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# Kinetic Study on Aminolysis of 4-Nitrophenyl Nicotinate and Isonicotinate: Factors Influencing Reactivity and Reaction Mechanism

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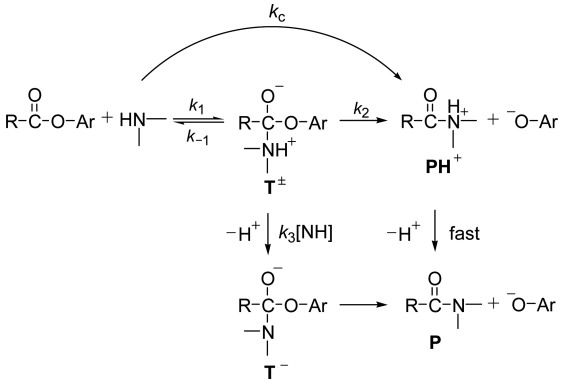
A kinetic study is reported on nucleophilic substitution reactions of 4-nitrophenyl nicotinate (**7**) and 4-nitrophenyl isonicotinate (**8**) with a series of cyclic secondary amines in $H_2O$ containing 20 mol % DMSO at 25.0 ºC. The Brønted-type plots for the reactions of **7** and **8** are linear with $\beta_{nuc}$ = 0.90 and 0.92, respectively, indicating that the reactions proceed through a stepwise mechanism with expulsion of the leaving group occurring in the rate-determining step. Comparison of the reactivity of **7** and **8** with that of 4-nitrophenyl benzoate (**2a**) and 4-nitrophenyl picolinate (**6**) has revealed that their reactivity toward the amines increases in the order **2a** < **7** < **8** < **6**, although the reactions of these substrates proceed through the same mechanism. Factors that control reactivity and reaction mechanism have been discussed in detail (*e.g.*, inductive and field effects, H-bonding interaction, solvent effect, *etc*.).

**Key Words :** Aminolysis, Brønsted-type plots, Field effect, Solvent effect, H-Bonding interaction

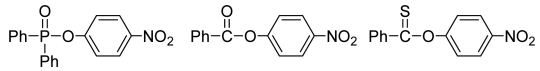
## Introduction

Aminolysis of esters has intensively been investigated due to the importance in synthetic applications and biological processes (*e.g.*, peptide biosynthesis and enzyme actions).[1-8] As shown in Scheme 1, nucleophilic substitution reactions of esters with amines have been reported to proceed either through a concerted mechanism or *via* a stepwise pathway with one or two intermediates (*e.g.*, a zwitterionic tetrahedral intermediate $T^{\pm}$ and its deprotonated form $T^{-}$).[2-8] The suggested factors that control reaction mechanisms are the nature of the electrophilic center, reaction medium, stability of reaction intermediate, structure of the leaving- and non-leaving-groups, *etc*.[2-8]

Reactions of 4-nitrophenyl diphenylphosphinate (**1**) with primary and secondary amines in $H_2O$ have been reported to proceed through a concerted mechanism on the basis of linear Brønsted-type plots with $\beta_{nuc}$ = 0.5 ± 0.1.[5] However, reactions of 4-nitrophenyl benzoate (**2a**) with a series of cyclic secondary amines have been suggested to proceed through a stepwise mechanism, in which expulsion of the leaving group from $T^{\pm}$ occurs in the rate-determining step (RDS), on the basis of a linear Brønsted-type plot with $\beta_{nuc}$ = 0.81.[8] Furthermore, the corresponding reactions of *O*-4-nitrophenyl thionobenzoate (**2b**) have been concluded to proceed with two intermediates (*e.g.*, $T^{\pm}$ and $T^{-}$) since the plots of $k_{obsd}$ *vs*. [amine] curved upward. These indicate that the nature of electrophilic centers (*e.g.*, P=O, C=O and C=S) is an important factor that controls the reaction mechanism.




