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The Effect of Medium on Rate and Mechanism: Aminolysis of *O*-4-Nitrophenyl Thionobenzoate in MeCN and H_2O

Ik-Hwan Um,* Jin-A Seok, Han-Tae Kim,† and Sun-Kun Bae†

Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea, and Department of Chemistry, Kunsan National University, Kunsan 573-701, Korea

ihum@mm.ewha.ac.kr

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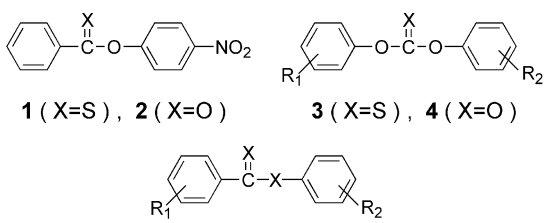
Pseudo-first-order rate constants (k_{obs}) have been measured spectrophotometrically for reactions of *O*-4-nitrophenyl thionobenzoate (**1**) with a series of alicyclic secondary amines in MeCN and H_2O at 25.0 ± 0.1 °C. The plot of k_{obs} vs amine concentration exhibits an upward curvature in all cases, indicating that the reactions proceed through two tetrahedral intermediates (a zwitterionic $T^{\pm}$ and its deprotonated anionic T^{-}) regardless of the amine basicity and the nature of the reaction medium. However, all the amines investigated have been found to be much less reactive in MeCN than in H_2O, although the amines are more basic in the former medium by 7−9 pK_a units.

Introduction

Since aminolyses of thiono compounds (e.g., **1**, **3**, **5**) have been much less investigated compared with those of the oxygen analogues (e.g., **2**, **4**, **6**), their reaction



mechanisms are not fully understood.[1−4] An intriguing question is whether the reaction proceeds through one or two tetrahedral intermediates, a zwitterionic $T^{\pm}$ and its deprotonated anionic T^{-}.[1−4] We have recently performed the reaction of *O*-4-nitrophenyl thionobenzoate (**1**) with a series of primary and secondary amines in H_2O (containing 20 mol % of DMSO) and found that the reaction with primary amines proceeds through one intermediate ($T^{\pm}$) while the corresponding reaction with secondary amines proceeds through two intermediates ($T^{\pm}$ and T^{-}).[2a] More systematic studies have been performed by Castro et al. for aminolyses of various thiono and dithio esters (e.g., **3** and **5**) in H_2O or in aqueous ethanol.[3] The reactions of **3** and **5** with weakly basic amines have been found to proceed through two tetrahedral intermediates, while the corresponding reactions with strongly basic amines proceed without the deprotonation process from the zwitterionic $T^{\pm}$.[3]

On the contrary, Lee et al. have studied the reactions of **5** with a series of aniline and benzylamine derivatives in pure MeCN and found that the reaction mechanism changes from rate-determining expulsion of the leaving group from $T^{\pm}$ for the reactions with weakly basic anilines to rate-determining nucleophilic attack for the reactions with more basic benzylamines.[4a] The deprotonation process from $T^{\pm}$, which has often been observed as the rate-determining step for the reactions performed in H_2O, has been found to be absent regardless of the amine basicity. On the other hand, Hanna et al. have found that reactions of various acetate esters with butylamine and pyrrolidine in MeCN proceed through the deprotonation process, while the corresponding reaction with piperidine proceeds without the deprotonation pathway although the basicity of these amines is similar.[5]

Since most studies have been performed only in H_2O or in an organic solvent separately, the effect of medium on rate and mechanism (particularly factors influencing the deprotonation process from $T^{\pm}$) cannot be compared directly. Therefore, we have performed the reaction of **1** with a series of alicyclic secondary amines in MeCN as well as H_2O (containing 20 mol % of DMSO). We have determined the microscopic rate constants associated with the aminolysis reaction in both MeCN and H_2O. We report here the effect of medium on rate and mechanism

* Address correspondence to this author at Ewha Womans University.
† Kunsan National University.

