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The Effect of Acylamino Groups in Diazo-coupling Reactions

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A kinetic study has been made of the coupling reactions of diazonium salts with *N*,*N*-dialkyl-*N*′-acyl-*m*-phenylenediamines, including *N*′-acetyl- (I, II), *N*′-benzoyl- (III), *N*′-carboethoxy- (IV), and *N*′-*p*-toluenesulfonyl derivatives (V, VI). It was found from the pH dependence of the apparent rate constant that the reactive species of a substrate varies with the pH of the medium, from an undissociated molecule to an anion formed by the ionization of an acylamino group. In the case of I, the activating effect of the dissociated acylamino group seems to be higher than that of the undissociated acylamino group by some 8 powers of ten.

Ordinary diazo-coupling reactions between diazonium ions and aromatic compounds activated by such an electron-releasing substituent as an amino- or phenoxide group are well-known electrophilic aromatic substitutions.[1] In a previous paper,[2] we have shown that a diazonium ion couples not only with the undissociated pyrrole, but also with the pyrrole anion, and that the coupling with the pyrrole anion takes place much more rapidly than that with the undissociated pyrrole, showing that the conjugate base of the pyrrole

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[1] H. Zollinger, "Azo and Diazo Chemistry," Interscience Publishers, New York, N.Y. (1961), p. 221.

[2] K. Mitsumura, Y. Hashida, S. Sekiguchi, and K. Matsui, This Bulletin, **46**, 1770 (1973).

is a powerfully reactive species for this reaction. Although, in the pyrrole, the N–H group participates in ring formation, a similar activation of an aromatic molecule by the ionization of a substituent can be seen in the cases of phenols.[1] However, there has been no study of the acceleration of an aromatic electrophilic reaction by the ionization of a substituent in an aromatic molecule other than those of phenolic substances. From the same point of view, it may be expected that an aromatic compound bearing an acylamino group will provide a reactive substrate for the electrophilic substitution by means of the ionization of the acylamino N–H bond. This assumption has not, however, been proved.

This paper will report on the activation caused by the ionization of an acylamino group in the coupling reaction with *m*-acylamino anilines.

Experimental

Materials. Commercial *N,N*-bis(2-hydroxyethyl)-*N'*-acetyl-*m*-phenylenediamine (I) was recrystallized from methanol. The *N,N*-dimethyl-*N'*-acetyl-*m*-phenylenediamine (II) and *N,N*-dimethyl-*N'*-benzoyl-*m*-phenylenediamine (III) were prepared from *N,N*-dimethyl-*m*-phenylenediamine by acetylation and benzoylation respectively. The *N,N*-dimethyl *N'*-carboethoxy-*m*-phenylenediamine (IV) was prepared from *N,N*-dimethyl-*m*-phenylenediamine and ethyl chloroformate by the method of Schmidt.[3] Recrystallization from petroleum ether gave an analytical sample; mp 59—60 °C. Found: C, 63.73; H, 7.85; N, 13.14%. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.44%. The *N,N*-dimethyl-*N'*-(*p*-toluenesulfonyl)-*m*-phenylenediamine (V) was prepared by the reaction of *N,N*-dimethyl-*m*-phenylenediamine with tosyl chloride. Recrystallization from aqueous methanol gave an analytical sample; mp 138—138.5 °C. Found: C, 62.43; H, 6.57; N, 8.17%. Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.07; H, 6.21; N, 8.27%. The *N,N,N'*-trimethyl-*N'*-(*p*-toluenesulfonyl)-*m*-phenylenediamine (VI) was prepared by methylating V with dimethyl sulfate in water in the presence of sodium hydroxide. Recrystallization from methanol gave an analytical sample; mp 154—156 °C. Found: C, 63.30; H, 6.49; N, 9.17%. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20%. The aromatic amines employed as diazo-components were purified by fractional distillation under reduced pressure before use.

pK_a *Measurements.* The pK_a values of the *N,N*-dimethylamino and *N,N*-(2-hydroxyethyl)amino derivatives (I—VI) were measured spectrophotometrically in the same solvent as that used in the kinetic experiment at 20 °C.

