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The Catalytic Effect of Bases on the O→N Migration of the *s*-Triazinyl Group in *O*-(*s*-Triazinyl)-2-aminophenols

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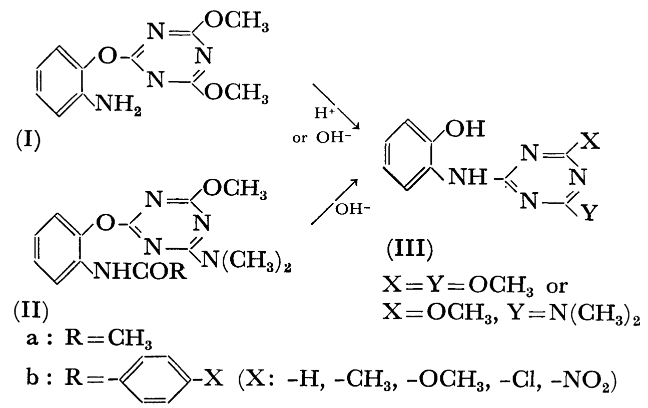
The catalytic effect of bases on the O→N migration of the *s*-triazinyl group in *O*-(*s*-triazinyl)-2-aminophenols has been studied kinetically. In the rearrangement of *N*-(acyl)-*O*-(*s*-triazinyl)-2-aminophenols (II) in alkaline aqueous methanol, the reactive species was found to be an ion formed by the ionization of the acylamino group. In the case of *O*-(*s*-triazinyl)-2-aminophenols (I), the rearrangement was subjected to a general base catalysis, although the extent was small.

Many examples of Smiles rearrangement have been known to be catalysed by an acid or a base.[1] In the course of our studies of the Smiles rearrangement of *s*-triazine derivatives, we reported[2-4] that *O*-(*s*-triazinyl)-2-aminophenols and N^1,N^1-bis(*s*-triazinyl)-*o*-phenylenediamines rearrange readily in protic solvents, especially in the presence of an acid or a base, to give *N*-(*s*-triazinyl)-2-aminophenols and N^1,N^2-bis(*s*-triazinyl)-*o*-phenylenediamines respectively. A similar O→N migration of the *s*-triazinyl group was also observed in the reaction of *N*-(acyl)- or *N*-(*s*-triazinyl)-*O*-(s-triazinyl)-2-aminophenol in the presence of a base.[2] However, these studies have been limited to qualitative discussions, and details of the effects of acids and bases on the rearrangement have not been sufficiently elucidated. This paper will report quantitative results on the influences of bases on the rearrangement.

Results and Discussion

O-(*s*-Triazinyl)-2-aminophenol (I) was prepared by a known method,[5] while *N*-acyl-*O*-(*s*-triazinyl)-2-aminophenols (IIa—b) were synthesized by acylating *O*-(4-dimethylamino-6-methoxy-*s*-triazin-2-yl)-2-aminophenol with acetic anhydride or 4-substituted benzoyl chlorides.[2] The new compounds thus obtained are listed in Table 1.



X=Y=OCH$_3$ or
X=OCH$_3$, Y=N(CH$_3$)$_2$

a : R=CH$_3$
b : R=$-C_6H_4-$X (X: -H, -CH$_3$, -OCH$_3$, -Cl, -NO$_2$)

Effect of a Base on the Rearrangement of N-*(Acyl)*-O-*(*s*-triazinyl)-2-aminophenols (II).* The compounds (II) are stable in neutral and acidic solutions, but give rearranged products (III)[5] under the hydrolytic cleavage conditions of the acyl group when dissolved in an alkaline solution. Since the molar extinction coefficients of the original compounds at the absorption maxima (280—310 nm) are much smaller than those of the rearranged products, the apparent rate constants of the rearrangement were obtained spectrophotometrically from Eq. (1):

$$k' = -\frac{2.303}{t}\log\frac{D_\infty - D_t}{D_\infty - D_0} \qquad (1)$$

where D_0, D_∞, and D_t denote the optical densities of a solution observed at initial and infinite times and at time t respectively. In every case, a plot of $\log D_\infty - D_t / D_\infty - D_0$ against the reaction time (t) gave a straight line.

The apparent rate constants (k') for the rearrangement of *N*-acetyl (IIa) and *N*-benzoyl (IIb) derivatives measured at various pH values are listed in Table 2. Fig. 1 shows the pH —rate profile in the case of (IIa).

