

## THE REACTIVITY OF ISOTHIOCYANATES CONTAINING A SULPHUR ATOM IN ADDITION TO THAT IN THE FUNCTIONAL GROUP

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The paper describes spectrophotometric determination of rate constants of the addition of glycine, thioglycolic acid and  $\text{OH}^-$  ions to seven series of isothiocyanates, containing a sulphur atom besides that present in the functional group. The effect is discussed of various groups on the electrophilic character of carbon in the NCS group, and, consequently, on the reactivity of the individual isothiocyanates toward the above-mentioned nucleophilic agents.

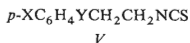
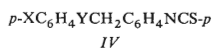
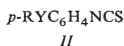
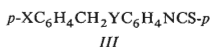
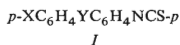
Reactions of isothiocyanates suggest a strongly electrophilic character of the carbon atom in the NCS group<sup>1-3</sup>, which is the cause of its reactivity with nucleophilic agents (reaction type  $\text{Ad}_\text{N}$ ). From the viewpoint of biological action, three types of addition reactions of isothiocyanates are important: the addition of amino groups, sulphhydryl groups and  $\text{OH}^-$  ions. A quantitative study of the reaction of isothiocyanates with these nucleophilic agents (glycine, thioglycolic acid,  $\text{OH}^-$  ion) has been made possible by the use of a sensitive spectrophotometric method. The three types of addition have been found to be bimolecular,  $\text{Ad}_\text{N}$ , and, under the given conditions, first-order reactions.

In the reaction of isothiocyanates with  $\text{OH}^-$  ions the apparent rate constants  $k'$  are linear functions of the concentration of hydroxyl ions if  $[\text{OH}^-] \gg [\text{RNCS}]$ . The choice of experimental conditions for investigating the reactions of isothiocyanate with glycine and thioglycolic acid was guided by the fact that the reaction rate is a linear function of the concentration of isothiocyanate as well as glycine or thioglycolic acid, and is strongly pH-dependent, because the amino acid reacts in its basic form whereas thioglycolic acid in the form  $(^-)\text{SCH}_2\text{-COOH}$ .

A complicating circumstance in following the rates of these two addition reactions is the fact that in a buffered medium with a higher concentration of  $\text{OH}^-$  ions there also proceeds a side reaction of isothiocyanate with hydroxyl ions. Consequently, the spectrophotometric measurement of the formation of an N-substituted thiocarbamoylmercaptoacetic acid (in the reaction with thioglycolic acid) or an N-substituted thiocarbamoylaminoacetic acid (in the reaction with glycine) includes the possible formation of monothiocarbamate. To simplify the calculation of rate constants we have introduced the assumption that the concentrations of the amino acid, mercaptoacetic acid and hydroxyl ions are constant throughout the course of the measurement.

Our previous paper<sup>4</sup> dealt with the reactivity of isothiocyanates of conjugated, conductive systems. The present communication treats the nucleophilic addition reactions of isothiocyanates with glycine, thioglycolic acid and hydroxyl ions.

The following series of isothiocyanates were employed:



Y = S, SO<sub>2</sub>

In series *I* we investigated the effect of a substituent at position 4 on the reactivity of the NCS group in isothiocyanates derived from diphenyl sulphide and diphenyl sulphone. As can be seen from the rate constants (Table I) the reaction rate increased with the increasing electron-withdrawing power of the substituent, whereas electron-releasing substituents retarded the reactions. These observations accord with the idea that the reaction under study is a nucleophilic addition to the carbon atom of the NCS group. Comparison of the individual rates of the reactions of isothiocyanates *I* with the three nucleophilic agents reveals that the addition of thioglycolic acid is orders of magnitude faster than the addition of glycine or hydroxyl ions, in agreement with the much stronger nucleophilic character of thioglycolic acid.

In the diphenyl-sulphide series the effect of a substituent on the reaction rate was estimated by means of a linear correlation of  $\log k$  with the  $\sigma_p$  constants of the substituents. The correlation coefficients ( $r_{\text{NH}_2} = 0.948$ ,  $r_{\text{OH}^-} = 0.973$ ,  $r_{\text{SH}} = 0.950$ ) suggest a good linearity of the relation of  $\log k$  to  $\sigma_p$ .

Table I further shows that the reactions of the NCS group with hydroxyl ions and with thioglycolic acid were faster in the case of diphenylsulphones, which is due to the electron-withdrawing effect of the SO<sub>2</sub> group, increasing the electron deficit on the carbon of the NCS group.

Comparison of the series of (*p*-isothiocyanatophenyl)alkyl sulphides and sulphones reveals that the addition of hydroxyl ions and sulphhydryl ions to the former (Table I) is controlled by the electron-releasing character of sulphur and the concerted +I effect of the bound alkyl groups, which somewhat reduces the electron density on the carbon in the NCS group. With the sulphones the addition rate of hydroxyl ions is an order of magnitude higher, owing to the strong -I effect of the SO<sub>2</sub> group. In the case of longer alkyls (n-octyl and n-decyl) the measured rates are substantially lower in either series of isothiocyanates, which is probably due to steric proximity of the terminal methyl to the NCS group.

