothiocyanate intermediate that decomposes rapidly to form ethylamine and COS as products. The $B_{Ac}2$ mechanism produces a tetrahedral intermediate in the slow step, which forms the products through several consecutive fast reactions. Neither of these mechanisms can be kinetically distinguished, as shown by eqs. [11] and [12].

$$[11] \qquad k_{obs} = \frac{k_E K_2}{a_{H^+} + K_2} \text{ (E1cb)}$$

$$[12] \qquad k_{obs} = \frac{k_2 K_w}{a_{H^+} + K_2} \text{ ($B_{Ac}2$)}$$

For ETE, the reciprocal plot from the $B_{Ac}2$ kinetic equation gave $k_2 = 2.58 \times 10^{-3}$ (mol/L)$^{-1}$ s^{-1} and the same pK_2 = 12.43 found from the E1cb equation. To hydrolyze by E1cb mechanism, the substrate must form the conjugate base by ionization of the N—H bond. Therefore, the basic hydrolysis of DETE must occur by the $B_{Ac}2$ mechanism. The hydrolysis rate constant of DETE increased linearly at 1–3 mol/L of NaOH with a second-order rate constant, $k_2 = 2.3 \times 10^{-4}$ (mol/L)$^{-1}$ s^{-1}, i.e., 10 times slower than the value expected for ETE. It has been noted in earlier works that *N*-alkyl carbamate esters hydrolyze more rapidly than *N*,*N*-dialkyl esters (27, 28).

Scheme 2. Mechanisms involved in the basic hydrolysis of ETE at 100 °C.



The alternative of either mechanism depends on the difference of free energy of activation to overpass the kinetic barrier. Comparison of $\Delta G^{\ddagger}$ of DETE and ETE results in a difference of ca. 1 kcal mol^{-1} more favorable to the E1cb path (Table 1). For ETE, the total barrier is divided into two terms: the basic N-H ionization to form the thioncarbamate anion (pK_2 = 13.6, Scheme 1, $\Delta G^{\ddagger}$ = 21.2 kcal mol^{-1}), and the expulsion of the ethoxide anion producing ethyl isothiocyanate ($\Delta G^{\ddagger}$ = 26.2 kcal mol^{-1}). In comparison to the carbamate analogues, the path through the E1cb mechanism of ETE is greatly favored because of the decrease in pK_2 owing to the strong electron-withdrawing effect of the thiocarbonyl group. It corresponds to a pK_a = 24.7 at 100 °C, or 16 pK units higher than ethylamine. This is a reasonable value because, for alkyldithiocarbamates, a decrease in the basicity of the N by 14 pK units with respect to the parent amine was calculated (29).

For the carbamate ester series, it was observed that reactions occurring through the E1cb mechanism were much faster than those ocurring through the $B_{Ac}2$ mechanism (25–27, 30) because of a sharp decrease in $\Delta H^{\ddagger}$ (25–27). The activation parameters of ETE and DETE are also consistent with this observation as shown in Table 1.

One important feature of the E1cb mechanism is the formation of the ethyl isothiocyanate intermediate. Experiments with ETE in 0.6 mol/L of NaOH in the presence of an excess of ethylamine showed the formation of diethyl thiourea (Scheme 2). Diethyl thiourea could only be formed from the isothiocyanate because ethylaminolysis of ethyl *O*-ethylxanthate produced only ethyl *N*-ethylthioncarbamate, and the reaction did not go further (31). Therefore, this result provides strong evidence that the basic hydrolysis occurs by the E1cb mechanism, the same as was found for aryl *N*-arylcarbamates (26), aryl *N*-arylthioncarbamates (32), and ethyl *N*-arylthioncarbamates (24).

The curve of the pH–rate profile in Fig. 2 was drawn using eq. [5], written as eq. [13]

$$[13] \quad k^{o}_{obs} = \frac{k_H}{K_1} a_{H^+} + k_N + \frac{k_E K_2}{a_{H^+} + K_2}$$

where $\log \frac{k_H}{K_1} = -5.36$.