**Scheme 1**

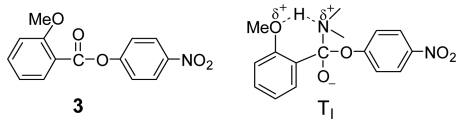


**1** **2a** **2b**

Aminolysis of 2,4-dinitrophenyl benzoate (a derivative of **2a**) in $H_2O$ has been reported to proceed through a stepwise mechanism with a change in the RDS on the basis of a curved Brønsted-type plot.[8a] However, the corresponding reaction in MeCN has been suggested to proceed through a concerted mechanism on the basis of a linear Brønsted-type plot with $\beta_{nuc}$ = 0.40,[8b] indicating that the nature of reaction medium also governs the reaction mechanism. This idea is consistent with the reports from gas-phase studies including theoretical calculations.[9] The existence of $T^{\pm}$ in the gas phase or in aprotic solvents has often been questioned, *e.g.*, Ilieva *et al*. failed to identify $T^{\pm}$ for the reaction of methyl formate with ammonia,[9a,b] while Sung *et al*. reported that at least five explicit water molecules are required to stabilize $T^{\pm}$ in the reaction of phenyl acetate with ammonia.[9c,d]

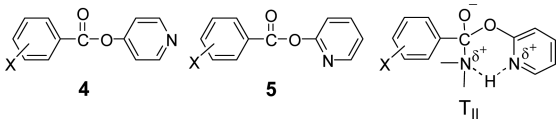
However, aminolysis of 4-nitrophenyl 2-methoxybenzoate (**3**) has been reported to proceed through a stepwise mechanism even in MeCN on the basis of a linear Brønsted-type plot with $\beta_{nuc}$ = 0.70.[10a] We have proposed a six-membered

cyclic intermediate as modeled by $T_I$, which is stabilized through the H-bonding interaction.[10a]



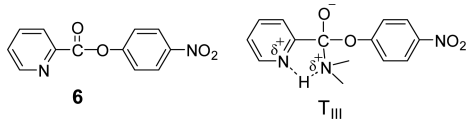
**3** $T_I$

Reactions of 4-pyridyl X-substituted-benzoates (**4**) have been concluded to proceed through a stepwise mechanism with two intermediates $T^{\pm}$ and $T^{-}$ when the substituent X is a strong electron-withdrawing group (EWG) such as 4-$NO_2$, 4-CN.[11a] In contrast, the corresponding reactions of 2-pyridyl X-substituted-benzoates (**5**) have been concluded to proceed through a concerted mechanism with a transition state (TS) structure similar to $T_{II}$ regardless of the electronic nature of the substituent X.[11b] We have proposed that the H-bonding interaction as illustrated in the cyclic intermediate $T_{II}$ increases the nucleofugality of the leaving group by decreasing the leaving-group basicity from strongly basic 2-pyridyloxide (p$K_a$ = 11.62 in $H_2O$) to weakly basic 2-pyridiniumoxide (p$K_a$ = 0.75 in $H_2O$) or its tautomer 2-pyridone.[11b] Thus, the enhanced nucleofugality has been suggested to force the reaction of **5** to proceed through a concerted mechanism by decreasing the lifetime of the intermediate $T_{II}$.[11b]



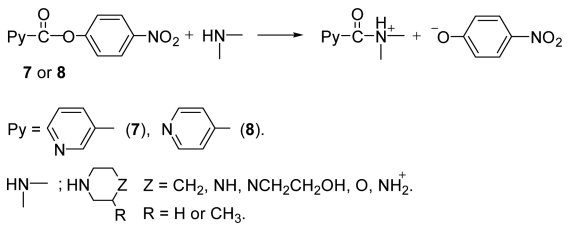
**4** **5** $T_{II}$

We have recently reported that aminolysis of 4-nitrophenyl picolinate (**6**) in $H_2O$ containing 20 mol % DMSO proceeds through a stepwise mechanism with a cyclic intermediate as modeled by $T_{III}$ on the basis of a linear Brønsted-type plot with $\beta_{nuc}$ = 0.78.[12] We have shown that **6** is over 35 times more reactive than **2a**.[12] Enhanced stability of the intermediate $T_{III}$ through the H-bonding interaction has been suggested to be responsible for the highly enhanced reactivity of **6** since such cyclic intermediate is structurally not possible for the reactions of **2a**.[12]



