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Kinetic Studies on the *N,N*-Type Smiles Rearrangement

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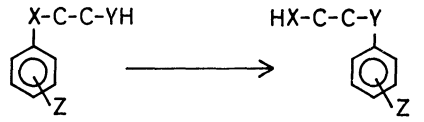
The Smiles rearrangement reaction of DL-2-aminododecanoic acid *N*-methyl-*p*-nitroanilide to DL-2-(*p*-nitrophenyl)aminododecanoic acid *N*-methylamide has been investigated in aqueous alkaline media containing 0—50% (v/v) acetonitrile or ethanol at 25 °C. It was found from the pH-rate profile that the reactive species is the free base form of the substrate. Acetonitrile content in the medium appreciably affected the rate with a maximum at *ca.* 20% in the acetonitrile content. The cationic CTAB micelles accelerated the rate 4.4-fold at pH 10, while the anionic SDS micelles suppressed the reaction almost completely. These effects of solvent and micelles were qualitatively correlated with the transition state of the reaction. A plausible mechanism for this reaction is the Smiles type rearrangement in which a spiro σ-complex is involved. The activation parameters obtained and suppression of the reaction rate by Cu(II) ion are in line with the proposed reaction mechanism.

Intramolecular nucleophilic aromatic substitution reaction (Eq. 1) is known as the Smiles rearrangement.[1]



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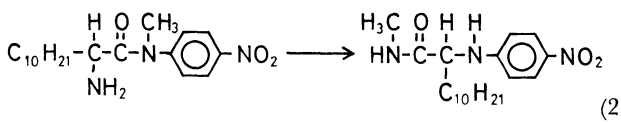
The original combination of SO_2 and OH for X and YH, respectively, was extended to a variety of combinations, *e.g.*, SO, S, and O for X and SH, NHR, and CONHR for YH.[1,2] Factors that influence the ease of the rearrangement are also well recognized.[2] Recent progress in this field has been achieved by the characterization of the common intermediate:[3,4]

However, detailed information on the reaction mechanism is restricted to a limited number of cases.

During the course of studies on the hydrolysis of carboxylate and carbonate esters or amides, we recently observed that in aqueous media DL-2-aminododecanoic acid *N*-methyl-*p*-nitroanilide (**1**) undergoes a rearrangement reaction, instead of normal hydrolysis, to give DL-2-(*p*-nitrophenyl)aminododecanoic acid *N*-methylamide (**2**). Gilman *et al.* suggested a similar



(2)

1 2

rearrangement in the reaction of 2-bromoacetanilides in methanolic ammonia.[5,6] Although they pointed out factors which affect the feasibility for the substrate to undergo the rearrangement, much remains to be clarified as regards the reaction mechanisms of the *N,N*-type rearrangement. The rearrangement reaction of **1** provides a good means for studying the micellar effects on organic reactions, since, a better understanding of the microscopic field effect that the aqueous micelles are expected to show will be obtained in unimolecular reactions such as the intramolecular rearrangement rather than bimolecular ones.[7,8] Since we obtained **1** as a stable hydrobromide, kinetic studies on the spontaneous and the micelle-catalyzed rearrangement of compound **1** have been performed. We have found that the reaction of **1** belongs to a normal Smiles-type rearrangement according to the S_Ni mechanism *via* an ionic transition state.

Experimental

Details of the synthesis of DL-2-aminododecanoic acid *N*-methyl-*p*-nitroanilide (**1**) were given in a previous paper.[9] DL-2-Aminododecanoic acid was prepared by α-bromination of dodecanoic acid followed by ammonolysis. After protection of the amino group with benzyloxycarbonyl group it was condensed with *N*-methyl-*p*-nitroaniline in the presence of phosphoryl chloride and pyridine. Removal of the protecting group with 12.6% HBr in acetic acid afforded the desired product (**1**) as the hydrobromide; mp 180—187 °C (dec); IR (KBr) 1640, 1580, 1465, 1330, 1100 cm^{-1}; NMR (DMSO-d_6) δ 0.88 (t, J=6 Hz, 3H, CH_3–), 1.24 (m, 16H, –$(CH_2)_8$–), 1.64 (m, 2H, –CH_2–CH–), 3.40 (s, 3H, *N*-CH_3), 4.06 (m, 1H, –CH–), 7.78 (d, J=8 Hz, 2H, phenyl), 8.30 (m, 3H, –NH_3^+), 8.32 (d, J=8 Hz, 2H, phenyl); UV (20% (v/v) aq acetonitrile) λ_{max} 285 nm (ε_{max} 9750). Found: C, 53.04; H, 7.53; N, 9.65%. Calcd for $C_{19}H_{32}N_3O_3Br$: C, 53.02; H, 7.49; N, 9.76%.