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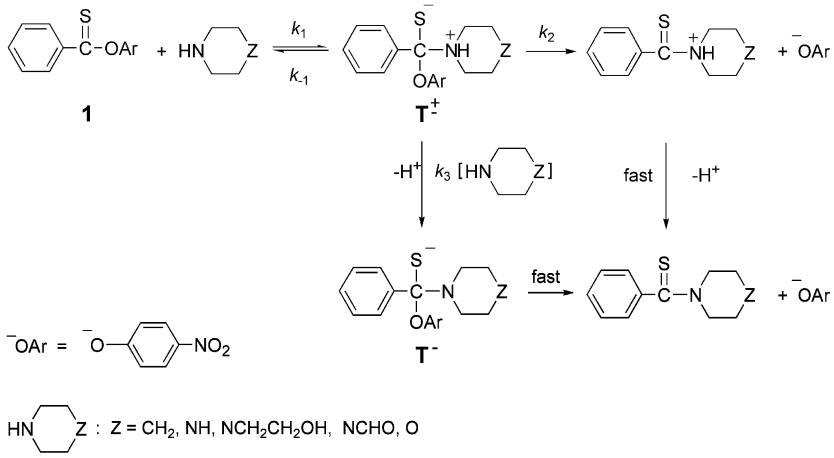
SCHEME 1



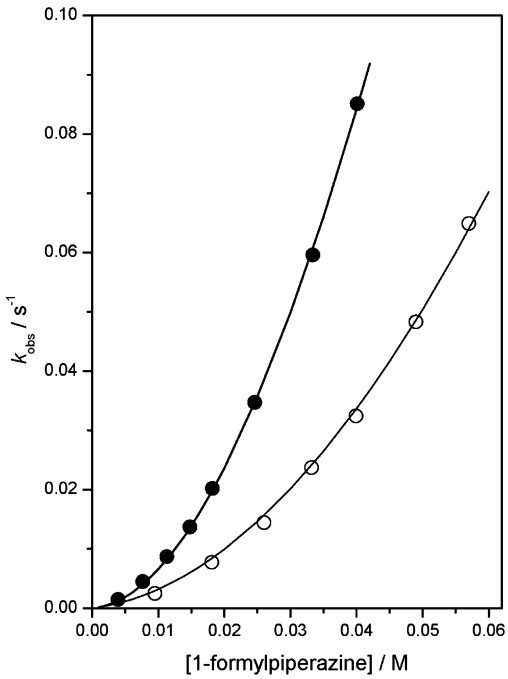


FIGURE 1. Plots of k_{obs} vs amine concentration for the reaction of **1** with 1-formylpiperazine in MeCN (○) and in H_2O containing 20 mol % of DMSO (●) at 25.0 ± 0.1 °C. The solid line was calculated through eq 2 with the parameters listed in Table S2.

together with factors which govern the presence or absence of the deprotonation process based on a quantitative analysis of the microscopic rate constants associated with the aminolysis reactions.

Results and Discussion

Reactions of **1** with all the amines studied proceeded with quantitative liberation of 4-nitrophenoxide and/or its conjugate acid. All the reactions in the present study obeyed first-order kinetics over 90% of the total reaction. Pseudo-first-order rate constants (k_{obs}) were calculated from the equation $\ln(A_\infty - A_t) = -k_{obs}t + C$. The k_{obs} values obtained in this way are summarized in Table S1 (Supporting Information) along with the kinetic conditions.

As shown in Figure 1, the plots of k_{obs} vs amine concentration exhibit an upward curvature for the reactions of **1** with 1-formylpieprazine performed in MeCN and H_2O. However, the reaction in MeCN is much slower than that in H_2O. A similar result has been obtained for the reactions of **1** with all the other amines studied (figure not shown). Such an upward curvature is typical of the reaction that proceeds through two tetrahedral intermediates, a zwitterionic $T^{\pm}$ and its deprotonated form T^{-}, as shown in Scheme 1.[2,3] One can derive a rate equation as eq 1 under the assumption of a steady-state condition for the zwitterionic intermediate $T^{\pm}$. Then the pseudo-first-order rate constant (k_{obs}) can be expressed as eq 2, in which [P], [$T^{\pm}$], [**1**], and [NH] represent the concentration of 4-nitrophenoxide (one of the products), the zwitterionic intermediate $T^{\pm}$, the substrate **1**, and the amine, respectively. [2,3]