As is shown in Fig. 1, the dependence of $\log k'$ on pH was linear with a unit slope. A similar relation was observed in the cases of *N*-benzoyl derivatives (IIb); however, no increase in the rate constant was

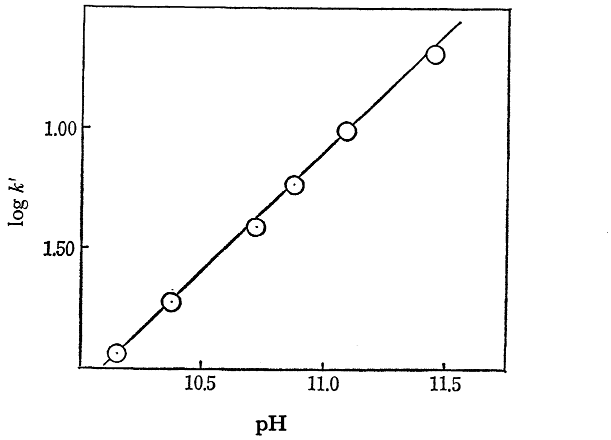


Fig. 1. pH Dependence of the apparent rate constants for the rearrangement of *N*-acetyl-*O*-(4-dimethylamino-6-methoxy-*s*-triazin-2-yl)-2-aminophenol (IIa).

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[1] For example, W. E. Truce, E. M. Kreider, and W. W. Brand, "The Smiles and Related Rearrangements of Aromatic Systems," in "Organic Reactions," Vol. 18, John Wiley & Sons, New York (1970), p. 99.

[2] T. Shiojima, T. Kuroda, S. Ohkawa, Y. Hasegawa, and K. Matsui, This Bulletin, **46**, 2549 (1973).

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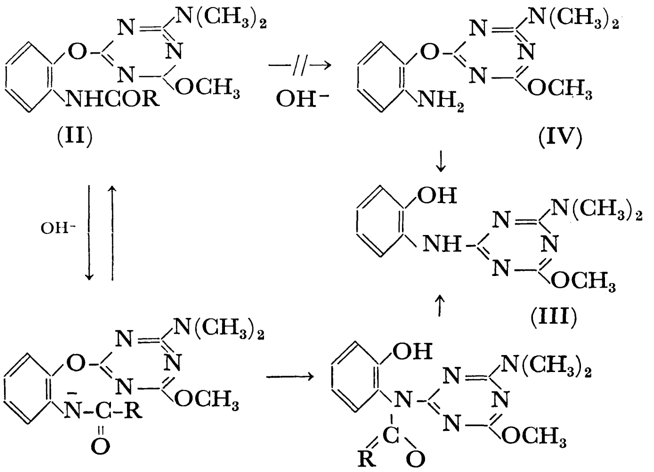
TABLE 1. *N*-(4-SUBSTITUTED BENZOYL)-*O*-(4-DIMETHYLAMINO-6-METHOXY-*s*-TRIAZIN-2-YL)AMINOPHENOLS (IIb)

Substituent (X) in IIb	Yield (%)	Mp (°C)	Solvent for recrystallization	Elemental analysis (%) Found C	H	Calcd C	H
OCH_3	98	159—160	Benzene	60.99	5.23	60.75	5.35
CH_3	95	124—125	Benzene	63.63	5.21	63.31	5.58
Cl	95	138—139	Benzene-Ligroin	57.14	4.61	57.07	4.54
NO_2	96	161—162	Benzene	55.93	4.54	55.60	4.42

TABLE 2. RATE CONSTANT FOR THE REARRANGEMENT OF *N*-ACETYL(IIa) AND *N*-BENZOYL-*O*-(4-DIMETHYLAMINO-6-METHOXY-*s*-TRIAZIN-2-YL)-2-AMINOPHENOL (IIb, X=H) IN 10% (vol) METHANOLIC BUFFER SOLUTIONS AT 20°C (μ=0.20)

(IIa)	pH	10.16	10.38	10.78	10.87	11.10	11.43
	k'(min^{-1})×10	0.116	0.195	0.382	0.572	0.974	1.99
(IIb, X=H)	pH	10.75	10.92	11.14		11.43	11.69
	k'(min^{-1})×10	0.442	0.686	1.09		1.99	3.47

observed in the presence of a base such as pyridine at a constant pH value, suggesting that the rate-determining step of the reaction does not involve an abstraction of a proton from the NH– acyl group. Therefore, two reaction sequences can be considered:



