The Reaction of *N*-Chlorocarbamoylethyl Starch with Amines in an Aqueous Alkaline Medium; Reactions of An Isocyanate Group[1)]

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The reactions of *N*-chlorocarbamoylethyl starch with simple monoamines were investigated in order to elucidate the mechanism of the reaction of an isocyanate group with amines in an aqueous alkaline medium. It was confirmed that the *N*-chloroamide group reacts with amines through the formation of an isocyanate group. The reactions of the isocyanate with amines in the presence of sodium hydroxide obeyed the following equation: (rate of isocyanate–amine reaction)/(rate of isocyanate–OH^- reaction) $= k_u[\text{amine}]/k_a[OH^-]$ showing no catalytic effects of reactants or products. The reactivities of most of the primary amino groups attached to primary carbon with the isocyanate are comparable to that of the hydroxide ion. The relative rates of the reactions of amines with the isocyanate are not always correlated to their basicities, even when differences in steric hindrance are not great. Both the enthalpy and entropy of activation for the isocyanate–amine reactions are smaller than those for the isocyanate–OH^- reaction.

Polymers bearing *N*-chloroamide groups are of interest because of the variety of reactions of the *N*-chloroamide groups. It is well known that *N*-haloamides in acid form (RCONHX) react as oxidizing agents or as halogenating agents,[2)] and that, in salt form or in ionized form ($RCONX^-$), they produce isocyanate groups through the Hofmann rearrangement.[3)]

The *N*-chlorocarbamoylethyl derivatives of polysaccharides can be readily synthesized and have some possibilities of practical use. With regard to the utilization of these derivatives, it may be most promising to exploit the reactions of the isocyanate group which is formed through the Hofmann rearrangement of the *N*-chloroamide group, leading to the syntheses of novel derivatives of polysaccharides.

On the reactions of isocyanates with active hydrogen compounds, although numerous papers have been published[4)] and some papers have dealt with the reaction of water with isocyanates, nothing is yet known concerning the reactions of isocyanates in aqueous medium. Therefore, the reactions of *N*-chlorocarbamoylethyl starch with amines were investigated in an attempt to elucidate the mechanism of the reaction of the isocyanate group with amines in an aqueous alkaline medium.

Results and Discussion

Course of the Reaction of the N-*chloroamide Group with Amines.* First, as it was possible that the *N*-chloroamide would not always react with amines only through the formation of the isocyanate group, the effects of amines on the rate of decomposition of the *N*-chloroamide and the material balance in the reaction were investigated in order to make the course of the reaction clear.

It is well known that the rate of the Hofmann rearrangement of *N*-chloroamides obeys a first-order equation:[5)]

$$-d[RCONCl^-]/dt = k[RCONCl^-] \qquad (1)$$

All the runs for various combinations of *N*-chlorocarbamoylethyl starch with amines employed in this study followed Eq. (1), and the concentration of the amines had no effect on the rate of the decomposition of *N*-chloroamide above pH 11.

The rate constants and energies of activation for the decomposition of *N*-chloroamide in the presence of amines were almost identical with those for the *N*-chloroamide–NaOH system, a typical case of Hofmann rearrangement.

Table 1 shows the material balance in the reaction of *N*-chlorocarbamoylethyl starch with methylamine. The amount of the *N*-chloroamide group decomposed is in agreement with the increase in the nitrogen content of the starch derivative and with half of the amount of methylamine consumed. This result is in accord with the following reaction sequence:

$$\begin{aligned}
&RCONHCl + R'NH_2 \xrightarrow{\text{instantaneous}} (RCONCl)^-(R'NH_3)^+ \\
&(RCONCl)^-(R'NH_3)^+ \xrightarrow{\text{slow}} RN{=}C{=}O + R'NH_3{}^+Cl^- \\
&RN{=}C{=}O + R'NH_2 \xrightarrow{\text{very fast}} RNHCONHR' \qquad (2)
\end{aligned}$$

The results on other amine–*N*-chloroamide systems were essentially identical with this.

From the facts discussed above, it may be concluded that the *N*-chloroamide reacts with amines through the formation of an isocyanate, and that any side reactions are negligible in these systems.