$$d[P]/dt = k_2[T^{\pm}] + k_3[T^{\pm}][NH] = \{(k_1k_2[NH] + k_1k_3[NH]^2)[\mathbf{1}]\}/(k_{-1} + k_2 + k_3[NH]) \quad (1)$$

$$k_{obs} = (k_1k_2[NH] + k_1k_3[NH]^2)/(k_{-1} + k_2 + k_3[NH]) \quad (2)$$

The further assumption of $k_{-1} \gg k_2 + k_3[NH]$ simplifies eq 2 to eq 3.

$$k_{obs}/[NH] = k_1k_2/k_{-1} + k_1k_3[NH]/k_{-1} \quad (3)$$

As shown in Figure 2, the plot of k_{obs}/[NH] vs [NH] is linear for the reaction of **1** with 1-formylpiperazine regardless of the nature of the reaction medium. A similar result has been obtained for the reactions with weakly basic amines such as morpholine and 1-(2-hydroxyethyl)piperazine (figure not shown), indicating that the assumption $k_{-1} \gg k_2 + k_3[NH]$ appears to be valid for the reactions with these weakly basic amines. Therefore, the k_1k_2/k_{-1} and k_1k_3/k_{-1} values have been determined from the intercept and the slope of the linear plot, respectively. However, the corresponding plot for the reactions with strongly basic amines (e.g., piperazine and piperidine) is linear only at a low amine concentration region but exhibits negative deviations as the amine concentration is greatly increased (Figure S1 in Supporting Information). Therefore, the assumption $k_{-1} \gg k_2 + k_3[NH]$ is valid only at a low amine concentration region for the reactions with the strongly basic amines (both in

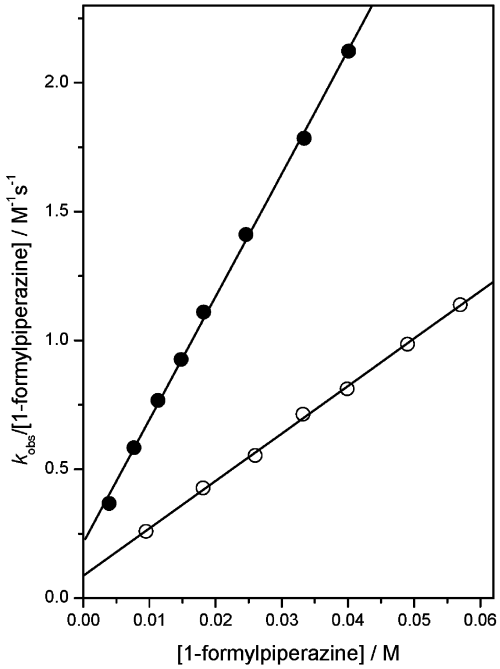


FIGURE 2. Plots of k_{obs}/[amine] vs [amine] for the reaction of **1** with 1-formylpiperazine in MeCN (○) and in H_2O containing 20 mol % of DMSO (●) at 25.0 ± 0.1 °C.

MeCN and in H_2O). One can explain this result as below: (1) The k_{-1} value would decrease with increasing amine basicity. (2) The term k_3[NH] increases with increasing [NH], although k_2 and k_3 values have been suggested to be insensitive to the amine basicity.[2,8,9]

$$[\mathrm{NH}]/k_{obs} = 1/k_1 + k_{-1}/k_1k_3[\mathrm{NH}] \qquad (4)$$

One can reduce eq 2 to eq 4 under the assumption $k_2 \ll k_3$[NH] at a high amine concentration region. As shown in Figure S2 (Supporting Information), the plot of [NH]/k_{obs} vs 1/[NH] is linear for the reaction of **1** with piperidine at a high amine concentration region but exhibits negative deviations at a low concentration region. A similar result has been obtained for the reactions with all the other amines studied, indicating that the assumption $k_2 \ll k_3$[NH] is valid only at a high amine concentration region. Therefore, the $1/k_1$ value has been estimated from the intercept of the linear part of the plot. The values of k_1, k_2/k_{-1}, and k_3/k_{-1} have been determined through the nonlinear least-squares fitting of eq 2 to the experimental data by using the estimated k_1 values, and summarized in Table S2 (Supporting Information).