One is a process involving a preferential hydrolytic cleavage of the acyl group to give (IV), followed by the O→N migration of the *s*-triazinyl group. However, under similar reaction conditions, no hydrolytic fission of an acyl group was observed in *N*-acyl arylamines. In addition, the rearrangement of (II) proceeded much more rapidly than that of (I) in the presence of alkali. Therefore, another path, one involving the rate-determining formation of the *N*-acyl-*N*-*s*-triazinyl derivative by the O→N rearrangement, followed by a hydrolytic cleavage of the acyl group, is considered to be reasonable. Although an intermediary *N*-acyl-*N*-triazinyl derivative was not obtained in every case, this reaction sequence may be supported by the consideration that generally, since the nucleophilic reactivity of a Ar–NH–acyl group is known to be lower than that of the parent amino group, the rearrangement of *N*-(acyl)-*O*-(2,4-dinitrophenyl)-2-aminophenols is slower than that of the parent aminoether.[6] Therefore, it seems unreasonable to consider that the reaction of (II) in the presence of alkali proceeds by a direct nucleophilic attack of the NH–acyl group; the reactive species may be assumed to be an anion formed by the dissociation of the NH–acyl group and the rate may be expressed by Eq. (2):

$$v = k\ (\text{Anion}) \tag{2}$$

This assumption is verified by the fact that the dependence of $\log k'$ on pH was linear with a unit slope; the result may be understood by assuming that the concentration of the anion increases by a factor of ten per pH unit under a given set of reaction conditions. Since these compounds rearrange readily in alkaline solutions, the measurement of their pK_a values is impossible experimentally; the concentration of the anion remains unknown, and the real value of the rate constant could not be determined.

Recently, it has been suggested[7] that the rearrangement of *O*-*s*-triazinyl-*N*-acyl derivatives of 1-amino-8-hydroxynaphthalene-3,6-disulfonic acid to *N*-*s*-triazinyl-*N*-acyl derivatives proceeds by means of a direct nucleophilic attack on the acylamino group. However, further examinations will be necessary before this postulation can be accepted.

The effect of a substituent in the benzoyl group of *N*-(benzoyl)-*O*-(*s*-triazinyl)-2-aminophenol (IIb) was also studied at a constant pH value. The results are

TABLE 3. RATE CONSTANTS FOR THE REARRANGEMENT OF *N*-(4-SUBSTITUTED BENZOYL)-*O*-(4-DIMETHYLAMINO-6-METHOXY-*s*-TRIAZIN-2-YL)-2-AMINOPHENOLS (IIb) IN 50% (vol) METHANOLIC BUFFER SOLUTIONS AT 20°C (pH=10.91, μ=0.20)

Substituent (X)	k'(min^{-1})
p-OCH_3	1.08×10^{-2}
p-CH_3	1.97×10^{-2}
H	3.80×10^{-2}
p-Cl	1.29×10^{-1}
p-NO_2	3.88×10^{-1}

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[6] K. C. Roberts and C. G. M. deWorms, *J. Chem. Soc.*, **1934**, 727; **1935**, 1309.

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Table 4. Rate constants for the rearrangement of *O*-(4,6-dimethoxy-*s*-triazin-2-yl)-2-aminophenol (I) in aqueous buffer solutions at 25°C (μ=0.10)

pH	8.75	9.50	10.15	10.61	11.36	12.66
k'(min^{-1})×10^2	1.02	1.12	1.14	1.14	1.24	2.29

Table 5. Base catalysis of pyridine derivatives for the rearrangement of *O*-(4,6-dimethoxy-*s*-triazin-2-yl)-2-aminophenol (I) in methanol at 25°C.

