[Chem. Pharm. Bull. 23(2) 340—345 (1975)]

UDC 547.551.04 : 547.269.3.04

Effect of *ortho*-Substituents on Methanesulfonic Acid Derivative of Substituted Aniline[1,2]

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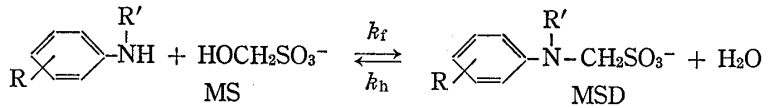
(Received July 17, 1974)

Formation and hydrolysis rates for methanesulfonic acid derivatives (MSD) of anilines including *o*-, *m*-, and *p*-carboxyaniline and various *ortho*-substituted anilines were studies as compared with those of the other substituted anilines. For *o*-, *m*-, and *p*-carboxyaniline, a practical pK_a was discussed on the relationship between logarithm of formation or hydrolysis rate constant and pK_a of the corresponding anilinium ion. Formation rates for the reaction of intramolecular H-bonding aniline with hydroxymethanesulfonate were about half to those for the other substituted anilines, which supported the assumption that the reactive H in NH_2 group became half owing to the intramolecular H-bonding. In the cases of anilines substituted by negatively charged group, formation and hydrolysis rates were fairly correlated to Hammett σ value of negative group and both the rates were slower than those of the other anilines. Hammett σ values of $NHCH_2SO_3^-$ group were determined and the values of σ_m and σ_p were -0.10 and -0.57 respectively. From these observations the structure of intermediate of the reversible MSD reaction was proposed.

During the course of the investigation on the methanesulfonate derivatives (MSD) of various aromatic amine drugs, it was found that N-phenylanthranilic acid did not react with hydroxymethanesulfonate (MS) to form MSD. N-Methylanthranilic acid and its methyl ester also did not form MSD. Anthranilic acid, however, was found to react with MS indicating that intramolecular H-bonding played a role for the reaction. Then kinetic studies concerning the effect of various *ortho* substitutents on MSD formation and on its hydrolysis were carried



out. These investigations indicated the structure of intermediate of the reversible reaction. The aniline derivatives studied include *o*-, *m*-, and *p*-carbonylanilines and various *o*-substituted anilines. The results were compared with those obtained in the previous studies[4,5] and the discussions on the effect of these substituents were presented.

Experimental

Synthesis of Substituted Aniline MSD——Synthesis was followed to the method of Neelakantan, *et al.*[6]

Kinetic Measurement——The difference of ultraviolet (UV) absorption spectra between parental aniline and its MSD enables the kinetic measurement. Buffer systems used were the same to those in previous studies.[4,7] Formation rates were determined in the pseudo first order conditions, where the concentration

1) Presented at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 1974.
2) This report constitutes Part VI of the studies entitled "Methanesulfonic Acid Derivative of Drug," where Part V is in; Y. Kurono, K. Ikeda, and K. Uekama, *Chem. Pharm. Bull.* (Tokyo), **22**, 1261 (1974).
3) Location: *Tanabe-dori, Mizuhoku, Nagoya*; *a*) Present address: *Faculty of Pharm. Sci. Kumamoto Univ., 5-1, Oe-honmachi, Kumamoto.*
4) K. Ikeda, K. Miyata, T. Iwata, F. Kawata, and K. Kurome, *Chem. Pharm. Bull.* (Tokyo), **18**, 440 (1970).
5) K. Ikeda, Y. Kurono, and T. Tukamoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 863 (1972).
6) L. Neelakantan and W.H. Hartung, *J. Org. Chem.*, **24**, 1943 (1959).
7) K. Ikeda and Y. Kurono, *Chem. Pharm. Bull.* (Tokyo), **21**, 1198 (1973).

of substituted aniline was from 5×10^{-5} to 1×10^{-4} M and that of MS was in excess, 5×10^{-2}—1×10^{-1} M.