Product Analysis. A solution of **1** (402 mg) in 1.0 l of 3% (v/v) aqueous ethanol containing 0.01 M (1 M=1 mol dm^{-3}) sodium hydroxide and 1 M potassium chloride was kept at room temperature for 2 d. The precipitated crystalline mass was collected and recrystallized from carbon tetrachloride: yield, 299 mg (92%); mp 116—117 °C; IR (KBr) 3380, 3275, 1650 cm^{-1}; NMR (DMSO-d_6) δ 0.93 (t, J=6 Hz, 3H, CH_3–), 1.34 (m, 16H, –$(CH_2)_8$–), 1.81 (m, 2H, –CH_2–CH–), 2.75 (d, J=5 Hz, *N*-CH_3), 4.10 (m, 1H, –CH–), 6.98 (d, J=9 Hz, 2H, phenyl), 7.62 (m, 2H, NH), 8.32 (d, J=9 Hz, 2H, phenyl); UV (20% (v/v) aq acetonitrile) λ_{max} 387 nm (ε_{max} 21000); mass spectrum *m/e* 349 (M^+). Found: C, 65.12; H, 9.03; N, 11.70%. Calcd for $C_{19}H_{31}N_3O_3$ (349.48): C, 65.30; H, 8.94; N, 12.02%.

Kinetic Measurements. A three ml aqueous solution containing appropriate amounts of acetonitrile or ethanol, potassium chloride, and buffer salts (below pH 11) or sodium hydroxide (above pH 11) was placed in a cuvette and thermally equilibrated. Thirty μl of a substrate solution in acetonitrile was then injected and the whole mixture was stirred quickly and thoroughly with a slim Teflon rod. The

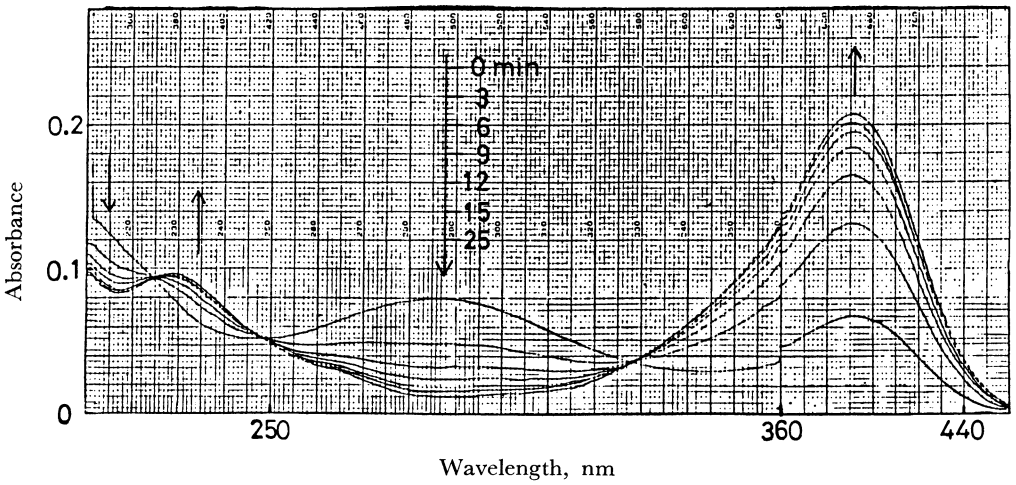


Fig. 1. Time-dependent spectral change in the rearrangement of **1** (9.90×10^{-6} M) in 29.7% (v/v) ethanol–1.0% (v/v) acetonitrile at 25 °C, μ=0.10 (KCl), and "pH" 10.

final concentration of each component in the reaction mixture is given under appropriate Figs. and/or Tables. The rate of rearrangement of **1** was followed spectrophotometrically by monitoring the appearance of the product **2** at 387 nm on a Hitachi 124 recording spectrophotometer. The reaction followed a good first-order kinetics and the apparent first-order rate constant was evaluated by the least-squares calculation. The correlation coefficients were better than 0.99. In some cases in which the concentration of organic solvent was low and precipitation of the product made it impossible to follow the appearance of product (387 nm), the disappearance of substrate was followed at 285 nm. The rapidly scanned spectra were measured on a Union Giken stopped-flow spectrophotometer Model RA-1300.

pH *Measurements.* The pH value of a reaction solution was determined with a TOA HM-5A pH meter connected to a TOA GS-135C combined electrode. For solutions containing a large amount of an organic solvent, the pH was calibrated by means of the conventional buffer salts dissolved in a medium of the same composition as that of the actual reaction solution. For this reason, the pH values given in this article are referred to as the apparent pH.

