BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 791—793 (1971)

The Kinetics of the Reaction of Thiol Acids with Anilines

Yoshio HIRABAYASHI, Masateru MIZUTA, Masana KOJIMA,
Yukio HORIO, and Hideharu ISHIHARA
Department of Industrial Chemistry, Faculty of Engineering, Gifu University, Kakamigahara, Gifu

(Received August 6, 1970)

Studies have been made of the kinetics of the reactions of thiol acids (thiostearic acid and thioacetic acid) with anilines, such as aniline and *p*-methoxy-, *p*-ethoxy-, *p*-methyl-, *m*-methyl-, *p*-chloro, *m*-chloro-, and *m*-nitro-substituted anilines, in a chlorobenzene solution. The rate is given by $k(\mathrm{RCO{-}SH})(\mathrm{X{-}C_6H_4{-}NH_2})$. The activation energy for the reaction of thiostearic acid with aniline is 5.3 kcal/mol. The Hammett plots give a straight line, with a value of $\rho = -2.40$ for the reactions of thiostearic acid or thioacetic acid with the anilines; the mechanism of the reaction of thiol acids with anilines is discussed.

Various observations in the literature[1] indicate that the thiol acids, RCO–SH, react with primary and secondary amines much more rapidly than the corresponding carboxylic acids, RCO–OH, and thiol acids have been frequently used as acylating agents. Some observations of Alliger *et al.*,[2] of Sheehan and Johnson,[3] and of Tarbell[1] suggest that the acylation of amines by thiol acids proceeds by a free-radical chain process. On the other hand, the kinetic study by Hawkins *et al.*[4] of the reaction of thiobenzoic acid with aniline to yield benzanilide indicates that the reaction rate in a chlorobenzene solution is given by $k(\mathrm{C_6H_5CO{-}SH})(\mathrm{C_6H_5NH_2})$, where the constant, k, varies with the presence of small amounts of benzoic acid as an impurity, and that the rate depends on the solvent.

The present authors have undertaken kinetic studies of the reactions of thiol acids (*i. e.*, thiostearic acid and thioacetic acid) with anilines in a chlorobenzene solution to yield acyl anilides (Eq. (1)) in order to determine the mechanism of the reaction of the thiol acids with the anilines.

$$\mathrm{RCO{-}SH} + \mathrm{X{-}C_6H_4{-}NH_2} \longrightarrow \mathrm{RCONHC_6H_4{-}X} + \mathrm{H_2S} \qquad (1)$$

R : heptadecyl or methyl group
X : H or substituent

Results and Discussion

The rate of the reaction of thiostearic acid or thioacetic acid with the anilines in a chlorobenzene solution was followed by the acid-base titration of the unreacted thiostearic acid or thioacetic acid after the hydrogen sulfide formed had been completely removed. The results gave good second-order rate constants for all the runs (Fig. 1.):

$$\text{rate} = k(\mathrm{RCO{-}SH})(\mathrm{X{-}C_6H_4{-}NH_2}) \qquad (2)$$

The observation of Hawkins *et al.*[4] of the reaction of thiobenzoic acid with aniline indicated that the

---

[1] D. S. Tarbell and D. P. Harrish, *Chem. Rev.*, **49**, 46 (1951).

[2] G. Alliger, G. E. P. Smith, Jr., E. L. Carr, and M. P. Stevens, *J. Org. Chem.*, **14**, 962 (1949).

[3] J. C. Sheehan and D. A. Johnson, *J. Amer. Chem. Soc.*, **74**, 4926 (1952).

[4] P. J. Hawkins, D. S. Tarbell, and P. Noble, Jr., *ibid.*, **75**, 4462 (1953).