Hydrolysis study was carried out as previously described.[5,8] For very slow reactions Guggenheim method[9] was used to determine the rate constant occasionally.

pK_a Measurement——The pK_a of MSD was determined by spectrophotometry. The values of pK_a were calculated from the following equation, where Ab_{AH}, Ab_A, and Ab are the absorbance at appropriate wave-length for free form, ionic form and their mixture respectively.

$$\log\frac{Ab-Ab_A}{Ab_{AH}-Ab} = -\log K_a - \mathrm{pH} \qquad (1)$$

Potentiometric method was also done using Toa Denpa HS-2A type pH-Stat.

Results and Discussion

Formation Rate of MSD

Figure 1 shows the pH-profile of logarithm of 2nd order formation rate constant, k_f, between carboxy aniline and MS at 37°. The dotted curves show the results reported previously.[4] That k_f's for *p*- and *o*-carboxyanilines are lower than that for *m*-carboxyaniline may be attributed to the resonance effect of *p*- and *o*-substituents which decrease the electron density of the amino group. The decrease of k_f below pH 3.5 may be ascribed to the protonation of amino group which is the object of the electrophilic attack of MS. The first step pK_1 values of *o*-, *m*-, and *p*-carboxyanilines from literature[10] are 2.11, 3.12, and 2.41 respectively, which have been generally attributed to the deprotonation of anilinium ion. However, the ionization equilibria of carboxy anilines are complicated as below.[11] Among their ionic species the reactive free amine forms are II_A and III. The stepwise decreases of k_f around pH 4.0—5.0, which are apparent in the order of *o*->*p*->*m*-carboxyaniline, may be the reflection of the secondary ionization from II_A+II_B to III. The second step pK_2 values for *o*-, *m*-, and *p*-carboxyaniline in literature[10] are 4.95, 4.74, and 4.85 respectively. The second order formation rate constants for III, k_{III}, which were estimated from the plateau region, pH 6.5—7.5, are 2.04×10^{-1},$4.17\times$

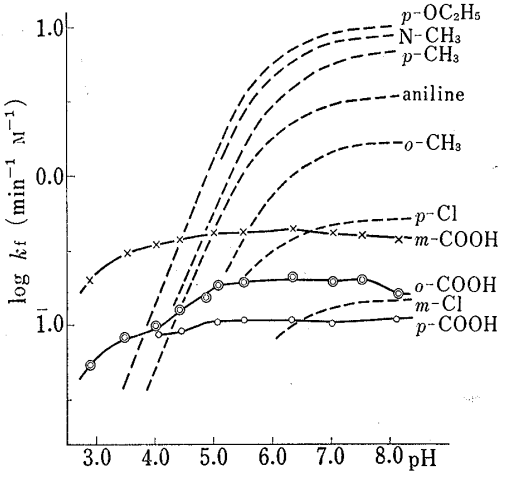
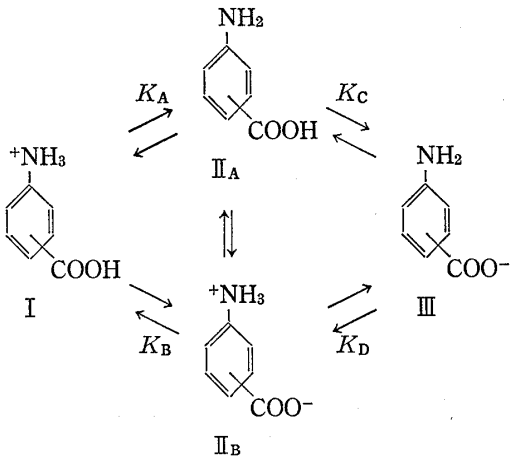


Fig. 1. The pH-profile of MSD Formation Rate, k_f, for Reactions of Substituted Aniline with Hydroxymethanesulfonate at 37°



8) K. Ikeda, Y. Kurono, and T. Tukamoto, *Chem. Pharm. Bull.* (Tokyo), **20**, 1621 (1972).
9) E.A. Guggenheim, *Phill. Mag.*, **2**, 538 (1926) [A.A. Frost and R.G. Pearson, "Kinetics and Mechanism," 2nd ed., Wiley International Edition, New York, N.Y., 1961, p. 49].
10) A. Albert and E.P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley & Sons Inc., New York, N.Y., 1962, p. 148.
11) P. Leggate and G.E. Dunn, *Can. J. Chem.*, **43**, 1158 (1965).