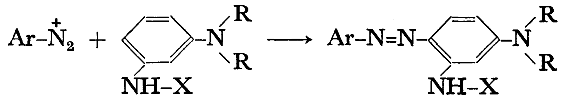
Kinetic Measurements. The rate of the coupling reaction was obtained by measuring the concentration of an azo-compound formed at an appropriate wavelength using a Hitachi 124 type spectrophotometer.[4,5] All the kinetic experiments were carried out in an approproate buffer solution at 20 °C under a constant ionic strength (μ; 0.04). The components of the buffer solution have been described elsewhere.[5] In the presence of a large excess of a substrate, the reaction followed a pseudo-first-order relationship (1):

$$k't = \ln \frac{E_\infty}{E_\infty - E_t} \tag{1}$$

where E_∞ and E_t denote the optical densities at an infinite time and at time *t*. In every case, the *k'* value thus obtained was reasonably constant up to at least 80—90% of the reaction. At the end of the kinetic measurements, the acidity of a reaction mixture was measured using a Toa HM-5A-type pH meter, thus confirming the constancy of the acidity of the medium during the reaction.

Results and Discussion

It is well known that *N,N*-dialkyl-*N'*-acyl-*m*-phenylenediamines couple with diazonium salts:[6,7]



R: H, CH_3, CH_2CH_3, CH_2CH_2OH, etc.
X: $COCH_3$, SO_2CH_3, $CONH_2$, etc.

In this investigation, *N,N*-bis(2-hydroxyethyl)-*N'*-acetyl-*m*-phenylenediamine (I), *N,N*-dimethyl-*N'*-acetyl-*m*-phenylenediamine (II), *N,N*-dimethyl-*N'*-benzoyl-*m*-phenylenediamine (III), *N,N*-dimethyl-*N'*-carboethoxy-*m*-phenylenediamine (IV), *N,N*-dimethyl-*N'*-(*p*-toluenesulfonyl)-*m*-phenylenediamine (V), and *N,N,N'*-trimethyl-*N'*-(*p*-toluenesulfonyl)-*m*-phenylenediamine (VI) were used as coupling components.

Although there was the possibility that more than one azo campound would be formed, thin-layer chromatograms of the reaction products obtained under the conditions employed in the kinetic measurements showed the presence of only one azo compound in every case.

The first-order dependence of the reaction rate on the concentration of a diazonium salt is apparent from the applicability of Eq. (1) to these reactions; the reaction rate (*k'*) also showed a first-order dependence on the substrate concentration at a constant pH. Thus, at any given acidity, the reaction rate can be expressed by Eq. (2):

$$\text{Rate} = k(\text{Ar--}\overset{+}{N}_2)(\text{Substrate}) \tag{2}$$

To establish the kinetic form of the substrate, the dependence of the apparent rate constant (*k'*) on the acidity of a medium was examined. The results are shown in Fig. 1 by plotting log *k'* against the pH values in the cases of Compounds I and II. From Fig. 1, it is obvious that there are three distinct regions in the pH-rate profile. For instance, in the case of Compound I, in the pH region below 5.0 log *k'* decreases with an increase in the acidity of a solution, while in the pH range between 5.0 and 7.0 *k'* is practically independent of the acidity of the solution. However, in the pH region above 7.0, log *k'* increases with a decrease in the acidity, and the slope of the line is close to unity in the pH range above 8.0. A similar pH-rate relation-

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[3] O. Schmidt, *Z. Phys. Chem.*, **58**, 516 (1907).

[4] Y. Hashida, K. Nakajima, S. Sekiguchi, and K. Matsui, *Kogyo Kagaku Zasshi*, **72**, 1132 (1969).

[5] Y. Hashida, M. Kobayashi, and K. Matsui, This Bulletin, **44**, 2506 (1971).

[6] K. H. Schünderhütte, "Methoden der Organischen Chemie (Houben-Weyl)," Band X/3, ed. by E. Müller, George Thieme Verlag, Stuttgart (1965), p. 245.

[7] J. Dickery and E. Towne, U.S. 265719 (1953); *Chem. Abstr.*, **49**, 1335f (1955).