With the isothiocyanate series *III* and *IV* the rate constants of the additions of thioglycolic acid and hydroxyl ions were practically equal, which indicates that the reaction rate is not influenced by the electron effects of the substituents. Similar results

TABLE I

Rate Constants of the Additions of Glycine ( $k_A$ ), Thioglycolic Acid ( $k_B$ ) and Hydroxyl Ions ( $k_{OH^-}$ ) to Isothiocyanates I–V at  $25 \pm 0.2^\circ\text{C}$

The dimension of the constants is  $\text{l mol}^{-1} \text{min}^{-1}$ .

X	Y	$k_A$	$k_B \cdot 10^4$	$k_{OH^-}$
Series I				
H	S	$31.06 \pm 0.48$	$2.75 \pm 0.27$	$11.99 \pm 0.02$
CH <sub>3</sub>	S	$27.82 \pm 0.50$	$5.05 \pm 0.20$	$11.98 \pm 0.03$
Cl	S	$38.08 \pm 0.51$	$4.66 \pm 0.70$	$14.37 \pm 1.15$
NO <sub>2</sub>	S	$42.37 \pm 0.60$	$6.31 \pm 0.42$	$23.33 \pm 0.45$
N(CH <sub>3</sub> ) <sub>2</sub>	S	$29.97 \pm 0.58$	$3.16 \pm 0.58$	$9.22 \pm 0.33$
Br	S	$37.76 \pm 1.56$	$5.09 \pm 0.30$	$17.07 \pm 0.45$
H	SO <sub>2</sub>	$40.67 \pm 0.50$	$10.20 \pm 0.05$	$91.63 \pm 1.04$
CH <sub>3</sub>	SO <sub>2</sub>	$38.56 \pm 0.46$	$18.55 \pm 0.97$	$86.34 \pm 1.05$
N(CH <sub>3</sub> ) <sub>2</sub>	SO <sub>2</sub>	$36.50 \pm 0.30$	$11.91 \pm 0.45$	$10.42 \pm 0.52$
NO <sub>2</sub>	SO <sub>2</sub>	$75.90 \pm 0.50$	$43.97 \pm 0.75$	—
NCS	SO <sub>2</sub>	—	$27.95 \pm 1.35$	$114.34 \pm 0.76$
Series II				
R				
CH <sub>3</sub>	S	—	$6.36 \pm 0.40$	$7.38 \pm 0.13$
C <sub>2</sub> H <sub>5</sub>	S	—	$6.15 \pm 0.50$	$10.63 \pm 0.57$
i-C <sub>3</sub> H <sub>7</sub>	S	—	$5.69 \pm 0.40$	$7.10 \pm 0.62$
n-C <sub>4</sub> H <sub>9</sub>	S	—	$5.80 \pm 0.30$	$9.06 \pm 0.85$
n-C <sub>6</sub> H <sub>11</sub>	S	—	$0.99 \pm 0.075$	$9.04 \pm 0.67$
n-C <sub>8</sub> H <sub>13</sub>	S	—	$0.80 \pm 0.03$	$5.14 \pm 0.34$
n-C <sub>10</sub> H <sub>15</sub>	S	—	$0.78 \pm 0.02$	$3.18 \pm 0.30$
CH <sub>3</sub>	SO <sub>2</sub>	—	$11.0 \pm 0.50$	$108.80 \pm 4.5$
C <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub>	—	$28.7 \pm 1.30$	$111.50 \pm 2.5$
i-C <sub>3</sub> H <sub>7</sub>	SO <sub>2</sub>	—	$15.95 \pm 0.85$	$122.20 \pm 4.3$
n-C <sub>4</sub> H <sub>9</sub>	SO <sub>2</sub>	—	$16.90 \pm 1.30$	$123.0 \pm 4.8$
n-C <sub>6</sub> H <sub>11</sub>	SO <sub>2</sub>	—	$27.30 \pm 1.70$	$106.50 \pm 1.0$
n-C <sub>8</sub> H <sub>13</sub>	SO <sub>2</sub>	—	—	$7.23 \pm 0.70$
n-C <sub>10</sub> H <sub>15</sub>	SO <sub>2</sub>	—	—	$1.76 \pm 0.19$
Series III				
H	S	$15.51 \pm 0.26$	$1.06 \pm 0.05$	$6.97 \pm 0.60$
Cl	S	$16.71 \pm 1.88$	$1.42 \pm 0.04$	$6.73 \pm 0.20$
Br	S	$15.26 \pm 0.34$	$1.73 \pm 0.32$	$6.48 \pm 0.05$
CH <sub>3</sub>	S	$12.82 \pm 2.94$	$1.38 \pm 0.27$	$8.95 \pm 0.84$
H	SO <sub>2</sub>	$17.44 \pm 0.07$	$20.01 \pm 1.09$	$13.50 \pm 0.50$
Cl	SO <sub>2</sub>	$17.23 \pm 0.10$	$38.55 \pm 0.92$	$13.86 \pm 0.48$
Br	SO <sub>2</sub>	$17.78 \pm 1.04$	$39.90 \pm 1.05$	$10.52 \pm 0.60$
CH <sub>3</sub>	SO <sub>2</sub>	$18.97 \pm 0.50$	$52.50 \pm 1.04$	$11.60 \pm 0.15$