10^{-1}, and 1.05×10^{-1} (M^{-1} min^{-1}) for *o*-, *m*-, and *p*-derivatives respectively. The intrinsic rate constants for form II_A, k_{IIA}, cannot be estimated, but the apparent rate constants for II (II_A+II_B), k_{II}, can be rationally estimated from the apparent rate constant at $[H^+]=\sqrt{K_1\cdot K_2}$, where the aniline is substantially II_A and II_B. The k_{II} values obtained are 8.51×10^{-2}, 3.47×10^{-1}, and 8.32×10^{-2} (M^{-1} min^{-1}) for *o*-, *m*-, and *p*-derivative respectively.

Figure 2 shows linear free energy relationship (LFER) between pK_a and log k_{III}, where K_a refers to the dissociation constant of substituted anilinium ion. The small dotts are the data presented previously[4] and fall well on a line with slope of unity. The plots for carboxyanilines which were plotted against pK_1 are far from the linear correlation. Considering the ionization scheme shown above, the following ionization constant, K, would be a better measure for the LFER.

$$K=\frac{(II_A+III)(H^+)}{(I+II_B)} \tag{2}$$

Because pK_a value as the abscissa of the LFER refers to the concentration of H^+ which equalifies the concentrations of anilinium ion and free aniline, the $-$logarithm of $[H^+]$ where $II_A+III=I+II_B$, would be an appropriate abscissa for the plots of carboxyanilines. From the stoichiometric relationships, $[H^+]$ which satisfies $I+II_B=II_A+III$ can be represented as

$$[H^+]=\frac{-K_1(1-2r)+\sqrt{K_1^2(1-2r)^2+4K_1K_2}}{2} \tag{3}$$

where $r=II_A/(II_A+II_B)=K_A/(K_A+K_B)=K_D/(K_C+K_D)$. Although microscopic dissociation constants, K_A, K_B, K_C, and K_D, have not been determined and the best abscissa for carboxyaniline can not be estimated, K_1 and K_2 have been determined.[10] Thus for a practical abscissa for LFER, log $1/\sqrt{K_1K_2}$ would be appropriate, where the assumption in Eq. (3) is $r=0.5$ or $II_A=II_B$, as is shifted by arrow in Fig. 2. The *o*-substituted anilines which are capable of intramolecular H-bonding,[12] *i.e.* *ortho*-OH, OCH_3, OC_2H_5, F, and Cl anilines, have k_f values

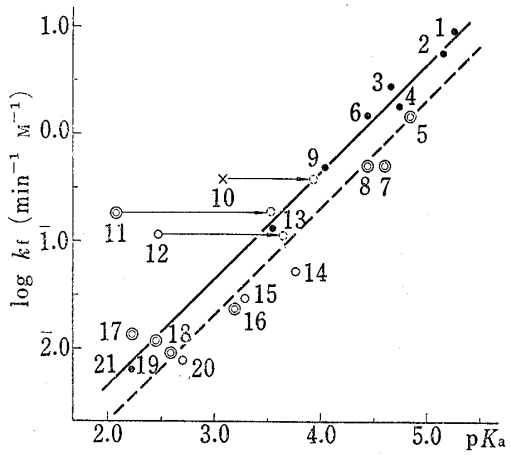


Fig. 2. Relationship between Formation Rate Constant at pH 7.0—7.5 (37°) and pK_a of Corresponding Anilinium Ion

Number in this figure shows the results of aniline derivatives containing the following substituent group.