**6** $T_{III}$

Our study has now been extended to the reactions of 4-nitrophenyl nicotinate (**7**) and 4-nitrophenyl isonicotinate (**8**) with a series of cyclic secondary amines in $H_2O$ containing 20 mol % DMSO to obtain further information on the reaction mechanism (Scheme 2). The kinetic results have been compared with those reported for the corresponding reactions of **2a** and **6** to investigate factors influencing reactivity and reaction mechanism.



**Scheme 2**

## Results and Discussion

The reactions of **7** and **8** were followed spectrophotometrically by monitoring the appearance of 4-nitrophenoxide under pseudo-first-order conditions (*e.g.*, the concentration of amines was kept in excess over that of the substrate). All of the reactions in this study obeyed first-order kinetics and the pseudo-first-order rate constants ($k_{obsd}$) were calculated from the equation, $\ln (A_\infty - A_t) = -k_{obsd}t + C$. The plots of $k_{obsd}$ *vs.* [amine] were linear with excellent correlation coefficients (*e.g.*, $R^2 \geq 0.9995$) and passed through the origin, indicating that general base catalysis by a second amine molecule is absent and the contribution of $H_2O$ and/or $OH^-$ from hydrolysis of amines to $k_{obsd}$ is negligible. Accordingly, the second-order rate constants ($k_N$) for the reactions of **7** and **8** were calculated from the slope of the linear plots. The $k_N$ values calculated in this way are summarized in Table 1 together with those reported previously for the corresponding reactions of **2a** and **6** to investigate the effect of changing the structure of the nonleaving group on reactivity and reaction mechanism.

**Reaction Mechanism.** Table 1 shows that reactivity of the amines decreases as the amine basicity decreases, *e.g.*, the $k_N$ value for the reaction of **7** decreases from 16.2 $M^{-1}s^{-1}$ to 3.65 $\times 10^{-1}$ and 7.80 $\times 10^{-4}$ $M^{-1}s^{-1}$ as the p$K_a$ value of the conjugate acid of amine decreases from 11.02 to 9.38 and 5.95, in turn. The effect of amine basicity on reactivity is illustrated in Figure 1.

As shown in Figure 1, the Brønsted-type plots for the reactions of **7** and **8** are linear with $\beta_{nuc}$ = 0.90 and 0.92, respectively, when the p$K_a$ and $k_N$ values were statistically corrected by using $p$ and $q$ (*i.e.*, $p$ = 2 except $p$ = 4 for piperazinium ion and $q$ = 1 except $q$ = 2 for piperazine).[14] A

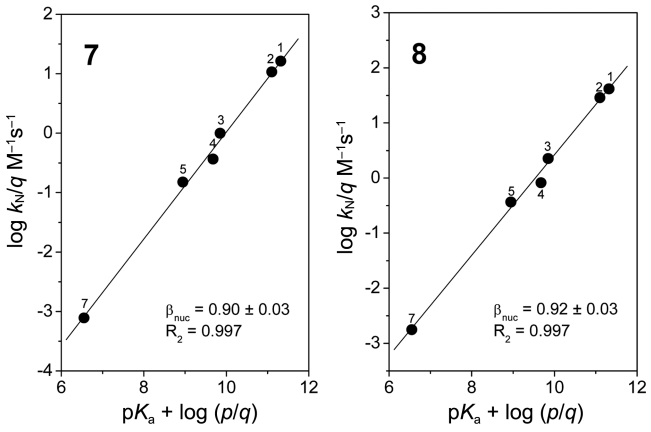



**Figure 1.** Brønsted-type plots for the aminolysis of 4-nitrophenyl nicotinate (**7**) and isonicotinate (**8**) in 80 mol % $H_2O$/20 mol % DMSO at 25.0 ± 0.1 °C. The identity of points is given in Table 1.