As shown in Table S2, the k_3/k_{-1} ratio is in the range of 1.17−7.94 and 4.89−104 M^{-1} for the reaction run in MeCN and in H_2O, respectively. Therefore, the inequality $k_{-1} \gg k_3$[NH] + k_2 appears not to be valid when the amine concentration is significantly high, especially for the reactions with highly basic amines run in H_2O. This argument is consistent with the fact that Figure S1 (Supporting Information) exhibits negative deviations when the amine concentration is greatly increased, and the deviation is more significant for the reaction run in H_2O than for that run in MeCN.

The k_3/k_2 ratios have been determined from the k_2/k_{-1} and k_3/k_{-1} ratios. Since the magnitude of k_2 and k_3 values has been suggested to be insensitive to the amine basicity,[2,8,9] one might expect that the k_3/k_2 ratio is nearly constant upon changing the amine basicity. However, as shown in Table S2, the k_3/k_2 ratio for the reactions with piperazine and morpholine is definitively larger than that for the reactions with the other amines. One can attribute the large k_3/k_2 ratio obtained from the reaction with piperazine to the fact that piperazine possesses two basic sites to deprotonate from $T^{\pm}$. Similarly, the oxygen atom of morpholine appears to deprotonate from $T^{\pm}$ based on the large k_3/k_2 ratio, although the basicity of the O site of morpholine is much lower than that of the N site.

Since the k_3/k_2 ratio is in the range of 136−482 and 744−1610 M^{-1} for the reaction in MeCN and in H_2O, respectively, the assumption $k_2 \ll k_3$[NH] is valid only when the amine concentration is significantly high, especially for the reaction run in MeCN. This argument accounts for the result that the plot of [NH]/k_{obs} vs 1/[NH] is linear at a high [NH] region, but exhibits negative deviations at a low [NH] region, and such a negative deviation is more significant for the reaction run in MeCN than in H_2O, as shown in Figure S2 (Supporting Information). Therefore, the microscopic rate constants determined through the nonlinear least-squares fitting of eq 2 are considered to be reliable, and support the proposed reaction mechanism.

Many studies have been performed to investigate factors influencing reaction mechanism, particularly the presence or absence of the k_3 pathway.[2−7,10−12] Jencks et al. have suggested that the aminolysis of esters proceeds through the k_3 pathway when the ester possesses a strongly basic leaving group but without the k_3 process when the leaving group is weakly basic, indicating that the basicity of the leaving group is an important factor.[7a] Gresser et al. have reported that the aminolysis of diaryl carbonates (e.g., **4**) proceeds without the k_3 process.[7b] However, Castro et al. have found that the reaction of diaryl thionocarbonates (e.g., **3**) with weakly basic amines proceeds through the k_3 pathway, while the one with strongly basic amines proceeds without the k_3 process.[3b−d] Therefore, the basicity of amines and the structure of the electrophilic center (e.g., C=S vs C=O) have been suggested to be important to determine the reaction mech-

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anism.[3] We have recently shown that the amine nature is also an important factor, since the reaction of **1** with various secondary amines (both cyclic and acyclic secondary amines) proceeds through the k_3 pathway while the corresponding reaction with primary amines proceeds without the k_3 process regardless of the amine basicity.[2a]

Lee et al. have reported that the k_3 pathway is absent in the aminolysis of aryl dithiobenzoates (**5**) performed in MeCN.[4] The absence of the k_3 process has been attributed to a greatly reduced mobility of proton in such an aprotic solvent.[4] However, the present aminolysis of **1** performed in MeCN proceeds through the k_3 pathway as mentioned in the preceding section. Therefore, one can suggest that the reduced rate of proton transfer in MeCN is not an important factor in determining the presence or absence of the k_3 process. This argument can be further supported from the previous reports that aminolyses performed in various aprotic solvents including MeCN proceed through the k_3 pathway.[5,10−12]