General catalysis

The E1cb mechanism in Scheme 2 involves a fast preequilibrium deprotonation by hydroxide ion followed by a slow elimination of the ethoxide ion. However, for weak bases the deprotonation step is the rate-determining step, followed by a fast elimination reaction. This mechanism leads to general base catalysis.

General base catalysis was observed for ETE in the pH 3–11 range (Table 2) for conjugate bases of oxy acids and ammonium ion. The rate constants increased linearly with increasing concentration of the general base. No catalysis was detected for acetate within the experimental error. For succinate, tetraborate, and carbonate, monoanion and dianion species are present at the experimental pH, and both can act as catalysts. The molar fractions of the monoanions and dianions were considered to calculate the second-order general base catalysis rate constant (k_B).

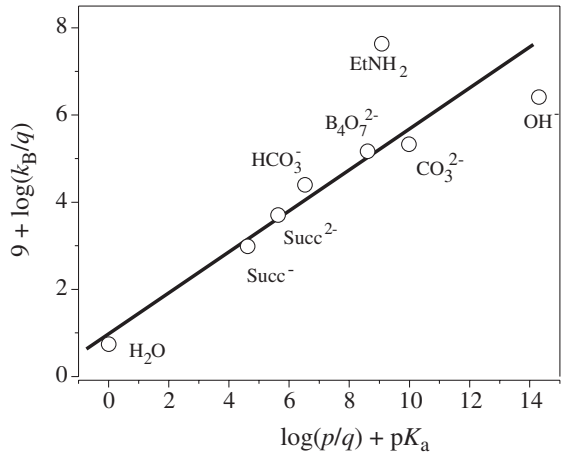
The Brønsted plot of logk_B vs. pK_a, statistically corrected (Fig. 6), gave a straight line for the conjugate bases of oxy acids (without hydroxide ion) with β = 0.48 ± 0.04 (r = 0.989). Ethylamine was about two orders of magnitude more

Table 2. General catalysis of the hydrolysis of ethyl *N*-ethylthioncarbamate at 100 °C.

Acid	Conjugate base	pK_a at 25 °C	pK_a at 100 °C	k_B ((mol/L)$^{-1}$ s^{-1})
Hydron				
H_3O^+	H_2O	(–1.75)	0.0	5.5×10^{-9}[a]
Succinic acid				
$HOOC(CH_2)_2COOH$	$HOOC(CH_2)_2COO^-$	4.21[b]	4.32[c,d,e]	9.75×10^{-7}
	$-OOC(CH_2)_2COO^-$	5.64[b]	5.93[c,d,e]	1.02×10^{-5}
Tetraborate monoanion				
$HB_4O_7^-$	$B_4O_7^{2-}$	9.24[c]	8.91[f]	2.94×10^{-4}
Carbonic acid				
H_2CO_3	HCO_3^-	6.35[b]	6.23[d]	2.50×10^{-5}
	CO_3^{2-}	10.33[c]	10.28[g]	4.27×10^{-4}
Ethylammonium ion				
$CH_3CH_2NH_3+$	$CH_3CH_2NH_2$	10.63[b]	8.60[d,h,i]	4.3×10^{-2}
Water				
H_2O	OH^-	15.74[j]	14.0[g]	2.58×10^{-3}[k]

[a] k_N at 1 mol/L concentration.
[b] V.E. Bower and R.G. Bates. *In* Handbook of analytical chemistry. 1st ed. *Edited by* L. Meites. McGraw Hill, New York. 1963.
[c] R.G. Bates and R. Gary. J. Res. Nat. Bur. Stand. **65A**, 495 (1961).
[d] H.S. Harned and N.D. Embree. J. Am. Chem. Soc. **56**, 1050 (1934).
[e] pK_{a1}: t_m = 46.60, pK_m = 4.185; pK_{a2}: t_m = 22.63, pK_m = 5.638.
[f] Reference 14*a*.
[g] Reference 14*b*.
[h] Reference 11.
[i] Calculated for ethylammonium (pK_m = 5.857, t_m = 334).
[j] H.S. Harned and R.A. Robinson. Trans. Faraday Soc. **36**, 973 (1940).
[k] From eq. [12] assuming a $B_{Ac}2$ mechanism.