Pyridine	c[a] (mol/l)×10	0.785	1.57	2.36	3.14	4.71
k_c=4.43×10^{-3}	k[b] (min^{-1})×10^3	2.53	2.98	3.31	3.58	4.32
γ-Picoline	c×10	0.774	1.55	2.32	3.10	4.64
k_c=6.53×10^{-3}	k×10^3	2.78	3.35	3.81	4.34	5.31
β-Picoline	c×10	0.750	1.50	2.25	3.00	4.50
k_c=5.59×10^{-3}	k×10^3	2.68	3.04	3.41	3.95	4.74
α-Picoline	c×10	0.615	1.23	1.85	2.40	3.69
k_c=4.24×10^{-3}	k×10^3	2.54	2.78	3.09	3.36	3.82
2,6-Lutidine	c×10	0.555	1.31	1.97	2.62	3.93
k_c=3.15×10^{-3}	k×10^3	2.66	2.74	2.98	3.18	3.66
2,4-Lutidine	c×10	0.611	1.32	1.98	2.64	3.97
k_c=5.27×10^{-3}	k×10^3	2.60	3.04	3.39	3.84	4.40
3,5-Lutidine	c×10	0.658	1.32	1.98	2.63	3.95
k_c=6.46×10^{-3}	k×10^3	2.71	3.15	3.50	4.05	4.82
s-Colidine	c×10	0.614	1.23	1.84	2.45	3.68
k_c=4.96×10^{-3}	k×10^3	2.53	2.69	3.00	3.47	3.97

a) Figures in the upper column indicate the concentrations of pyridine derivatives. b) Figures in the lower column indicate the rate constants.

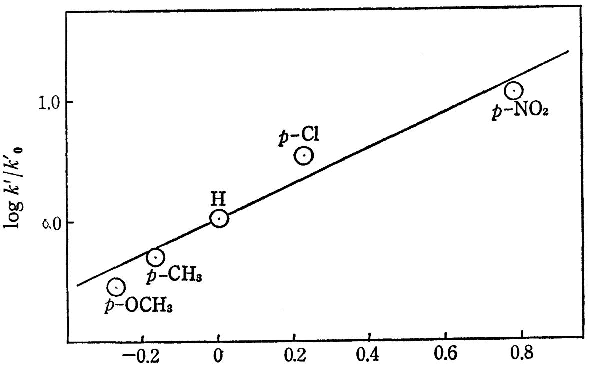


Fig. 2. Plot of the rate constants for the rearrangement of *N*-(4-substituted benzoyl)-*O*-(4-dimethylamino-6-methoxy-*s*-triazin-2-yl)-2-aminophenols (IIb) against the substituent constants.

given in Table 3, while a plot of log k'/k'_0 (where k' and k'_0 denote the apparent rate constants of substituted and unsubstituted benzoyl derivatives respectively) against the σ-value of the substituent is shown in Fig. 2. The substituent effect may be considered from two points of view. One is the effect upon the pK_a value of the benzamido group, namely, the effect on the concentration of the reactive anion, and the other is the effect upon the nucleophilic reactivity of the attacking anion. In the former, an electron-attracting substituent favors the rearrangement by increasing the concentration of the anion, while an electron-releasing substituent favors the latter.

As is shown in Fig. 2, it can be seen that the effect on the concentration of the anion dominates the rate change.

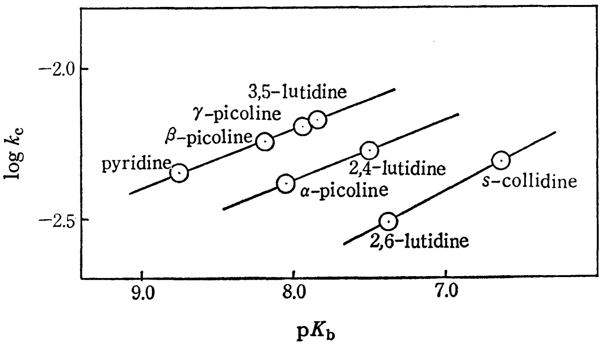


Fig. 3. Brönsted plot for the base-catalytic rearrangement of *O*-(4,6-dimethoxy-*s*-triazin-2-yl)-2-aminophenol (I).

Effects of Bases on the Rearrangement of O-(*s-Triazinyl*)-*2-aminophenols (I).* In Table 4 are listed the rate constants for the rearrangement of (I) at various pH values. It is obvious from Table 4, that the rate constant (k) increases slightly with an increase in pH value in the pH range above 11.5. In this case, however, it is unlikely that an abstraction of the proton from the amino group occurs prior to the rearrangement, because an increase in the rate constant was not proportional to an increase in the pH value.