1: *p*-OC_2H_5	8: *o*-OC_2H_5	15: *p*-SO_3^-
2: *p*-CH_3	9: *p*-Cl	16: *o*-F
3: H (aniline)	10: *m*-COO^-	17: *o*-$COOCH_3$
4: *m*-CH_3	11: *o*-COO^-	18: *o*-SO_3^-
5: *o*-OH	12: *p*-COO^-	19: *o*-Cl
6: *o*-CH_3	13: *m*-Cl	20: *p*-$COCH_3$
7: *o*-OCH_3	14: *m*-SO_3^-	21: *p*-SO_2NH_2

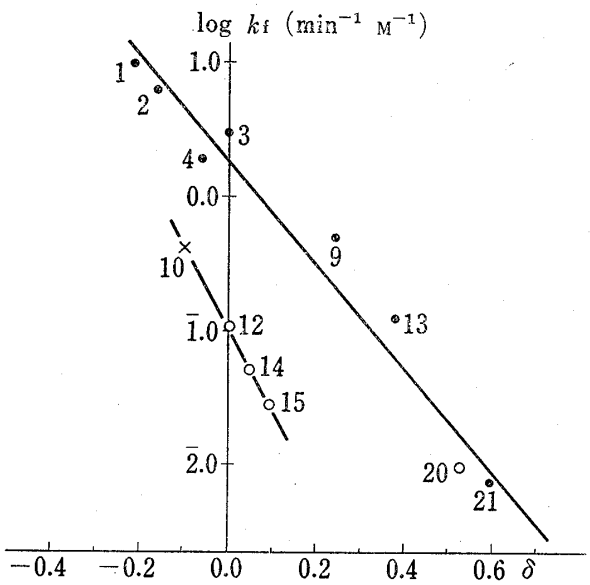


Fig. 3. Relationship between Formation Rate Constant at pH 7.0—7.5 (37°) and Hammett δ Value

Number in this figure corresponds to that in Fig. 2.

12) P.J. Kruegar, *Can. J. Chem.*, 42, 201 (1964).

lower from LFER. These values are fairly on the dotted parallel line with a distance of 0.301, which shows that their k_f values are about half to those predicted from the parental LFER. These observations indicate that the reactive H in primary amino group becomes half owing to the intramolecular H-bonding, which will be illustrated latter. *o*-Carboxymethylaniline, however, has a value higher than the prediction, which may indicate that the intramolecular H-bonding with carboxyl oxygen facilitates the reaction inspite of the loss of reactive hydrogen. The distance from the dotted line may be attributed to the net effect of the intramolecular H-bonding. Another factor which is unfavorable for the reaction is the electrostatic properties of the reactants. The lower values for *m*- and *p*-SO_3^- derivatives may be the reflection of the charge repulsion between negative carboxylate or sulfonate ion and negative MS ion. *o*-SO_3^- aniline falls fairly on LFER, but this may be explained by assumption that the hindrance between charges and the facility due to the H-bonding with S→0 as was expected for *o*-COOH are compensated. The lower value for *p*-$COCH_3$ aniline may be due to the resonance effect which dislocates its plot from the LFER in other reaction systems in general.

The effect of the ionic substituent is clearly shown in Fig. 3, where log k_f is plotted against Hammett's σ constant. The ionic substituent group consists different LFER and has a negatively higher ρ value. It is apparent that negatively charged anilines are sensitive to polar effect, σ.

Hydrolysis Rate of MSD

Figure 4 shows pH-profile of the logarithm of the first order hydrolysis rate constant, k_h, of *o*-, *m*-, and *p*-carboxyaniline MSD. As has been reported previously,[4,5] the hydrolysis rate is pH-independent at neutral region. The hydrolysis rates of *m*-and *p*-carboxyaniline MSDs increase in acidic region, which indicates hydrogen ion catalysis.[7] That only k_h of *o*-carboxyaniline MSD is pH-independent may be explained by the supposition that this MSD predominantly is in the zwitter ionic form, (Chart 1) in acidic region owing to the intramolecular H-bonding. Studies on the acid catalyzed hydrolysis of MSD and on the ionization characteristic of MSD are being carried out in the author's laboratory, which will be reported in the following paper.

