A Mechanistic Study for Aminolysis of *p*-Nitrophenyl Phenylacetate

Ik-Hwan Um*, E-Suk Yeom, Hye-Jin Kwon, and Dong-Sook Kwon

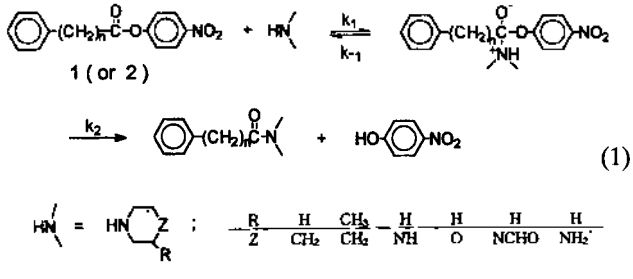
Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea
Received May 26, 1997

Second-order rate constants have been measured spectrophotometrically for the reactions of *p*-nitrophenyl phenylacetate (**1**) and benzoate (**2**) with a series of alicyclic amines in H_2O containing 20 mole % DMSO at 25.0 °C. **1** appears to be more reactive than **2** toward all the amines studied, although phenylacetic acid is a weaker acid than benzoic acid. The higher reactivity of **1** can be attributed to resonance and/or steric effect, since the ground state of **2** can be stabilized by resonance and **1** would experience less steric hindrance due to the presence of CH_2 group between phenyl and C=O group. The reactivity of the amines increases with increasing their basicity. The Brönsted-type plots for aminolysis of **1** and **2** show good linearity with β_{nuc} values of 0.81 and 0.85, respectively, indicating that the TS structures of the aminolyses of **1** and **2** are similar. Besides, the linear Brönsted plots obtained in the present system clearly suggest that there is no mechanism change for the given series of the amines and the reactions of **1** and **2** proceed in a same mechanism.

Introduction

Aminolysis of carbonyl esters has been intensively studied due to the interest in biology and chemistry, and the reaction mechanisms have been fairly well known.[1-5] The most frequently used tool for mechanistic investigation is linear free energy relationships such as Brönsted and Hammett type correlations.[6] A break in Brönsted type plots has often been observed in aminolysis of carboxylic esters containing a good leaving group such as 2,4-dinitrophenoxide, and the break has been suggested as evidence for a change in the rate determining step (RDS).[1-5] In general, the RDS of aminolysis of carboxylic esters has been suggested to be dependent on the basicity of the leaving group and the incoming amine, *i.e.* the RDS changes from rate-determining leaving group departure (k_2 step) to nucleophilic attack (k_1 step) as the basicity of the nucleophilic amine increases.[1-5]

Recently, Lee and Yoh performed the reaction of *p*-nitrophenyl phenylacetate (**1**) with 4 secondary cyclic amines in H_2O at 40 °C, and observed a curvature at pK_a near 10 in the Brönsted type plot.[7] Accordingly, the curvature was attributed to a change in the RDS.[7] However, the observation of the curvature at pK_a 10 appears to be quite unusual in aminolysis of carboxylic esters, since a change in the RDS for aminolysis of aryl acetates has been generally suggested to occur when the basicity of the incoming amine becomes about 4-5 pK_a units higher than that of the leaving aryloxides.[1-5]



1 (or 2)

(1)

n=1, *p*-nitrophenyl phenylacetate (**1**)
n=0, *p*-nitrophenyl benzoate (**2**)

Aminolysis of **1** may proceed either by $B_{AC}2$ pathway or by E1cB mechanism. The latter mechanism would be predominant when the nucleophilic amine is bulky and basic enough to deprotonate the α-hydrogens in **1**.[8] Therefore, the curvature observed by Lee and Yoh could be possibly due to a change in the reaction pathway from $B_{AC}2$ to E1cB mechanism as the basicity of the secondary amine increases. In order to reexamine the reaction mechanism of the aminolysis of **1**, we performed the reactions of **1** with 6 cyclic amines as shown in Eq. (1).