Fig. 6. Brønsted plot of the general catalysis of the hydrolysis of methyl *N*-methylthioncarbamate at 100 °C. Without considering ethylamine and hydroxide ion, $\beta = 0.48 \pm 0.04$ ($r = 0.989$).



effective as a catalyst than the corresponding oxy acid, which is to be expected, since it is a better nucleophile toward the thiocarbonyl group. The second-order rate constant k_B for OH^- was calculated assuming the $B_{Ac}2$ mechanism (eq. [12]), and its low value is attributed to the high hydration of the ion (13). Nevertheless, the fast and reversible deprotonation of ETE at 25 °C (see Experimental) showed that the specific basic catalysis must form the ester anion in a fast step at 100 °C, which slowly decomposed to produce ethyl isothiocyanate by the E1cb mechanism.

For the series of carbamate and thioncarbamate esters, only a small general base catalysis was observed for *p*-nitrophenyl *N*-methylcarbamate (30), and no general catalysis was observed for alkyl *N*-arylthioncarbamates (24) or aryl *N*-arylthioncarbamates (32). The slow proton transfer step from ETE is a consequence of the high pK_a (24.7) of the N-H dissociation. For *N*-arylthioncarbamates, the dissociation is ca. 3 pK units more favorable.

Water catalysis

The Brønsted plot showed that water acts as a general base in the pH-independent region of the pH–rate profile, and therefore in that region, k_{obs} can be expressed by eq. [14], where k_N is the water-catalyzed (pseudo-)first-order rate constant, and k_B is the catalytic coefficient of the general bases.

$$[14] \quad k_{obs} = k_N + k_B[B]$$

The value of $k_N = 3.06 \times 10^{-7}$ s^{-1} was obtained from the average of k_{obs} extrapolated to zero buffer concentration in the pH 2–6.5 range. The total molecularity of the reaction is at least two, but the exact value cannot be determined from the kinetic data, since the water concentration remained constant. In the absence of other general bases, the water-catalyzed, pH-independent hydrolysis is the only reaction.

The activation parameters for the water catalysis are shown in Table 1. It is known that water can catalyze a reaction as a nucleophile, a general acid, or a general base. The hydrolysis of activated amides and carboxylic esters are water-catalyzed between pH 2.0 and 5.5 via a dipolar activated complex in which two water molecules, one acting as a nucleophile and one acting as a general base, are involved (33). In carboxylic ester hydrolysis, values of the entropy of activation of –30 to –40 cal mol^{-1} K^{-1} are common (34),

while for primary and secondary halides and sulfonates they are ca. –10 cal mol^{-1} K^{-1} (35). For reactions where the nucleophilic attack of water on a thiocarbonyl is catalyzed by a second molecule of water, the entropy of activation is in the –40 to –25 cal mol^{-1} K^{-1} range (36). The value of the entropy of activation (–27.3 cal mol^{-1} K^{-1}) for the water catalysis of ETE is consistent with the postulated mechanism, considering the lack of examples where water catalyzes a reaction exclusively as a general base. The large value of β = 0.48 obtained from the Brønsted plot suggests that the transition state is highly polar resulting in electrostriction of the bulk solvent, inducing a number of water molecules to be tightly constrained, which results in a large negative entropy of activation.

Conclusions

The acid hydrolysis of ETE at 100 °C occurs through an A1 mechanism, most likely with N-protonation and formation of ethylamine by N—C bond breakage, and an ethyl thionformyl cation ($S=C^{+}$-OEt) that hydrolyzes rapidly to produce COS and ethanol.

At pH 2–6.5, where the main species is the neutral substrate, the hydrolysis is pH-independent and is catalyzed by water as a general base. General bases catalyze the slow proton transfer from the neutral species to form an isothiocyanate intermediate.

The ETE anion hydrolyzes with specific basic catalysis by E1cb mechanism, forming ethyl isothiocyanate in the rate-determining step, which decomposes rapidly to products.

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