**Table 1.** Summary of Kinetic Data for the Reactions of 4-Nitrophenyl Benzoate (**2a**), Picolinate (**6**), Nicotinate (**7**) and Isonicotinate (**8**) with Cyclic Secondary Amines in $H_2O$ Containing 20 mol % DMSO at 25.0 ± 0.1 °C

| | amines | p$K_a$ | $k_N$/$M^{-1}s^{-1}$ | | | |
|---|---|---|---|---|---|---|
| | | | **2a**[a] | **6**[a] | **7** | **8** |
| 1 | piperidine | 11.02 | 5.94 | 211 | 16.2 | 41.4 |
| 2 | 3-methylpiperidine | 10.80 | - | 162 | 10.7 | 28.7 |
| 3 | piperazine | 9.85 | 0.851 | 50.5 | 1.99 | 4.51 |
| 4 | 1-(2-hydroxyethyl)piperazine | 9.38 | 0.195 | 11.2 | 0.365 | 0.822 |
| 5 | morpholine | 8.65 | 0.0876 | 5.63 | 0.150 | 0.365 |
| 6 | 1-formylpiperazine | 7.98 | 0.0100 | - | - | - |
| 7 | piperazinium ion | 5.95 | - | 0.0417 | 0.000780 | 0.00176 |
| 8 | $CH_3CH_2O^-$ | | 10.5[b] | 436[b] | 748[b] | 4510[b] |

[a]The kinetic data for the aminolysis of **2a** and **6** were taken from refs. 6 and 12, respectively. [b]The kinetic data for the reactions with $CH_3CH_2O^-$ were taken from ref. 13.

$\beta_{nuc}$ value of 0.90 ± 0.1 is much larger than that reported for reactions proceeding through a concerted mechanism (*e.g.*, $\beta_{nuc}$ = 0.5 ± 0.1 for aminolysis of **1** and its thio analogue 4-nitrophenyl diphenylphosphinothioate),[5] but is typical for reactions reported previously to proceed through a stepwise mechanism with expulsion of the leaving group occurring in the RDS.[2-8] In fact, the corresponding reactions of **2a** and **6** have previously been reported to proceed through a stepwise mechanism, in which expulsion of the leaving group from $T^{\pm}$ occurs in the RDS, on the basis of a linear Brønsted-type plot with $\beta_{nuc}$ = 0.81[6] and 0.78,[12] respectively. Thus, one can suggest that the aminolyses of substrates **2a**, **6**, **7** and **8** proceed through the same mechanism (*i.e.*, a stepwise mechanism with expulsion of the leaving group being the RDS).

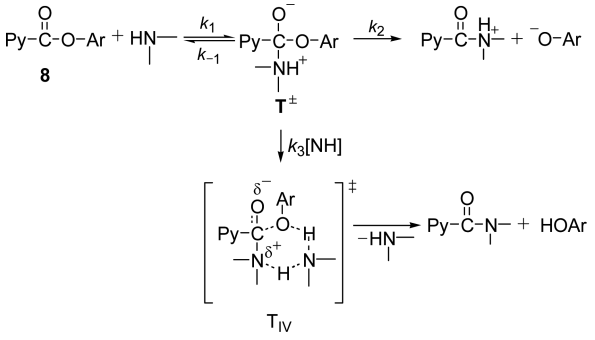
**Effect of Nonleaving-Group Structure on Reactivity.** It is well known that reactivity of esters is strongly influenced by the electronic nature of the substituent in the leaving group or in the nonleaving group. An EWG would increase the reactivity of esters by increasing either the nucleofugality of the leaving group or the electrophilicity of the reaction center. Since substrates **2a**, **6**, **7** and **8** possess the same leaving group (*i.e.*, 4-nitrophenoxide ion), their reactivity should be dependent mainly on the electrophilicity of the reaction center.