TABLE 1. MATERIAL BALANCE IN THE REACTION OF *N*-CHLOROCARBAMOYLETHYL STARCH WITH METHYLAMINE[a)]

Reaction time (min)	Relative[b)] amount of *N*-chloroamide decomposed	Relative[c)] amount of amine consumed	Relative[d)] increase in nitrogen content
10	0.156	0.310	0.155
30	0.398	0.795	0.400
60	0.637	1.277	0.635
100	0.815	1.634	0.813
210	0.971	1.940	0.970
420	1.00	2.01	0.997

a) Initial concentrations: *N*-chloroamide 0.05 mol/l, methylamine 0.35 mol/l, temperature: 45 °C. b, c, and d) On the basis of the initial amount of the *N*-chloroamide group. d) Nitrogen content: Nitrogen content of the starch derivative obtained.

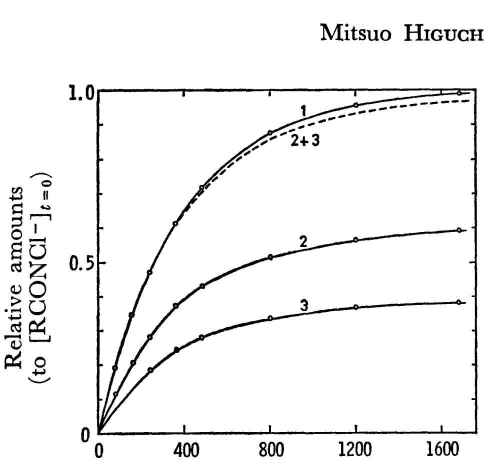

Fig. 1. A typical case of the reaction course in *N*-chloroamide-amine-NaOH system.
[*N*-chloroamide]$_{t=0}$: 0.05 mol/l, [Methylamine]$_{t=0}$: 0.2 mol/l, [NaOH]$_{t=0}$: 0.2 mol/l, temp: 30 °C.
1: Amount of the *N*-chloroamide group decomposed.
2: Amount of the urea derivative formed (evaluated from the increase in nitrogen content of the starch derivative).
3: Amount of the aminoethyl group formed.

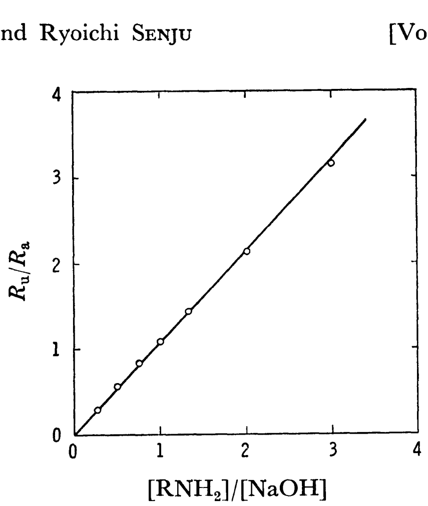

Fig. 2. Relation between R_u/R_a and [RNH$_2$]/NaOH]. [*N*-chloroamide]$_{t=0}$: 0.02 mol/l, [Ethylamine]: 0.125—0.5 mol/l, [NaOH]: 0.125—0.5 mol/l, temp: 30 °C.

Reaction of the Isocyanate Group with Amines in the Presence of Sodium Hydroxide. As can be seen from the results shown in Table 1, in the absence of caustic alkalies almost all of the reaction products consisted of the corresponding urea derivatives when more than a four-∼fivefold excess of amines was employed. This fact indicates that the reactivity of H_2O with the isocyanate group is negligible in comparison with those of amines.

In the presence of sodium hydroxide, however, a considerable amount of the aminoethyl group was produced. Figure 1 shows a typical case of the reaction course. The sum of the amounts of the aminoethyl group and the urea derivative (evaluated from the increase in nitrogen content of the starch derivative) is in good agreement with the amount of the *N*-chloroamide decomposed, though a slight discrepancy appears in the late stage of the reaction. This discrepancy was significant when the concentration of amines was too low or when the reactivities of amines were too low, as in the cases of aniline and *tert*-butylamine. This may be attributed to the formation of an intramolecular urea derivative, *i. e.*, the product of the reaction of the isocyanate group with the aminoethyl group formed by the Hofmann degradation.

The relative rate of the isocyanate–amine reaction to the isocyanate–OH$^-$ reaction, R_u/R_a, can be readily calculated from the ratio of the amount of the urea derivative to that of the aminoethyl group formed.