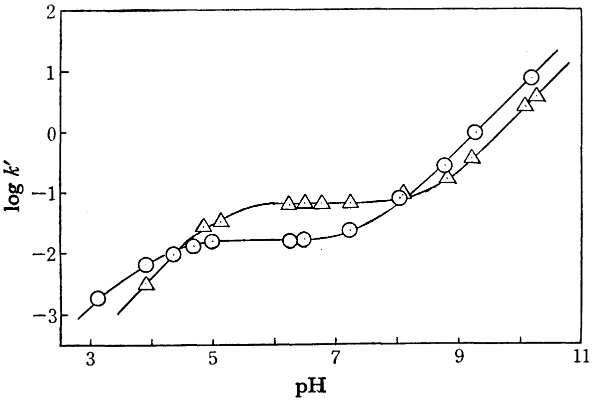


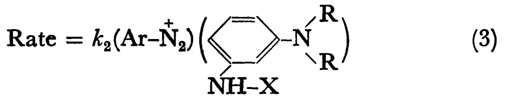
Fig. 1. pH-Rate profile for the reaction of *p*-methylbenzenediazonium salt with *N*,*N*-bis(2-hydroxyethyl)-*N*′-acetyl-*m*-phenylenediamine (I) (circles, ○), and with *N*,*N*-dimethyl-*N*′-acetyl-*m*-phenylenediamine (II) (triangles, △) in aqueous solution. (Initial concentration of substrate: 4×10^{-3} M. Initial concentration of diazonium salt: 4×10^{-5} M. k' in min^{-1})

TABLE 1. IONIZATION CONSTANTS OF *N*,*N*-BIS(2-HYDROXYETHYL)AMINO- OR *N*,*N*-DIMETHYLAMINO GROUPS OF COMPOUNDS (I—IV)

Compound	Solvent	pK_a
I	Water	3.55
II	Water	4.70
III	50% Methylcellosolve	3.80
IV	50% Methanol	4.36
V	50% Methylcellosolve	3.27
VI	50% Methylcellosolve	3.35

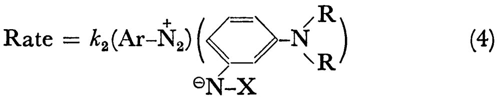
ship was also found to hold in the case of Compound II.

The pK_a value of I is 3.55, as is shown in Table 1. Therefore, the finding that the k' value decreased with an increase in the acidity of the medium in the pH region below 5 can be explained from the fact that the concentration of the free amine decreases with an increase in the acidity by means of the protonation at the *N*,*N*-bis(2-hydroxyethyl)amino group. The observed constancy of k' in the pH range between 5.0 and 7.0 may be due to the constancy of the concentration of the free amine in this region. Consequently, in the pH region below 7.0 the kinetic expression is given by Eq. (3), which is entirely consistent with that of the coupling reaction of ordinary aromatic amine:1)



$$\text{Rate} = k_2(\text{Ar-}\overset{+}{\text{N}}_2)\left(\text{C}_6\text{H}_4(\text{NH-X})\text{-N}\begin{smallmatrix}\text{R}\\ \text{R}\end{smallmatrix}\right) \qquad (3)$$

However, the finding in the pH region above 8.0 indicates the presence of a reactive species other than a free amine; the reactive species may be an anion formed by the ionization of the acylamino group, judging from the fact that the slope of the line in the pH-rate profile is close to unity, which may be understood by assuming that the concentration of the reactive anion increases by a factor of ten per pH unit in the given pH range. Accordingly, the kinetic equation in this pH region is expressed by Eq. (4):



$$\text{Rate} = k_2(\text{Ar-}\overset{+}{\text{N}}_2)\left(\text{C}_6\text{H}_4(\overset{\ominus}{\text{N}}\text{-X})\text{-N}\begin{smallmatrix}\text{R}\\ \text{R}\end{smallmatrix}\right) \qquad (4)$$

It is well known that, in the coupling reaction of phenol, it is the phenoxide ion that reacts with a diazonium ion in a neutral or weak acidic solution. Although *N*,*N*-dialkyl-*N*′-acyl-*m*-phenylenediamine may be a weaker acidic substance than phenol, it is reasonable to assume that their conjugate bases also couple with a diazonium ion in a manner similar to that described above, even in a neutral solution.