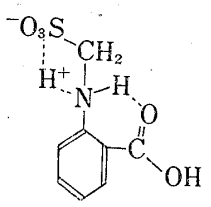


Chart 1

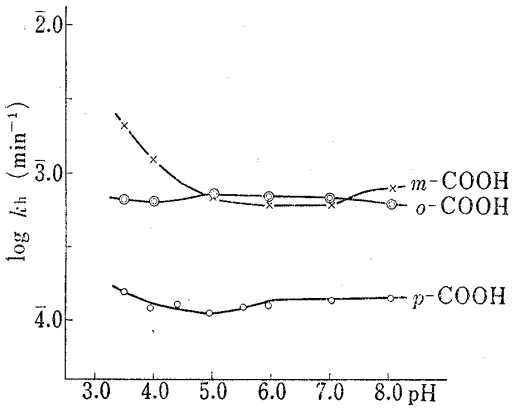


Fig. 4. The pH-profile of Hydrolysis Rate, k_h, of *o*-, *m*-, and *p*-Carboxy Aniline MSD at 37°

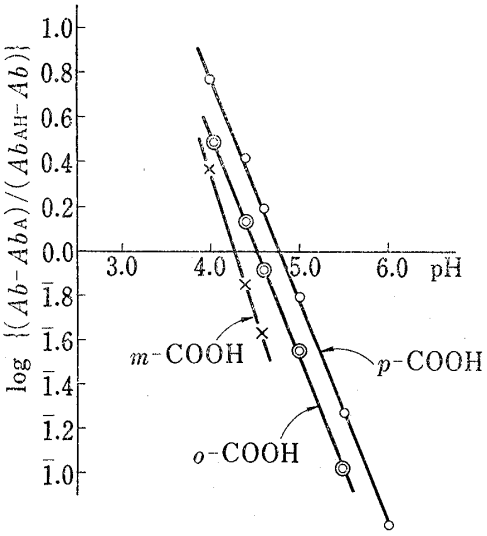


Fig. 5. Spectrophotometric Determination of the Acid Dissociation Constant of *o*-, *m*-, and *p*-COOH Aniline MSD at 25°

Another factor which may affect the hydrolysis rates of these carboxyaniline MSDs is the protonation or deprotonation of carboxyl groups. Thus the pK_a of carboxyl group was determined as follows. The UV spectra of carboxy aniline MSD change within pH range of 4.0—5.0, which is not observed for other MSD of the substituted aniline. Because this change is specific for carboxy derivatives, it may be assigned for the secondary ionization scheme of carboxy aniline. The protonation to $-CH_2SO_3^-$ may be disregarded in the range pH 4.0—5.0. Figure 5 shows that the spectrophotometric method is applicable to the determination of apparent K_2 values. The apparent pK_2 values obtained for *o*-, *m*-, and *p*-carboxyaniline MSD are 4.52, 4.30, and 4.77 respectively. These values agreed with those obtained from the potentiometric method. Considering the pH-profiles in Fig. 4 from these pK_a values for *m*- and *p*-carboxyaniline MSDs, the difference of the rates of the ionic and free form is small.

Using these pK_a values, Hammett σ values for aminomethanesulfonic group ($NHCH_2SO_3^-$) could be determined with Hamett's equation.

$$\log \frac{K}{K_0} = \rho \cdot \sigma_{m \text{ or } p} \qquad (4)$$

where K_0 and K are dissociation constants of benzoic acid and substituted benzoic acid at 25° respectively. The values of ρ and $\sigma_{m \text{ or } p}$ are a reaction parameter and substituent constant respectively and the suffix, *m* or *p*, indicates the position of substituent on benzene ring. The values of σ_m and σ_p for $NHCH_2SO_3^-$ group were −0.10 and −0.57 respectively.