As Fig. 2 shows, a linear relationship was observed between R_u/R_a and [Amine]/[NaOH] when the concentrations of amine and sodium hydroxide were not too low or not too high. This result indicates that the catalytic effects of reactants or products, which have often been observed in the reactions of isocyanates in some nonaqueous media,[4] are absent in this isocyanate–amine–NaOH system, and that the reactions obey simple second-order kinetics;

$$\mathrm{d[Urea\ derivative]}/\mathrm{d}t = k_u\mathrm{[Isocyanate][Amine]} \tag{3}$$

$$\mathrm{d[Aminoethyl\ group]}/\mathrm{d}t = k_a\mathrm{[Isocyanate][OH^-]} \tag{4}$$

$$\frac{\mathrm{d[Urea\ derivative]}/\mathrm{d}t}{\mathrm{d[Aminoethyl\ group]}/\mathrm{d}t} = \frac{R_u}{R_a} = \frac{k_u}{k_a}\frac{\mathrm{[Amine]}}{\mathrm{[OH^-]}} \tag{5}$$

The k_u/k_a ratio represents the relative reactivity of amine to the hydroxide ion in the reaction with the isocyanate.

The Arrhenius plots of k_u/k_a are shown in Fig. 3. The energies of activation for the isocyanate–amine reactions are smaller than that for the isocyanate–OH$^-$ reaction.

Relative Reactivities of Amines. The rate constant ratios, k_u/k_a, at 30 °C and the derived activation parameters are summarized in Table 2. The relative reactivities of primary amines are in this order: amino groups attached to primary carbon>attached to secondary carbon>attached to tertiary carbon; this result is in agreement with the order in the extent of steric hindrance. It is noteworthy that the reactivities of most of the primary amino groups attached to primary carbon are comparable to that of the hydroxide ion, and that the

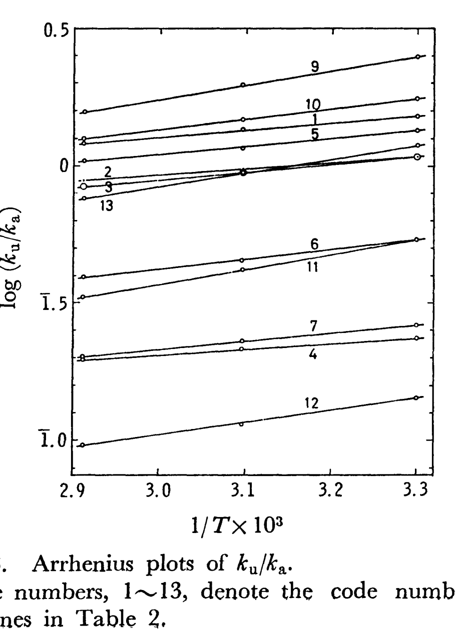

Fig. 3. Arrhenius plots of k_u/k_a.
The numbers, 1∼13, denote the code numbers for amines in Table 2.

TABLE 2. RELATIVE REACTIVITIES OF AMINES IN THE REACTION WITH THE ISOCYANATE GROUP

Amine	pK_a	k_u/k_a (30 °C)	$\Delta\Delta H^{\neq}$ a) (kcal/mol)	$\Delta\Delta S^{\neq}$ b) (cal/deg·mol)
1 Methylamine	10.62c)	1.54	-1.21 ± 0.1	-3.1 ± 0.3
2 Ethylamine	10.63c)	1.07	-1.09 ± 0.1	-3.5 ± 0.3
3 *n*-Propylamine	10.53c)	1.07	-1.33 ± 0.1	-4.2 ± 0.3
4 Isopropylamine	10.63c)	0.47	-0.94 ± 0.2	-4.7 ± 0.6
5 *n*-Butylamine	10.62c)	1.35	-1.55 ± 0.2	-4.5 ± 0.6
6 Isobutylamine	10.43c)	1.09	-1.63 ± 0.2	-5.2 ± 0.6
7 *sec*-Butylamine	10.56c)	0.52	-1.36 ± 0.1	-5.8 ± 0.3
8 *tert*-Butylamine	10.45c)	0.04		
9 Dimethylamine	10.87c)	2.52	-2.42 ± 0.1	-6.1 ± 0.3
10 Diethylamine	10.98c)	1.73	-1.68 ± 0.1	-4.5 ± 0.3
11 Ethyl aminoethyl ether	9.89	0.52	-2.48 ± 0.1	-9.5 ± 0.3
12 Ammonia	9.21c)	0.14	-2.10 ± 0.3	-10.8 ± 0.9
13 Benzylamine	9.34c)	1.19	-2.36 ± 0.1	-7.4 ± 0.3
14 Aniline	4.6c)	<0.01		