The difference between the activating effects of an acetylamino and its conjugate base can be obtained by comparing their reactivities. The second-order rate constant (k_2) can be calculated according to Eq. (3) or Eq. (4) by dividing the first-order rate constant (k') by the stoichiometric concentration of the undissociated substrate or by the anion concentration respectively. However, the calculation of the anion concentration requires the pK_a value of an acetylamino compound. Unfortunately, in water, the measurements of the pK_a value of an acetylamino compound is impossible because of its high reactivity to hydrolytic cleavage in a strong alkaline solution. Therefore, the exact concentration of an anion under kinetic conditions can not be accurately determined. However, in isopropyl alcohol the acidity of acetanilide is known to be close to that of methanol.8) On the other hand, the pK_a value of methanol was measured to be 15.5 in water.9) Therefore, the pK_a value of acetanilide in water may also be close to this value. On the basis of the presence of an electron-releasing *N*,*N*-dialkylamino group in the *meta* position, I is assumed to be a weaker acid than acetanilide; therefore, we assume that the pK_a value of I is 16.0. By using this value, we obtained the rate constants (k_2) of 4.1 ($\text{l}\cdot\text{mol}^{-1}\cdot\text{min}^{-1}$) for the reaction of the undissociated molecule and 1.1×10^9 ($\text{l}\cdot\text{mol}^{-1}\cdot\text{min}^{-1}$) for the reaction of the anion; this implies that the activating effect of the conjugate base of an acetylamino group is higher than that of

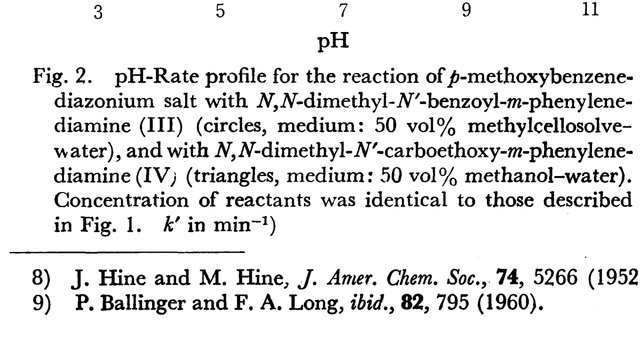


Fig. 2. pH-Rate profile for the reaction of *p*-methoxybenzenediazonium salt with *N*,*N*-dimethyl-*N*′-benzoyl-*m*-phenylenediamine (III) (circles, medium: 50 vol% methylcellosolve-water), and with *N*,*N*-dimethyl-*N*′-carboethoxy-*m*-phenylenediamine (IV) (triangles, medium: 50 vol% methanol–water). Concentration of reactants was identical to those described in Fig. 1. k' in min^{-1})

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8) J. Hine and M. Hine, *J. Amer. Chem. Soc.*, **74**, 5266 (1952).
9) P. Ballinger and F. A. Long, *ibid.*, **82**, 795 (1960).

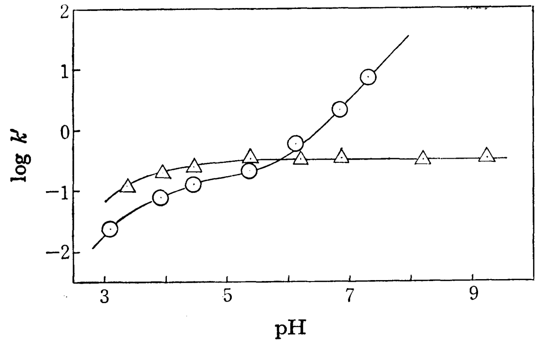

Fig. 3. pH-Rate profile for the reaction of *m*-methylbenzenediazonium salt with *N,N*-dimethyl-*N'*-(*p*-toluenesulfonyl)-*m*-phenylenediamine (V) (circles), and with *N,N,N'*-trimethyl-*N'*-(*p*-toluenesulfonyl)-*m*-pnenylenediamine (VI) (triangles) in 50 vol% methylcellosolve-water. (Concentration of reactions was identical to those described in Fig. 1. k' in min^{-1})

the parent group by some 8 powers of ten.

From a similar point of view, the coupling reactions with *N'*-benzoyl- (III), *N'*-carboethoxy- (IV), and *N'*-(*p*-toluenesulfonyl) (V) derivatives were also investigated. The pH dependences of the rate constant (k') in these cases are given in Figs. 2 and 4.

From these figures, it is obvious that the pattern of the pH-rate profile of these reactions is esesntially the same as that in the case of Compound I, although the pH region in which an anion enters the reaction varies considerably.

Additional evidence for the pariticpation of an anion was obtained from the reaction of *N,N,N'*-trimethyl-*N'*-(*p*-toluenesulfonyl)-*m*-phenylenediamine (VI), containing no acidic hydrogen atom in the acylamino group. In this case, the reaction rate was found to be independent of the pH value, even in an alkaline region, as can be seen in Fig. 3; this finding supports the validity of the view presented above.