BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 52 (7), 2171—2172 (1979)

Kinetics of the Aminolysis of α-Chloropropionic Acid. Reactivity of Aliphatic Amines[1)]

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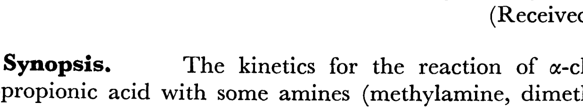
(Received January 31, 1979)

Synopsis. The kinetics for the reaction of α-chloropropionic acid with some amines (methylamine, dimethylamine, trimethylamine, ethylamine, and diethylamine) and ammonia have been studied in an aqueous solution. The reactivity of amines is discussed on the basis of the Swain-Scott and Taft equations.

The steric as well as polar effect was found to be important in the reaction of ammonia, alanine, and α,α′-iminodipropionic acid with α-chloropropionic acid.[2)] Hall Jr.[3)] reported that the data for the reaction of 30 amines with 15 substrates including chloroacetic acid are correlated by the Swain-Scott equation. We have studied the rate of the reaction of some amines with α-chloropropionic acid (CPA), forming *N*-alkylated alanine.

Discussion is given on the reactivity of amines on the basis of the Swain-Scott[4)] and Taft equations.[5)]

Results and Discussion



$$CH_3CHClCO_2H + R^1R^2R^3N \xrightarrow[-Cl^-]{\text{in } H_2O} \underset{\underset{R^1\,R^2\,R^3}{N^+}}{CH_3CHCO_2H} + \underset{OH}{CH_3CHCO_2H} \quad (1)$$

	2a	2b	2c	2d	2e	2f
R^1	H	Me	Me	Me	Et	Et
R^2	H	H	Me	Me	H	Et
R^3	H	H	H	Me	H	H

Aminolysis was conducted at 60 °C in an aqueous solution and the chloride ion produced was measured in order to follow the rate of reaction. The pseudo-first-order rate constants (k_{obsd}) were measured at various concentrations of amines. The plot of the pseudo-first-order rate constants against the initial concentrations of amines gives a straight line with an intercept. The rate equation fits the equation,

$$\frac{d}{dt}[Cl^-] = (k_1 + k_2[\text{Amine}]_{ex})[CPA]. \quad (2)$$

Where $[\text{Amine}]_{ex}$ is the excess concentration of amine to that of α-chloropropionic acid, *i.e.*, effective amine concentration. Rate constants, k_1 and k_2, evaluated from the intercept of the plot and the slope, are given in Table 1.

Independent experiments for pure hydrolysis of CPA were carried out. The first- and second-order rate constants thus obtained for the hydrolysis of CPA are $0.35\times10^{-5}\,s^{-1}$ (S_N1) and $0.76\times10^{-5}\,s^{-1}\,M^{-1}$ (S_N2), respectively (60 °C).

Thus, in the case of methylamine (**2b**), dimethylamine (**2c**), trimethylamine (**2d**), and ethylamine (**2e**), the hydrolysis is negligible, the rate equation being of second-order: $v=k_2[\text{Amine}]_{ex}[CPA]$.

In order to examine the effect of substituent on amines, Taft equations[5)] with $\log k_{2rel}=\rho_\sigma E_\sigma+\delta E_s$ and $\log k_{2rel}=\rho^*\sigma^*$ were applied, where k_{2rel} is the relative rate constant. The former equation including a steric term, δE_s, gave poor correlation (ρ_σ ranging −2.50—59.5 and δ ranging −58.1—2.76), and we could not determine values of ρ_σ and δ, whereas the latter equation including only a polar term gave ρ^* value of −1.8 from the plot of $\log k_{2rel}$ against $\sum\sigma^*$ (summation of Taft polar substituent constants), except **2d** and **2f** (Fig. 1). In other words, electron-releasing groups promote the reaction. This is expected from the nucleophilic nature of amines, but the steric effect becomes important for the reaction of **2d** and **2f.**

The Swain-Scott equation[4)] is given by

$$\log (k/k_0) = sn \quad (3)$$

where s is the sensitivity to nucleophiles and n is the nucleophilic parameter. The plot of $\log k_2$ against n gave a straight line except for **2d** and **2f**. The s value of 1.05 was obtained for the reaction of CPA

TABLE 1. RATE CONSTANTS FOR THE REACTION OF α-CHLOROPROPIONIC AND CHLOROACETIC ACIDS WITH AMINES $R^1R^2R^3N$ IN AN AQUEOUS SOLUTION

	R^1	R^2	R^3	$CH_3CHClCO_2H$ (60 °C)		$ClCH_2CO_2H$ (25 °C)[6)]	$n^{a)}$
				$k_1\times10^{-5}\,s^{-1}$	$k_2\times10^{-5}\,s^{-1}\,M^{-1}$	$k_2\times10^{-5}\,s^{-1}\,M^{-1}$	
2a	H	H	H	0.67	0.97	0.633	4.13
2b	Me	H	H	0.00	10.0	11.5	5.18
2c	Me	Me	H	0.00	43.0	47.0	5.63
2d	Me	Me	Me	0.00	12.1	58.3	5.98
2e	Et	H	H	0.00	8.0	7.0	5.03
2f	Et	Et	H	0.40	1.5	5.0	4.83

a) *n*-Values are the average of the caluculated values from Ref. 3.