Results

Stoichiometry of Reaction. The product analysis indicates that **1** undergoes rearrangement in an aqueous alkaline medium to afford almost quantitatively the product **2** (see Experimental). The ^{1}H NMR spectrum of the product supports the structure of **2**: the original singlet of *N*-CH_3 proton signal changed to a doublet due to the coupling with the hydrogen attached to the amide nitrogen. In addition, signals of the hydrogens attached to 2- and 6-positions of the phenyl ring shifted upfield (0.8 ppm) upon the rearrangement. The absorption spectral change of the reaction as a function of time is shown in Fig. 1. The absorption at 285 nm decreased with the progress of reaction, a new band appearing at 387 nm. Isosbestic points were observed at 224.5, 248, and 328 nm throughout the reaction, indicating the absence or no accumulation of stable intermediate during the course of transformation of **1** into **2**. The potential hydrolysis product, *N*-methyl-*p*-nitroaniline was not detected by TLC analysis [silica gel, benzene–methanol (10:1 by volume)]. R_f-Values of **1**, **2**, and *N*-methyl-*p*-nitroaniline were 0.02, 0.16, and 0.55, respectively.

Effect of Solvent Content. The effect of acetonitrile content in the reaction medium on the rearrangement rate was studied at 25 °C and apparent pH 10. As seen in Fig. 2, the rate increases with acetonitrile content until the maximum rate is attained at a concentration of *ca.* 20% (v/v). Thereafter, the rate decreases almost linearly with the acetonitrile content.

pH-*Rate Profile.* The pH-rate profile of the rearrangement reaction was constructed as shown in Fig. 3. The profile is of typical sigmoid shape, indicating the presence of an acid dissociation process (pK_a= 10.34). The pK_a-value is quite reasonable for the acid dissociation constant of the primary amino group of **1**. The profile also demonstrates that the free base of **1** is by far the more reactive with the specific rate constant of 1.84×10^{-3} s^{-1} at 25.0 °C in 20% (v/v) aq acetonitrile. The reactivity of the ammonium species is too poor to estimate the specific rate constant

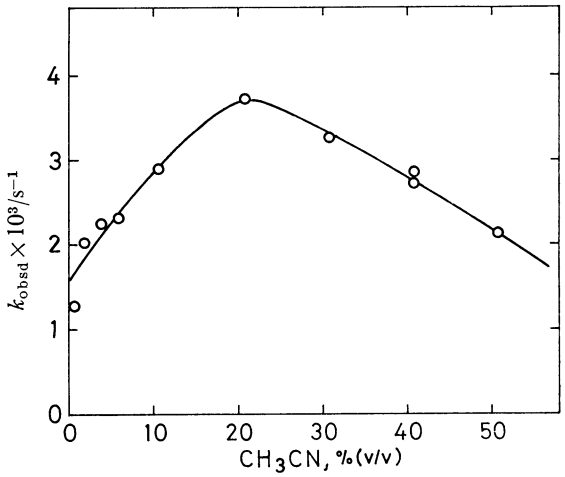


Fig. 2. Effect of acetonitrile content in the medium on the rearrangement rate of **1** (9.90×10^{-6} M) at 25 °C and "pH" 10,

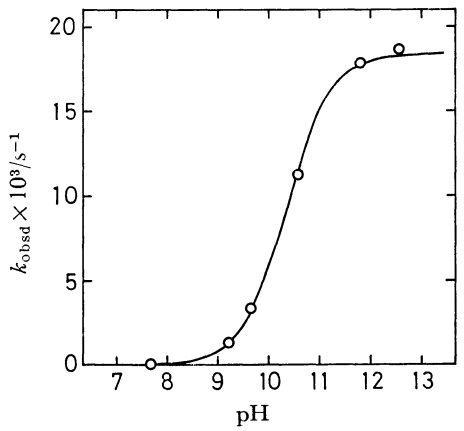


Fig. 3. pH-Rate profile for the rearrangement of **1** (9.90×10^{-6} M) in 20.8% (v/v) acetonitrile at 25 °C and μ=0.10 (KCl).

accurately under the present conditions.