It is interesting that the aminolysis that proceeds through the k_3 pathway has a small k_2/k_{-1} ratio either by deceasing the k_2 value or by increasing the k_{-1} value. The introduction of a poor leaving group as in the Jencks'system[7a] decreases the k_2 value. Similarly, the replacement of the C=O bond in the substrate by the C=S bond as in Castro's system would also decrease the k_2 value due to the decreased ability of $C-S^-$ to form a C=S bond compared with the ability of $C-O^-$ to form a C=O bond.[3] On the other hand, the k_2/k_{-1} ratio also can be decreased by using weakly basic amines, since the k_{-1} value increases with decreasing amine basicity. Besides, we have recently shown that the k_{-1} value is much larger for the reactions of **1** with secondary amines than those with primary amines.[2a] As shown in Table S2, the k_2/k_{-1} ratio is in the range of $(4.90-31.7) \times 10^{-3}$ and $(6.58-97.1) \times 10^{-3}$ for the reactions run in MeCN and in H_2O, respectively. These values are much smaller than those reported in the literature for the reactions proceeding without the k_3 pathway, i.e., ca. 1−25 for the reactions of **1** with various primary amines.[2a] Therefore, the small k_2/k_{-1} ratio is considered to be a common feature for the aminolysis reaction that proceeds through the k_3 pathway.

Figure S3 (Supporting Information), which is statistically corrected by using p and q,[13] exhibits a linear Brønsted-type plot with a β_1 value of 0.45 for the aminolysis of **1** performed in MeCN. A similar result has been shown in the inset of Figure S3 for the corresponding reactions performed in the aqueous medium with a β_1 value of 0.39. Figure S4 (Supporting Information) demonstrates that the plot of log k_2/k_{-1} vs pK_a is also linear for reactions performed both in MeCN and in H_2O with a $-\beta_{-1}$ value of 0.29 and 0.39, respectively. Since there is little difference in the β_{eq} value for the reactions in MeCN ($\beta_{eq} = 0.74$) and H_2O ($\beta_{eq} = 0.78$), one can suggest that the effect of the medium on the structure of the transition state is insignificant in the present aminolysis.

As mentioned in the preceding section, the reaction performed in MeCN is much slower than that run in H_2O. One can explain the effect of medium on the reaction rate as follows. The k_1 process yields a zwitterionic intermediate $T^{\pm}$ as shown in Scheme 1. Since MeCN cannot stabilize such an ionic species,[14] the k_1 value is expected to be smaller in MeCN than in H_2O. In fact, the k_1 value shown in Table S2 for the reactions run in MeCN is slightly smaller than that for the reactions run in H_2O (except for the reaction with 1-formylpiperazine), although the amines are more basic in MeCN than in H_2O by ca. 7−9 pK_a units. On the other hand, the breakdown of the intermediate $T^{\pm}$ to the reactants (the k_{-1} process) would be faster in MeCN than in H_2O, since $T^{\pm}$ would be more unstable in the former medium. However, the medium effect on the rate of the decomposition of $T^{\pm}$ to T^- (the k_3 process) or to the products (the k_2 process) is expected to be insignificant, since both processes yield another ionic species from the zwitterionic $T^{\pm}$. Therefore, the k_2/k_{-1} and k_3/k_{-1} ratios are expected to be smaller in MeCN than in H_2O. In fact, as shown in Table S2, the k_2/k_{-1} and k_3/k_{-1} ratios have been determined to be much smaller for the reactions performed in MeCN than for those in H_2O.

Lee et al. have recently proposed that the k_3 value would be diminished greatly in MeCN since the H^+ mobility decreases in the aprotic solvent.[4a] Such a solvent effect on the k_3 value would cause a further decrease in the k_3/k_{-1} ratio for the reacion run in MeCN. This argument is consistent with the fact that the k_3/k_{-1} ratio decreases much more significantly than the k_2/k_{-1} ratio upon the medium change from H_2O to MeCN. Therefore, one can suggest that the decreased k_3/k_{-1} ratio is the most responsible contributor to the decreased reaction rate upon the medium change from H_2O to MeCN. To the best of our knowledge, the effect of medium on the microscopic rate constants for ester aminolyses has never been analyzed quantitatively.