a) Calculated from the slopes of the lines for Arrhenius plots of k_u/k_a (Fig. 3). $\Delta\Delta H^{\neq}=\Delta H_u^{\neq}-\Delta H_a^{\neq}=E_u-E_a$. b) $\Delta\Delta S^{\neq}=\Delta S_u^{\neq}-\Delta S_a^{\neq}=2.303\,R\,\log\,(k_u/k_a)+\Delta\Delta H^{\neq}/T$. c) Taken from the paper of H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1957).

relative reactivities of amines are not always in agreement with the concept, accepted for the reactions in some nonaqueous media, that the more basic amines react faster when the differences in steric hindrance are not great.

The negative values of $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ suggest that the hydration of the reactants plays an important role in the reaction of the isocyanate group with amines in aqueous alkaline media. It is conceivable that, in forming the transition-state complex with the isocyanate, the hydroxide ion requires a larger energy than amines do because of the greater extent of hydration, in spite of its greater basicity. The larger value of the entropy of activation for the isocyanate–OH^- reaction in comparison with those for the isocyanate–amine reactions may be attributed to the larger amount of the water molecule released on the formation of the transition-state complex. Differences in the extent of hydration of amines may also be reflected in their relative reactivities.

Experimental

Materials. Carbamoylethyl starch was prepared by means of a Michael reaction of acrylamide with corn starch; the degree of substitution was 0.9.[6]

Amines purchased from commercial sources were purified by distillation under a N_2 atmosphere. Ethyl aminoethyl ether (a model for the aminoethyl group attached to polysaccharide) was prepared by means of the Hofmann degradation of ethyl carbamoylethyl ether; $C_2H_5OC_2H_4NH_2=89$, bp 108.5 °C.

Reaction Procedure. The chlorination of carbamoylethyl starch was carried out under these conditions: amide group concentration: 0.2 mol/l; sodium hypochlorite concentration: 0.22 mol/l; temperature: 0 °C, and reaction time: 7 hr. The degree of *N*-chlorination was 99% on the basis of the amide group. After this process, acetone was added to the reaction mixture (1 vol%) in order to eliminate the excess hypochlorite.[7] After 10 hr the solution was neutralized to pH 5.5 with dilute HCl and diluted to 0.1 mol/l on the basis of the *N*-chloroamide group.

Adequate portions of this solution and an amine solution and/or a NaOH solution were mixed under cooling with ice-water, and 15-ml portions of the mixture were enclosed in 20-ml Pyrex ampoules. The ampoules were immersed in a constant-temperature bath under vigorous shaking for the desired times, then cooled with ice–water and subjected to analysis.

Analytical Methods. The *N*-chloroamide group was analyzed by iodometry. The nitrogen contents of the starch derivatives were determined by the following procedure.

A 10-ml portion of the reaction mixture was pipetted out and transferred into a 200-ml beaker containing 50 ml of methanol, 100 ml of acetone, and 1 ml of acetic acid. The mixture was then agitated by a magnetic stirrer until the starch derivative had been precipitated completely. Then the supernatant liquid was removed, and the precipitate was redissolved with 10 ml of a 1 M acetic acid aqueous solution and reprecipitated by the addition of 100 ml of acetone. After the completion of the precipitation, the supernatant liquid was removed and the precipitate was washed with ethanol and dissolved with 30 ml of 20% sulfuric acid and then subjected to Kjeldahl analysis. The complete precipitation of starch derivatives and the complete removal of the unreacted amine were confirmed by testing the samples of zero reaction time.

The amino-group contents of the starch derivatives were determined by colloid titration;[8] a 2-ml (or 5-ml) portion of the reaction mixture was pipetted out, put into 150 ml of 0.1 M acetic acid aqueous solution, and then titrated with a M/400 potassium polyvinyl sulfate solution, using toluidine blue as an indicator.

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6) A 0.9 mol of the amide group/162 g of starch.

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