Activation Parameters. In order to gain an insight into the energetics of the rearrangement, kinetic experiments were carried out in 29.7% ethanol–1.0% acetonitrile at pH 10 and at temperatures 20, 25, 30, and 35 °C (Table 1). The activation energy E_a obtained from the conventional Arrhenius plot was 17.7 kcal/mol, from which the following activation parameters were evaluated: 17.1 kcal/mol for the enthalpy of activation, 7.1 e.u. for the entropy of activation, and 14.9 kcal/mol for the free energy of activation at 303 K.

Effect of Additives. Since the substrate has several potential coordination sites, the effect of copper(II) ion on the reaction rate was investigated at 25 °C and pH 8 in 20.6% (v/v) acetonitrile. Addition of an equimolar amount of Cu(II) ion to the substrate showed little effect on the reaction rate, but 13-fold excess of Cu(II) ion brought about an appreciable suppression of the rate. That the reaction pathway was not changed even in the presence of Cu(II) ion was confirmed by product analysis.

Effects of three different micelles on the rate were also studied. The cationic CTAB micelles brought about 4.4-fold rate enhancement at pH 10.0, while the anionic SDS micelles almost completely suppressed the reaction. Nonionic Brij 35 micelles showed little effect. This difference among the three detergents should reflect the electrostatic nature of the intermediate or transition state of the reaction.

Table 1. Rate constants for the rearrangement of **1** at several different temperatures[a)]

Temperature °C	$k_{obsd} \times 10^3$ s^{-1}
20	3.07, 3.33
25	5.38, 5.45
30	8.47, 9.12
35	13.2, 13.7

a) Experimental conditions: Medium, 29.7% (v/v) ethanol-1.0% (v/v) acetonitrile; μ=0.10 (KCl); pH 10.

Table 2. Effect of additives on the rate of rearrangement of **1** at 25 °C[a)]

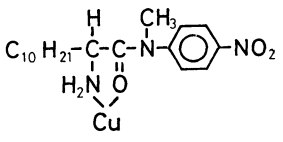
Additive	Concentration M	pH	$k_{obsd} \times 10^4$ s^{-1}
None[b)]		8.01	1.42
Cu(II)[b)]	1.09×10^{-5}	7.94	1.29
Cu(II)[b)]	1.29×10^{-4}	8.09	0.763
None[c)]		10.0	12.7±0.3
CTAB[c)]	5.01×10^{-3}	10.0	55.3±0.8
SDS[c)]	4.99×10^{-2}	10.0	≈0
Brij 35[c)]	5.45×10^{-4}	10.0	13.5±0.6

a) Experimental conditions: Initial substrate concentration, 9.90×10^{-6} M; μ=0.10 (KCl) except for SDS. b) Medium, 20.6% (v/v) acetonitrile. c) Medium, 1.0% (v/v) acetonitrile.

Discussion

Gilman *et al.* reported the first example of *N,N*-type Smiles rearrangement.[5,6)] However, they carried out the reaction in methanolic ammonia using 2-bromoacetanilides as a starting material for the most part, and postulated the intermediacy of 2-aminoacetanilides. In the present investigation, it was confirmed that amino acid *N*-methyl-*p*-nitroanilides undergo the rearrangement reaction and that the reactive species in the reaction is the free base of the substrate. It is well recognized that a strong base is required to generate a powerful nucleophile, Y^- species (Eq. 1), which brings about a rearrangement.[2)] When YH is the amino group, it was suggested that a nitride ion might be necessary for the rearrangement to take place.[10)] This, however, does not seem to be the case at least in our present system. The neutral amino group is a sufficiently strong nucleophile to displace the acylamido moiety.

As expected, the addition of Cu(II) ion to the system significantly prohibited the rearrangement, which is attributed to the masking of the reaction site by the coordination of the metal ion. The metal chelation seems to take place at the α-amino and amide carbonyl moieties (**3**), which might lead to facilitation of the amide bond cleavage.[11)] Contrary to what might be



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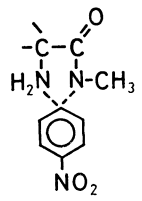
expected, no formation of hydrolyzates was observed during the course of reaction in the presence of Cu(II) ion. Hence, the chelation of copper(II) is not so effective as to alter the reaction pathway of the substrate **1**.