Experimental

Materials. *p*-Nitrophenyl phenylacetate was prepared easily from the reaction of phenylacetyl chloride and *p*-nitrophenol in the presence of triethylamine in methylene chloride (mp 61-63 °C, lit[7] 60-61.5 °C). Other chemicals including the amines used were of the highest quality available from Aldrich (or Tokyo Kasei for 3-methylpiperidine) and generally recrystallized or distilled before use. Doubly glass distilled water was further boiled and cooled under a nitrogen atmosphere just before use.

Kinetics. The reactions were followed by monitoring the appearance of the leaving p-nitrophenoxide at 410 nm (or *p*-nitrophenol at 350 nm for the reaction with piperazinium ion) using a Hitachi U-2000 UV-VIS spectrophotometer equipped with a Neslab RTE-110 model constant temperature circulating bath to keep the temperature in the reaction cell at 25.0±0.1 °C. All the reactions were performed under pseudo-first-order conditions in which the amine concentrations were in much excess of the substrate concentration. The amine solutions were prepared by dissolving equivalent amount of free amine and the conjugate acid of the amine to keep the pH constant. 20 mole % of DMSO was added to the reaction medium (H_2O) to eliminate solubility problems. All the solutions were transferred by Hamilton gas-tight syringes under a nitrogen atmosphere. Other detailed methods for the experiment were described in previous papers.[5]

Table 1. Experimental Conditions and Pseudo-first-order Rate Constants (k_{obs}) for Aminolysis of *p*-Nitrophenyl Phenylacetate (**1**) in H_2O Containing 20 mole % DMSO at 25.0 °C±0.1 °C

Amine; >NH	$[>NH]_{free}/10^{-3}$, M	pH	$k_{obs}/10^{-3}$ s^{-1}
piperazinium ion	91.3-103	5.95±0.04	0.235-0.285
1-formylpiperazine	42.7-66.3	7.98±0.02	2.83-4.36
morpholine	9.40-39.3	8.65±0.03	4.40-16.3
piperazine	9.60-26.2	9.85±0.02	40.0-100
3-methylpiperidine	1.98-9.50	10.80±0.03	26.0-134
piperidine	1.96-9.60	11.02±0.02	35.3-163

Result and Discussion

Pseudo-first-order rate constants (k_{obs}) were obtained from the equation, ln $(A_\infty - A_t) = -k_{obs} \cdot t + c$, and apparent second-order rate constants (k_{app}) were calculated from the slope of plots of k_{obs} versus amine concentration. The estimated error in any particular measured rate constant is less than 3%. The kinetic results are summarized in Table 1 together with the kinetic conditions.

As shown in Figure 1, the plots of k_{obs} *vs* amine concentration give good linear correlation, indicating that general acid/base catalysis is absent. The intercepts of Figure 1 are close to zero, implying that contribution by H_2O or HO^- from solvolysis of amines to k_{obs} is negligible. Other amines (not shown in Figure 1) also give similar results.

In Table 2 are summarized apparent second-order rate constants for the reaction of **1** with 6 secondary amines in H_2O containing 20 mole % DMSO at 25.0±0.1 °C. For a comparison purpose, the data for the corresponding reaction of *p*-nitrophenyl benzoate (**2**) in 20 mole DMSO at 25.0 °C and for the reaction of **1** in H_2O at 40 °C are also given. As