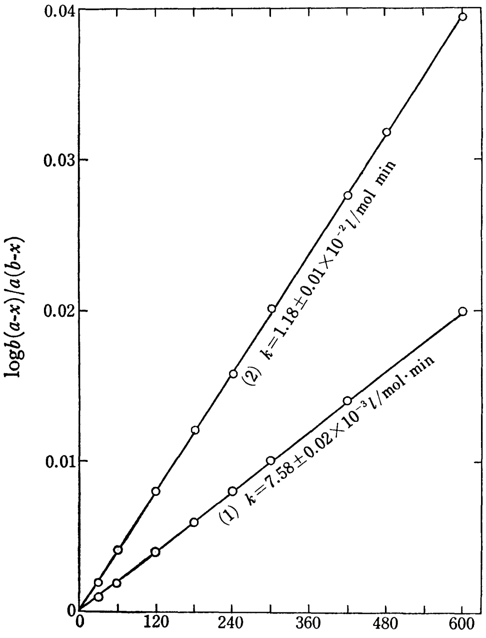


Fig. 1. The second-order plots for the reaction of thiol acid with aniline.
a and *b* are the initial concentrations of the thiol acid and aniline, respectively; *x* is the decrease of concentration of the thiol acids at time *t*.
(1) thiostearic acid: *a*, 0.1298 mol/*l*; *b*, 0.1198 mol/*l*; at 50.0°C; reaction 2.3—34.6%.
(2) thioacetic acid: *a*, 0.2435 mol/*l*; *b*, 0.2303 mol/*l*; at 40.0°C; reaction 7.7—63.0%.

reproducibility of the rate constants was not satisfactory, even though the purity of the thiol acid was better than 99%, and that this fluctuation in different samples might be due to the catalytic activity of benzoic acid present as an impurity. Accordingly, the thiostearic acid and thioacetic acid used in the present investigation were carefully purified. Thiosteric acid, with a purity of 99.3%, gave a reproducible rate constant, $(7.58\pm0.02)\times10^{-3}$ *l*/mol·min, for the reaction with aniline at 50.0°C. In thioacetic acid, the rate constants of the reactions with aniline at 40.0°C varied from one sample of thioacetic acid to another, the extreme variations being $(1.85—0.849)\times10^{-2}$ *l*/mol·min, even though the thiol acid was more than 99% pure. The sample of the thioacetic acid (purity, 99.3%), preserved in small ampoules under nitrogen and kept in an ice-box until use, gave the reproducible rate constant of $(1.18\pm0.01)\times10^{-2}$ *l*/mol·min for the reaction with aniline at 40.0°C.

Table 1 shows the rate constants of the reactions of thiostearic acid with aniline in chlorobenzene solutions at different temperatures. From the runs, the temperature coefficient of the rate constants was found to be small, and the Arrhenius plot of log *k* *vs.* $1/T$ for the data tabulated gave a straight line; the Arrhenius activation energy was found to be 5.3 kcal/mol. This value is smaller than that of the reaction of thiobenzoic acid with aniline, 7.4 kcal/mol.[4]

TABLE 1. THE RATE CONSTANTS OF THE REACTION OF THIOSTEARIC ACID WITH ANILINE IN CHLOROBENZENE AT DIFFERENT TEMPERATURES

Temp. °C	$k^{a)}\times10^3$ *l*/mol·min	Temp. °C	$k^{a)}\times10^3$ *l*/mol·min
30.0	4.51	50.0	7.58
42.3	6.31	70.0	15.4

a) This is the bimolecular rate constant, determined from the plot of log $b(a-x)/a(b-x)$ *vs.* time.

TABLE 2. THE RATE CONSTANTS OF THE REACTION OF THIOSTEARIC ACID WITH THE SUBSTITUTED ANILINES ($X-C_6H_4-NH_2$) IN CHLOROBENZENE AT 50.0°C

Substituents X	Rate constant $k^{a)}\times10^4$ *l*/mol·min	Substituents X	Rate constant $k^{a)}\times10^4$ *l*/mol·min
p-OCH_3	356 ±4	H	75.8 ±0.2
p-OC_2H_5	407 ±5	*p*-Cl	25.0 ±0.2
p-CH_3	223 ±3	*m*-Cl	8.82±0.05
m-CH_3	97.1±0.5	*m*-NO_2	2.22±0.05

a) The bimolecular rate constant; see note a) to Table 1. Each rate constant is the average value of three runs.