To investigate the effect of medium on rate and basicity, the plot of log $k_1^{H_2O}/k_1^{MeCN}$ vs ΔpK_a has been constructed, in which $k_1^{H_2O}$, k_1^{MeCN}, and ΔpK_a represent the k_1 values in H_2O and in MeCN, and the difference in the pK_a of the conjugate acid of amine in the two solvents (i.e., ΔpK_a = pK_a in MeCN − pK_a in H_2O), respectively. As shown in Figure S5 (Supporting Information), the plot is linear with a slope of 0.30. One can also see a linear correlation between $\log(k_1k_2/k_{-1})^{H_2O}/(k_1k_2/k_{-1})^{MeCN}$ and ΔpK_a with a slope of 0.62 (Figure S6 in the Supporting Information). The linearity shown in Figures S5 and S6 suggests that the effect of medium on the amine basicity (ΔpK_a) is reflected in the effect of medium on the k_1 value as well as the equilibrium (k_1/k_{-1}). However, the medium effect appears to be more significant on the basicity (ΔpK_a) than on the k_1 value or on the k_1/k_{-1} ratio, since the slopes of Figures S5 and S6 are much smaller than unity.

In conclusion, we have found the following. (1) The aminolysis of **1** proceeds through rate-limiting deprotonation from $T^{\pm}$ to give T^- both in MeCN and in H_2O. (2)

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The reaction is much slower in MeCN than in H_2O, although the amines studied are more basic in the former medium by ca. 7−9 pK_a units. (3) The k_3/k_{-1} ratio decreases more significantly than the k_1 value or the k_2/k_{-1} ratio upon the medium change from H_2O to MeCN, which is most responsible for the slower reaction rate in MeCN.

Experimental Section

Materials. *O*-4-Nitrophenyl thionobenzoate (**1**) was synthesized as reported previously.[1,6] The purity of **1** was checked by means of the melting point and spectral data such as IR and ^{1}H NMR characteristics. Amines and other chemicals used were of the highest quality available. MeCN was distilled over P_2O_5. DMSO was treated with CaH_2 overnight and distilled at a reduced pressure (bp 64−66 °C at 6−7 mmHg) and stored under nitrogen. Doubly glass distilled water was further boiled and cooled under nitrogen just before use. When the reactions were performed in aqueous medium, 20 mol % of DMSO was added to H_2O due to the low solubility of **1** in pure H_2O.

Kinetics. All the reactions were carried out under pseudo-first-order conditions in which the amine concentrations were at least 30 times greater than the substrate concentration. The reaction was followed by monitoring the appearance of the leaving 4-nitrophenoxide at 400 nm with a UV−vis spectrophotometer for slow reactions ($t_{1/2} \geq 10$ s) or with a stopped-flow spectrophotometer for fast reactions ($t_{1/2} < 10$ s) equipped with a constant temperature circulating bath to keep the reaction temperature at 25.0 ± 0.1 °C. The amine stock solution of ca. 0.2 M was prepared by dissolving 2 equiv of free amine and 1 equiv of standardized HCl solution to keep the pH constant by making a self-buffered solution for the reactions run in H_2O. However, for the reactions run in MeCN, the amine stock solutions were prepared only with free amines. All the solutions were prepared fresh just before use under nitrogen and transferred by gastight syringes.

Product Analysis. 4-Nitrophenoxide (and/or its conjugate acid) was identified as one of the products of the aminolysis of **1** by comparison of the UV−vis spectrum at the end of reaction with the authentic sample under the same kinetic conditions. Other products (e.g., *N*-thiobenzoylpiperidine) were analyzed by HPLC by comparison with the authentic sample. The flow rate was 1 mL/min, and the eluent was 50% MeCN in MeOH (v/v).

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Supporting Information Available: Tables S1 and S2 giving reaction conditions and the kinetic results and Figures S1−S6 showing kinetic results. This material is available free of charge via the Internet at http://pubs.acs.org.

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