TABLE I  
 (Continued)

X	Y	$k_A$	$k_B \cdot 10^4$	$k_{OH^-}$
Series IV				
H	S	—	$5.72 \pm 0.35$	$10.97 \pm 0.02$
CH <sub>3</sub>	S	—	$2.69 \pm 0.11$	$9.49 \pm 0.82$
NCS	S	—	$14.30 \pm 0.50$	$19.16 \pm 0.38$
H	SO <sub>2</sub>	—	$13.75 \pm 0.15$	$89.23 \pm 0.72$
CH <sub>3</sub>	SO <sub>2</sub>	—	$11.97 \pm 2.42$	$77.38 \pm 0.25$
NCS	SO <sub>2</sub>	—	$67.20 \pm 2.50$	$107.67 \pm 0.50$
Series V				
H	S	$7.01 \pm 0.05$	$1.77 \pm 0.09$	$8.22 \pm 0.52$
Cl	S	$5.51 \pm 0.25$	$1.70 \pm 0.02$	$7.59 \pm 0.19$
C <sub>2</sub> H <sub>5</sub> O	S	$9.81 \pm 0.75$	$1.66 \pm 0.10$	$5.72 \pm 0.66$
Br	S	$7.52 \pm 0.10$	$1.57 \pm 0.25$	$6.68 \pm 0.72$
NO <sub>2</sub>	S	$13.03 \pm 1.88$	$2.91 \pm 0.01$	$10.52 \pm 0.20$
H	SO <sub>2</sub>	$28.19 \pm 1.85$	$8.26 \pm 0.13$	$1.80 \pm 0.20$
Cl	SO <sub>2</sub>	$31.73 \pm 0.25$	$9.60 \pm 0.50$	$2.04 \pm 0.10$
C <sub>2</sub> H <sub>5</sub> O	SO <sub>2</sub>	$23.98 \pm 0.88$	$6.42 \pm 0.09$	$3.45 \pm 0.82$
Br	SO <sub>2</sub>	$47.15 \pm 0.50$	$8.16 \pm 0.09$	$3.93 \pm 0.28$
NO <sub>2</sub>	SO <sub>2</sub>	—	$15.43 \pm 0.05$	$15.25 \pm 0.50$

were observed in the series of 4-substituted phenyl-2-isothiocyanatoethyl sulphides and sulphones. In the series of the sulphones the rate constants were higher (the -I effect of the SO<sub>2</sub> group).

## EXPERIMENTAL

The syntheses of the isothiocyanates studied are described in papers previously published<sup>5-8</sup>. All the isothiocyanates were recrystallized or redistilled before use. The solvents were spectrally pure, the buffer constituents, thioglycolic acid and glycine, were A. G. chemicals.

The kinetics were measured with a recording spectrophotometer Specord UV VIS Zeiss at  $25 \pm 0.2^\circ\text{C}$  in a region that proved suitable by comparing the spectra of the starting isothiocyanate and its addition product. The reaction kinetics in the three cases were investigated by following spectrally the decrease in the content of isothiocyanate at a suitable wave length. The apparent rate constants were calculated from the linear plot of  $\log \Delta E$  vs time, the actual rate constants were calculated from the apparent ones by dividing them by the concentrations of the reacting forms of the agents (concentration of  $^{(-)}\text{SCH}_2\text{COO}^-$  at the given pH, concentration of  $\text{NH}_2\text{CH}_2\text{COO}^-$ ); the first-order kinetic equations were employed.

*Addition of glycine.* The reactions of isothiocyanates with glycine were investigated in a mixture composed of 10 ml of methanol, 7.8 ml of a 0.1M borate buffer (pH 9.8), 2 ml of 0.05M aqueous glycine and 0.2 ml of a methanolic solution of an isothiocyanate; its starting concentration in the resulting mixture was  $1 \cdot 10^{-5}$ M to  $5 \cdot 10^{-5}$ M.

*Addition of hydroxyl ions.* To follow the reaction of isothiocyanates with hydroxyl ions we employed a mixture composed of 10 ml of methanol, 9.8 ml of 0.2M, 0.4M or 0.1M-NaOH (depending on the expected reactivity of the NCS group) and 0.2 ml of methanolic isothiocyanate; its starting concentration in the mixture was (2 to 5)  $\cdot 10^{-5}$ M.

*Addition of thioglycolic acid.* The reaction was conducted in a 0.1M Mc Ilvain buffer, pH 7.53; the product was an N-substituted rhodanine (the addition reaction is immediately followed by ring closure). The medium employed: 9.0 ml of the buffer, 0.5 ml of 0.1M aqueous thioglycolic acid and 0.5 ml of 0.001M isothiocyanate in dioxan.

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