TABLE 3. THE RATE CONSTANTS OF THE REACTION OF THIOACETIC ACID WITH THE SUBSTITUTED ANILINES ($X-C_6H_4-NH_2$) IN CHLOROBENZENE AT 40.0°C

Substituents X	Rate constant $k'^{a)}\times10^4$ *l*/mol·min	Substituents X	Rate constant $k'^{a)}\times10^4$ *l*/mol·min
p-OCH_3	593±7	H	118 ±1
p-OC_2H_5	672±7	*p*-Cl	36.0 ±0.4
p-CH_3	329±4	*m*-Cl	16.2 ±0.2
m-CH_3	148±2	*m*-NO_2	2.31±0.04

a) The bimolecular rate constant; see note a) to Table 1. Each rate constant is the average value of three runs.

Tables 2 and 3 show the bimolecular rate constants, *k* and *k'*, of the reactions of thiostearic acid and thioacetic acid respectively with anilines in chlorobenzene. Figure 2 shows the plots of log (k/k_0) and log (k'/k_0') *vs.* the Hammett σ-values for the substituents (k_0 and k_0'

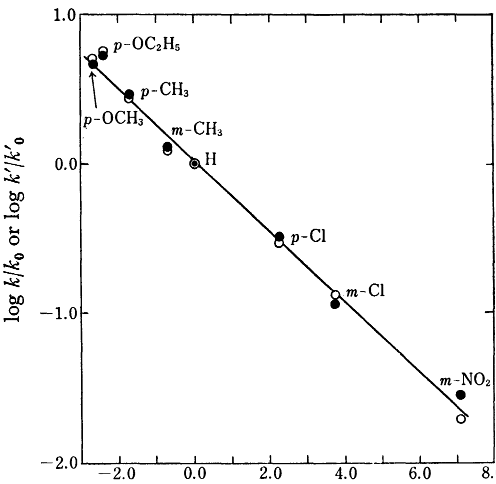
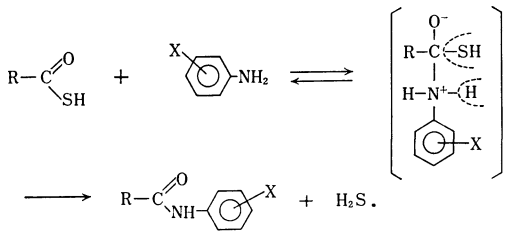


Fig. 2. Hammett's plots for the reactions of thiol acids with anilines in chlorobenzene.
● : thiostearic acid(log k/k_0); at 50.0°C
○ : thioacetic acid (log k'/k'_0); at 40.0°C.

are the rate constants of the reactions of thiostearic acid with aniline and of thioacetic acid with aniline respectively). Both plots gave straight lines, satisfying the Hammett equation; the ρ values in the Hammett equation were found to be -2.40 ± 0.09 for thiostearic acid and -2.40 ± 0.06 for thioacetic acid.

These facts indicate that the reactions between thiol acids and anilines proceed by the following pathway (Eq. 3):



(3)

The reaction is initiated by the nucleophilic attack of the aniline on the carbonyl carbon of the thiol acid; this step probably is rate-determining and is followed by the step yielding acyl anilide and hydrogen sulfide. Consequently, the reaction is facilitated by the introduction of electron-releasing substituents into the phenyl group, but is retarded by that of electron-attracting substituents.

Experimental

Materials. *Thiostearic acid*,[5] prepared from stearoyl chloride and sodium hydrogen sulfide, was purified by repeated recrystallizations from *n*-hexane (mp 39.8—40.3°C). Its purity, as determined by the iodine method, was 99.3%. (Found: S, 10.60%. Calcd for $C_{18}H_{36}OS$: S, 10.67%).