The Smiles rearrangement may be classified into two categories:[2)] (a) the rearrangement proceeds in a concerted fashion through transition state **4**,[12)] (b) the reaction proceeds through a stabilized intermediate **5** or **6** (Eq. 3). Depending on the stability of the intermediate σ-complex, either formation or decomposi-



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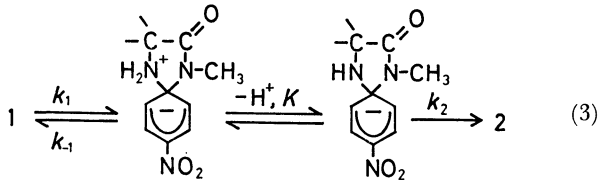

5 6 (3)

tion of the complex becomes the rate-determining step. When the complex is stable, it can be detected by conventional spectroscopy to verify that it takes part in the transformation of the substrate.[3,4] If the complex is not sufficiently stable, however, it is very difficult to confirm its existence.[6]

According to Okada and Sekiguchi,[4] the latter pathway appears to be plausible for the present rearrangement reaction. If we assume that the rate-determining step involves the formation of σ-complex ($k_1 \ll k_{-1}$, k_2), the pK_a obtained experimentally merely reflects the acid dissociation of the substrate, *i.e.*, ammonium$\rightleftarrows$free amine. Since no formation of intermediates was observed between **1** and **2** even by a rapid scanning spectroscopic technique, the subsequent steps should take place very rapidly.

When the decomposition of the complex is the rate-determining step ($k_2 \ll k_1$, k_{-1}), the observed rate constant (k_{obsd}) would be correlated with the specific rate constants of respective stages and equilibrium constant by

$$k_{obsd} = \frac{k_1 k_2 K}{(k_1 + k_{-1})[H^+] + k_1 K} \quad (4)$$

which conforms to the observed pH-rate profile (see Results). Rearrangement of Eq. 4 leads to

$$\frac{1}{k_{obsd}} = \frac{k_1 + k_{-1}}{k_1 k_2 K}[H^+] + \frac{1}{k_2}. \quad (5)$$

The intercept of the straight line based on the relationship between $1/k_{obsd}$ and $[H^+]$ gives the specific rate constant for the decomposition step (k_2), while a composite of rate and equilibrium constants (k_1, k_{-1}, and K) is obtained from the slope (120×10^{10} $s^{-1} M^{-1}$). Since we can not observe the individual steps independently, each constant can not be defined. However, on the basis of certain assumptions we can estimate roughly each constant as follows. The pK_a value of 10.34 obtained experimentally is too high to be assigned to intermediate **5**. If we arbitrarily assume as an upper limit that the pK of **5** is 7, the ratio k_1/k_{-1} becomes 4.5×10^{-4}. This indicates that the steady state concentration of the intermediates is very low to escape the conventional spectroscopic detection. If the pK value were close to the apparent pK_a and hence the ratio k_1/k_{-1} were somewhere around unity, we could have detected the intermediates **5** and/or **6**. Thus, these two mechanisms are kinetically indistinguishable.

Whichever mechanism is correct, the transition state has anionic or at least more polar character as compared with both the initial and final states. This is generally true for the Smiles rearrangement, polar solvents being favorable for the reaction.[2] The solvent effect observed over the acetonitrile concentration range higher than 20% (v/v) is in line with this consideration. Since substrate **1** carries a long alkyl chain it may entangle itself to form less reactive aggregates in the media of lower acetonitrile concentration,[13] resulting in the stabilization of the ground state. The increase in acetonitrile content defrosts the aggregation, leading to promotion of the rearrangement. Above *ca.* 20% of acetonitrile in the medium, the polarity effect of solvent to destabilize the polar transition state predominates and the reaction rate decreases with increasing acetonitrile concentration.

The observed positive effect of the cationic micelles is explicable in terms of the character of the transition state or intermediates. If the breakdown of the σ-complex intermediates is rate-determining, the CTAB micelles increase the steady state concentration of the anionic complex,[14,15] which is quite low in the absence of such micelles. This leads directly to enhancement of the observed rate constant.

According to the above discussion on the character of the transition state or intermediates, a negative value would be expected for the entropy of activation. The experimental value of +7.1 e.u. is apparently not compatible with this prediction. The discrepancy may have arisen from the fact that the experimental value contains several factors such as solvation to ground and transition states, not taken into consideration in the above argument. In any event, the value does not differ much from zero, indicating that the reaction is essentially unimolecular.

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