Figure 6 shows the relationship between pK_a of substituted anilinium ion and logarithm of the first order hydrolysis rate constant, k_h, of MSD of substituted aniline at pH 7.0—7.5. The small dotts are data previously reported,[4,5] In this relationship also the plots for carboxy aniline MSDs against pK_1 are out of the correlation. As has been mentioned for k_f, $-\log \sqrt{K_1K_2}$ would be a practical abscissa for the LFER. The plots for *ortho* substituted anilines fall fairly on linear relationship, which is in contrast to k_f where *ortho* substituted derivatives have generally lower from the LFER.

Hammett plot for k_h is shown in Fig. 7, where the ionic substituent group seems to consist different LFER as was observed for k_f.

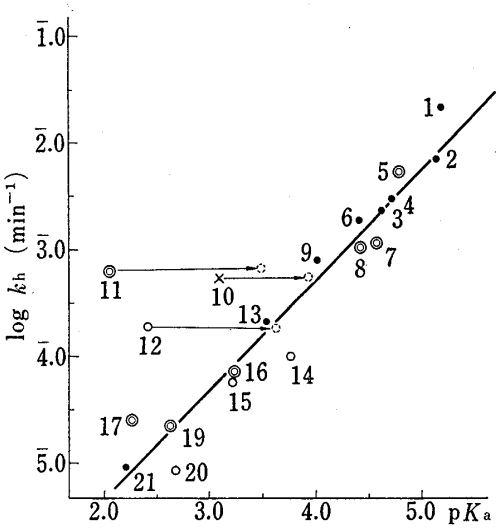


Fig. 6. Relationship between Hydrolysis Rate Constant at pH 7.0—7.5 (37°) and pK_a of Corresponding Anilinium Ion

Number in this figure corresponds to that in Fig. 2.

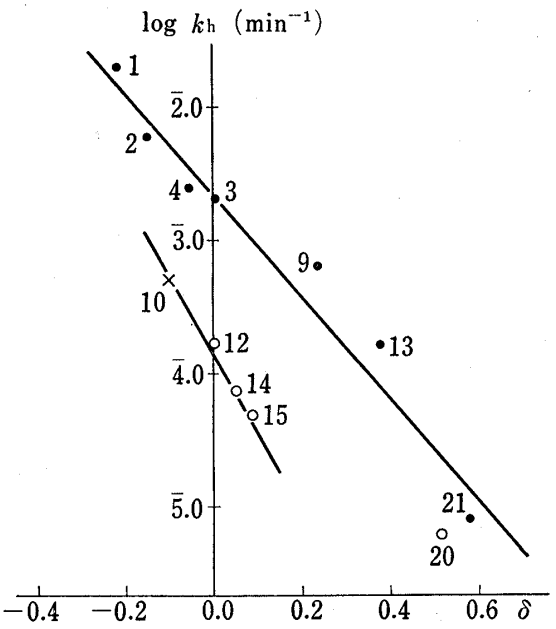


Fig. 7. Relationship between Hydrolysis Rate Constant at pH 7.0—7.5 (37°) and Hammett σ Value

Number in this figure corresponds to that in Fig. 2.

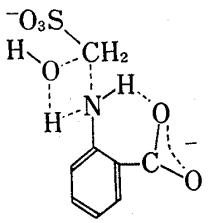


Chart 2

Possible Structure of Intermediate

From the results in thi sstudy and those reported previously,[4,5] the intermediate for the formation and hydrolysis reaction of aniline MSD could be illustrated as Chart 2. This structure interpretes the results; (1) k_f value for *ortho* substituted aniline which are capable intramolecular H-bonding are about half to those for other derivatives, (2) N-methyl- or N-phenyl-*o*-carboxyaniline and their systems do not react with MS. This structure satisfies the basic chracteristic of the reaction; (1) the attack of MS on N is electrophilic, (2) the hydrolysis of MSD is pH-independent at neutral region.