As is shown in Table 5, the rearrangement was also accelerated by such organic bases as pyridine and its methyl derivatives. Under the present reaction conditions, the rates were proportional to the concentration of bases. Therefore, the rate constant in the presence of a base can be expressed by Eq. (3):

$$k = k_0 + k_c \text{ (Base)} \qquad (3)$$

where k, k_0, and k_c represent the rate constant observed, the rate constant in pure methanol, and the catalytic constant by the base respectively. The catalytic constants obtained are summarized in Table 5, while Fig. 3 shows the relations between the log k_c and pK_b values of pyridine derivatives, which are given in three parallel lines.

Pyridine derivatives containing no methyl group in the α-position belong to Type 1, while those containing one methyl group in the α-position belong to Type 2 and those containing two methyl groups in the α,α′-positions belong to Type 3; among the pyridine derivatives of the same series, the Brönsted rule was found to hold. These facts indicate that the steric hindrance plays an important role in the catalytic efficiency of pyridine derivatives.

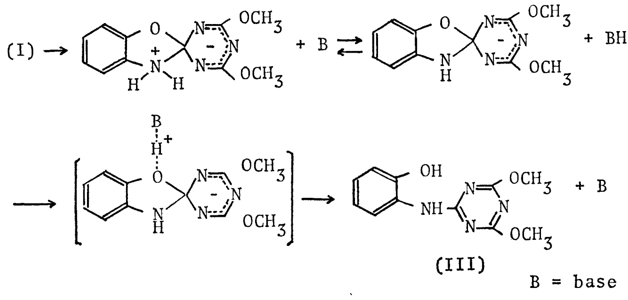
An acceleration of rearrangement was also observed in triethylamine; the catalytic constant in this case was found to be $k_c = 6.58 \times 10^{-3}$.

Furthermore, a similar catalytic effect by triethylamine was observed in the rearrangement of *O*-(2,4-dinitrophenyl)-2-aminophenol in methanol at 25 °C ($k = 2.88 \times 10^{-2}$), indicating that the base catalysis is not limited to the case of the *s*-triazine derivative.

Ordinary nucleophilic substitution reactions of activated aromatic halogen or aryloxy compounds with nucleophiles are considered to proceed by means of an addition-elimination process involving the intermediary formation of the σ-complex.[8,9] When an amine is used as a nucleophile, the catalytic effect by a base has been observed.[9,10] In the reaction of 2,4-dinitrophenyl phenyl ether with piperidine, the catalytic functions of bases have been interpreted in terms of the reaction mechanism involving the reversible transformation of the intermediate complex into its conjugate base, followed by the general acid-catalyzed detachment of the leaving group.[11,12]

Generally, Smiles rearrangements including the reaction of compound (I) can be considered to proceed in a manner similar to that of the ordinary nucleophilic aromatic substitution involving the formation of an intermediate complex;[13] this assumption may be supported by the facts observed in the rearrangement of 4- and 2-nitro-2′-hydroxydiphenyl sulfones,[14] in which the reactions are accompanied by a striking color change from deep-red to pale yellow, suggesting the formation of a Meisenheimer-type intermediate.

From these facts and considerations, it may be reasonable to consider that, in the rearrangement of *O*-(*s*-triazinyl)-2-aminophenol (I), a base participates in the proton transfer and detachment of the leaving group in the intermediate complex, as is shown below:



Experimental

All the melting points are uncorrected. The ultraviolet spectra were recorded on a Hitachi-124 UV-VIS spectrophotometer. The elemental analyses were performed at the Microanalytical Center of Gunma University.

Materials. N-*(4-Substituted benzoyl)*-O-*(*s*-triazinyl)-2-aminophenols*: A typical preparation is shown below in the case of *N*-(4-chlorobenzoyl)-*O*-(4-dimethylamino-6-methoxy-*s*-triazin-2-yl)-2-aminophenol. Into a mixture of 2.6 g (0.01 mol) of *O*-(4-dimethylamino-6-methoxy-*s*-triazin-2-yl)-2-aminophenol and 0.8 g (0.01 mol) of sodium bicarbonate in 10 ml of water in 50 ml of acetone, was added 1.7 g (0.01 mol) of *p*-chlorobenzoyl chloride in 30 ml of acetone dropwise with stirring at room temperature. After having been stirred for 6 hr at room temperature, the reaction mixture was poured into 500 ml of ice-water; the precipitate thus obtained was filtered and dried.

Kinetic Measurements. The kinetic measurements were carried out in buffered solutions at a constant ionic strength.

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