It is apparent that the N atom in the pyridine ring of substrates **6-8** would increase the electrophilicity of the reaction center, since a pyridine ring is considered as a π-deficient heterocycle and an analogue of benzene ring that carries an EWG due to the electronegative N atom. Thus, one can suggest that the polar effects (*e.g.*, field and inductive effects) exerted by the electronegative N atom in substrates **6-8** are responsible for the kinetic results that substrates **6**, **7** and **8** exhibit much larger $k_N$ values than **2a** regardless of the amine basicity (Table 1).

One might expect that the electronic effect exerted by the N atom in substrates **6-8** would be transmitted either through space (*i.e.*, field effect) or *via* bonds (*i.e.*, inductive effect). It is evident that the inductive effect would decrease as the number of bonds between the N atom and the electrophilic center increases. Thus, one might expect that the reactivity of substrates **6-8** would decrease in the order **6** > **7** > **8**, if the inductive effect exerted by the N atom is more important than the field effect. However, **8** exhibits larger $k_N$ values than **7** regardless of the amine basicity, indicating that the inductive effect is not responsible for the reactivity order shown by substrates **7** and **8**. Furthermore, Table 1 shows that the $k_N$ value for the reactions of **6-8** with $CH_3CH_2O^-$ increases in the order **6** < **7** < **8**. This is contrary to the expectation if the inductive effect is a more important factor than the field effect.

The dipole moment of pyridine is 2.37 debyes.[1c] Since the negative dipole end is on the N atom, nucleophilic attack by an anionic nucleophile (*e.g.*, $CH_3CH_2O^-$ ion) would experience electronic repulsion more strongly as the N atom is closer to the reaction center (*e.g.*, the field effect). This idea is consistent with the order of reactivity of **6-8** toward the anionic nucleophile $CH_3CH_2O^-$ ion (*i.e.*, **6** < **7** < **8**). It is apparent that such electronic repulsion through the space (*i.e.*, the field effect) would be significant for the reactions with anionic nucleophiles but would be less significant for the reactions with neutral amines. Besides, the aminolysis of **6** has been reported to proceed through a stepwise mechanism with the cyclic intermediate $T_{III}$, which is stabilized through the H-bonding interaction.[12] In contrast, such a five-membered cyclic intermediate is structurally not possible for the reactions of **7** and **8**. Thus, one can propose that the field effect exerted by the N atom of the pyridine ring in substrates **6-8** together with the stabilization of $T_{III}$ through the H-bonding interaction is responsible for the reactivity order shown in Table 1.

**Solvent Effect on Reaction Mechanism.** We have recently reported that the reactions of **8** with a series of cyclic secondary amines in MeCN proceed through a stepwise mechanism with two intermediates (*i.e.*, $T^{\pm}$ and $T^-$) when the incoming amines are weakly basic (p$K_a \leq 18.5$), but the deprotonation process to form $T^-$ from $T^{\pm}$ by a second amine molecule is absent for the reactions with strongly basic amines.[15] In contrast, the current aminolysis of **8** in $H_2O$ containing 20 mol % DMSO has been proposed to proceed through a stepwise mechanism with $T^{\pm}$ (but without $T^-$) as



**Scheme 3**

an intermediate regardless of the amine basicity. This demonstrates convincingly that the nature of reaction medium is an important factor that controls the reaction mechanism.

To account for the contrasting reaction mechanisms, we propose that the aminolysis of **8** in MeCN proceeds through a stepwise mechanism with $T^{\pm}$ and a cyclic TS (*i.e.*, $T_{IV}$) rather than an anionic intermediate $T^{-}$. As shown in Scheme 3, the second amine molecule in $T_{IV}$ deprotonates from the aminium moiety of $T^{\pm}$ as a general base catalyst and simultaneously donates its proton to the O atom of the leaving group as a general acid catalyst.