Thioacetic acid,[6] prepared from acetic anhydride and hydrogen sulfide in the presence of sodium hydroxide, was purified by repeated fractional distillations in nitrogen (bp 87.0—87.5°C). Its purity, as determined by the iodine method, was 99.3%. (Found: S, 41.84%. Calcd for C_2H_4OS: S, 42.13%).

Chlorobenzene, obtained commercially, was washed with concd. sulfuric acid with a dilute sodium bicarbonate solution, and then with water, dried over anhydrous calcium chloride, and distilled. The fraction with a bp of 131—132°C was used.

Aniline and Substituted Anilines: All were reagent-grade chemicals obtained from the Tokyo Kasei Kogyo Co. and were purified by recrystallization or by distillation under reduced pressure in nitrogen; the materials having the following mps or bps were used: aniline, bp 82.5—83.0°C/20 mmHg; *p*-anisidine, mp 57.2—58.0°C; *p*-phenetidine, bp 127.0—128.0°C/8 mmHg; *p*-toluidine, mp 44.8—45.1°C; *m*-toluidine, bp 203.0—204.0°C; *p*-chloroaniline, mp 70.1—70.5°C; *m*-chloroaniline, bp 117.0—118.0°C/20 mmHg; *m*-nitroaniline, mp 112.9—113.1°C.

Kinetic Procedure. A standard solution of a thiol acid in chlorobenzene, prepared before each run, was pipetted into a 100-cc volumetric flask containing some chlorobenzene and a weighed sample of aniline or a substituted aniline. The volume of the solution was made up to 100 cc (thiostearic acid 0.12—0.13; thioacetic acid 0.16—0.25 mol/*l*); 10-m*l* aliquots were then removed and placed in 100-cc glass-stoppered round-bottomed flasks, which had previously been flushed with dry, oxygen-free nitrogen, in an thermostat at a prescribed temperature (accuracy ±0.1°C). The first 10-m*l* aliquot was pipetted directly into an excess of the standard base (the thioacetic acid runs: 25 cc of 0.2N potassium hydroxide; the thiostearic acid runs: 40 cc of 0.1N ethanolic potassium hydroxide and 20 cc of neutralized ethanol), and the excess base was back-titrated immediately with 0.1N hydrochloric acid by the use of thymolphthalein as the indicator. The samples were removed at regular time intervals, and the flask was immediately chilled in an ice bath; in the thioacetic acid runs, a steady stream of dry, oxygen-free nitrogen was passed through the contents of the flask for 10 min, while in the thiostearic acid runs, the flask was aspirated by a water-pump for 5 min. These procedures had been determined by preliminary experiments aimed at the complete removal of hydrogen sulfide. An excess of the standard base, mentioned above, was added to the contents of the flask, and the residual thiol acid was determined by back-titration, as has been mentioned above. In the thioacetic acid runs, it had been found, from preliminary experiments carried out under the same conditions as those used for chlorobenzene solutions of different thioacetic acid-hydrogen sulfide concentrations, that a small amount of thioacetic acid had been lost, together with the hydrogen sulfide removed; accordingly, the residual amount of thioacetic acid at each reaction time was corrected by the amounts determined for different concentrations of thioacetic acid. On the other hand, the following blank test was carried out in order to determine whether or not the thiol acid itself was changed in chlorobenzene during the reaction with aniline. Another part of the standard solution of thiol acid in chlorobenzene was diluted with chlorobenzene, and the concentration of thiol acid in the solution was made equal to that of the above thiol acid-aniline chlorobenzene solution; the subsequent treatment of the solution was just the same as has been described above. These blank samples were also removed at regular time intervals, together with the above samples, and the amount of residual thiol acid was determined; the amount of the residual thiol acid of the blank sample, determined after the removal of hydrogen sulfide, was always practically identical with that of the initial blank sample at each reaction time during the run, though the above correction value had to be taken into consideration in the thioacetic acid runs.

---

[5] Y. Hirabayashi, M. Mizuta, and T. Mazume, This Bulletin, **37**, 1002 (1964).

[6] E.K. Ellingboe, "Organic Syntheses," Vol. 31, p. 105 (1951).