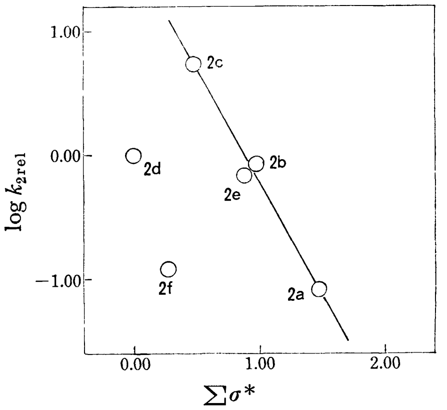


Fig. 1. Plot of $k_{2\mathrm{rel}}$ against $\sum\sigma^*$ for the reaction of α-chloropropionic acid with some amines in an aqueous solution at 60 °C.

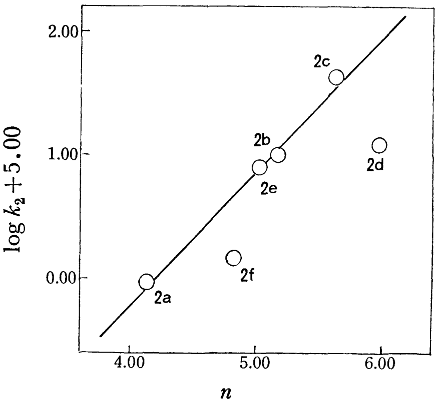


Fig. 2. Swain-Scott plot for the reaction of α-chloropropionic acid with some amines in an aqueous solution at 60 °C.

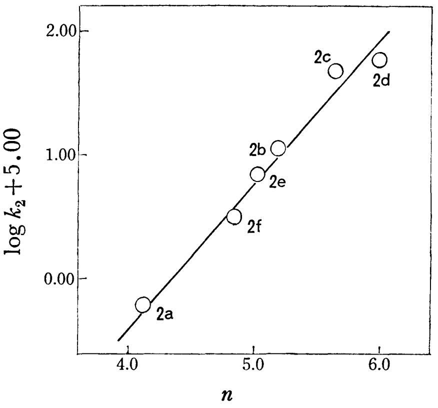


Fig. 3. Swain-Scott plot for the reaction of chloroacetic acid with some amines in an aqueous solution at 25 °C.

with some amines. Deviation from the straight line is larger with CPA (Fig. 2) than with chloroacetic acid (Fig. 3, s=1.2), especially with **2d** and **2f**. Since **2d** is tertiary and **2f** is secondary, the deviation may be due to the steric hindrance in the transition state. In aminolysis of phenethyl nitrite,7) successive substitution of hydrogen by the methyl group in NH_3 leading to Me_3N always increases the relative rate, whereas in the reactions with CPA bearing α-methyl group, there is more interaction between substituent of amines than in those with chloroacetic acid or phenethyl nitrite, so that steric requirement decreases not only the reactivity of trimethylamine but also that of diethylamine.

Experimental

Materials. α-Chloropropionic acid bp 92—93 °C/15 Torr (lit,8) 82.5—83.5 °C/12 Torr), aqueous 40% methylamine, 50% dimethylamine, 50% trimethylamine, 70% ethylamine, and 28% ammonia, and diethylamine of guaranteed reagent grade were used.

Kinetics. A solution of α-chloropropionic acid (1 M, 5 ml) was added to an aqueous solution of amines (1.2—3.5 M, 45 ml) in a glass-stoppered flask, which had attained thermal equilibrium at 60±0.1 °C in a thermostat. Aliquots (5 ml) were pipetted out at regular intervals and cold dil. HNO_3 was added to stop the reaction. The chloride ion concentration was determined by the Volhard method.9) The pseudo-first-order rate was measured up to 30—60% conversion.

Products. NMR spectra were recorded on a Hitachi R-24B spectrometer. Under the kinetics conditions, the main product was *N*-alkylated alanine. On the basis of NMR spectra, the reaction products of α-chloropropionic acid with ammonia were found to be a mixture of alanine and lactic acid, and the products from diethylamine a mixture of *N*,*N*-diethyl alanine and lactic acid. They were produced by competitive aminolysis and hydrolysis, respectively. On the other hand, no lactic acid was detected in the case of the other amines.

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