The proposed mechanism for the aminolysis of **8** in MeCN shown in Scheme 3 can be supported by the following reasons: (1) It is well known that proton transfer occurs in the RDS for reactions in which a second amine molecule behaves as a general acid (or a general base) catalyst. However, one might expect that the deprotonation process from the aminium moiety of $T^{\pm}$ by a second amine molecule would occur rapidly. This implies that the role of a second amine molecule would not be limited just to the deprotonation from the aminium moiety of $T^{\pm}$ to form $T^{-}$. (2) It is firmly understood that anions are highly destabilized in MeCN due to the electronic repulsion between anions and the negative dipole end of MeCN.[16] Thus, the aminolysis of **8** in MeCN would not proceed through the anionic intermediate $T^{-}$ to avoid the electronic repulsion. Instead, it would proceed through the cyclic TS as modeled by $T_{IV}$, in which the positive and negative charges are delocalized through the H-bonding interactions. (3) It is apparent that a more basic amine would deprotonate from the aminium moiety of $T^{\pm}$ more rapidly, while the aminium ion would tend to hold its proton more strongly as the amine becomes more basic. Accordingly, the deprotonation process to form $T^{-}$ from $T^{\pm}$ by a second amine molecule should be independent of amine basicity, if $T^{-}$ is formed from $T^{\pm}$ upon deprotonation by a second amine molecule. However, as mentioned above, the reaction mechanism is dependent on the amine basicity. This indicates that $T^{-}$ is not formed for the reaction of **8** in MeCN. (4) In contrast, a weakly basic amine in $T_{IV}$ would donate its proton to the O atom of the leaving group more easily than a strongly basic amine or *vice versa*. This accounts for the kinetic result that only weakly basic amines catalyze the reaction of **8** in MeCN, and supports the proposed mechanism shown in Scheme 3 (*i.e.*, $T_{IV}$ but not $T^{-}$).

## Conclusions

The current study has allowed us to conclude the following: (1) Linear Brønsted-type plots with $\beta_{nuc} = 0.90$ or 0.92 obtained from the aminolysis of **7** and **8** carried out in $H_2O$ containing 20 mol % DMSO suggest that the reaction proceeds through a stepwise mechanism, in which expulsion of the leaving group occurs in RDS. (2) Substrates **6-8** are more reactive than **2a** due to the presence of an electronegative N atom in the pyridine ring. (3) The fact that **8** is more reactive than **7** implies that the field effect is more important than the inductive effect. (4) Stabilization of the intermediate $T_{III}$ is responsible for the result that **6** is more reactive than **7** and **8** toward amines. (5) Solvent effect is an important factor that controls the reaction mechanism.

## Experimental Section

**Materials.** Substrates **7** and **8** were readily prepared from the reaction of 4-nitrophenol with nicotinyl chloride and isonicotinyl chloride, respectively, under the presence of triethylamine in anhydrous diethyl ether as reported previously.[17] The crude products were purified by short pathway silica gel column chromatography. Their purity was checked by their melting point, $^1$H and $^{13}$C NMR spectra. Amines and other chemicals were of the highest quality available.

**Kinetics.** Kinetic study was carried out by using a UV-Vis spectrophotometer for slow reaction (*e.g.*, $t_{1/2} \geq 10$ s) or a stopped-flow spectrophotometer for fast reactions (*e.g.*, $t_{1/2} < 10$ s) equipped with a constant-temperature circulating bath to maintain the reaction temperature at 25.0 ± 0.1 °C. All reactions were carried out under pseudo-first-order conditions in which the concentration of amines was kept at least 20 times greater than that of the substrate. Typically, the reaction was initiated by adding 5 μL of a 0.01 M of substrate stock solution in MeCN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of solvent and the amine nucleophile. Reactions were followed generally up to 9 half-lives and $k_{obsd}$ were calculated using the equation, $\ln (A_\infty - A_t) = -k_{obsd}t + C$.

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