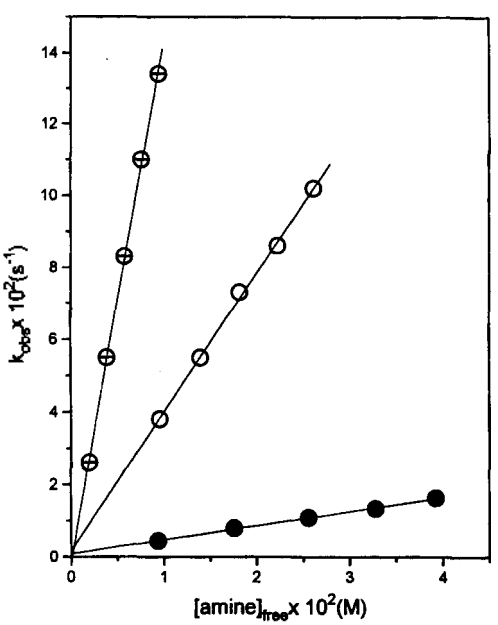


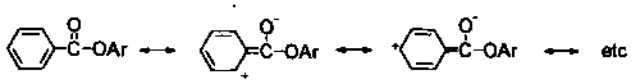
Figure 1. Plots showing dependence of k_{obs} on amine concentration for the aminolysis of *p*-nitrophenyl phenylacetate (**1**) in H_2O containing 20 mole % DMSO at 25.0±0.1 °C. ●; morpholine, ⊖; piperazine, ○; 3-methylpiperazine.

Table 2. Summary of Apparent Second-order Rate Constants (k_{app}) for Aminolysis of *p*-Nitrophenyl Phenylacetate (**1**) and Benzoate (**2**) in H_2O Containing 20 mole % DMSO at 25.0±0.1 °C

Amine	pK_a[a]	$k_{app}/M^{-1}s^{-1}$	
		1	**2**[b]
1. piperazinium ion	5.95	2.74×10^{-3}	4.66×10^{-4}
2. 1-formylpiperazine	7.98[c]	0.0641 (0.0200)[d]	-
3. morpholine	8.65	0.390 (0.0590)	0.0841
4. piperazine	9.85	3.68 (0.294)	0.841
5. 3-methylpiperidine	10.80	14.5	3.55
6. piperidine	11.02	16.5 (0.186)	5.29

[a] pK_a values are obtained from ref. 5a measured in 20 mole % DMSO, otherwise noted. [b] Rate data are taken from ref. 5a. [c] pk_a value from ref. 2d. [d] The rate data in parentheses are obtained from ref. 7 measured in H_2O at 40 °C.

shown in the table, the reactivity of amines increases with increasing amine basicity for all the systems. Interestingly, **1** appears to be about 3-6 folds more reactive than **2** toward all the amines studied. It has been recently reported that the reactivity of *p*-nitrophenyl substituted benzoates increases with increasing acid strengthening ability of the acyl substituents.[9] Since phenylacetic acid is a weaker acid than benzoic acid, one might expect that **2** is more reactive than **1**. However, the present result is contrary to the expectation. Accordingly, the difference in acidity between benzoic and phenylacetic acids is not considered to be responsible for the difference in reactivity between **1** and **2**. The insertion of a CH_2 group between the phenyl ring and the carbonyl group in **2** would reduce the crowdedness of the reaction center, the carbonyl carbon. Furthermore, **1** cannot have resonance stabilization as in **2** as shown below. Therefore, the reduced steric hinderance or absence of resonance effect in the ground state of the substrate **1** is considered rather to be responsible for the high reactivity of **1** compared with **2**.



In order to see the effect of amine basicity on the reactivity of **1** and **2**, Brönsted type plots have been constructed in Figure 2. Excellent Brönsted type correlation is obtained for the aminolysis of **1** and **2**, when log k_{app} and pK_a's are 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) for all the amines studied.[10] Such a good linearity obtained in Figure 2 clearly indicates that there is no RDS change for the aminolysis of **1** and **2**.

The magnitude of β_{nuc} value has been understood to give useful information about the reaction mechanism, particularly about the degree of charge development at the transition state (TS).[6] The β_{nuc} value for the aminolysis of **1** appears to be similar to the one for the corresponding aminolysis of **2**, *i.e.* β_{nuc} values are calculated to be 0.81 and 0.85 for the aminolysis of **1** and **2**, respectively. Therefore, it is considered that the aminolysis of **1** and **2** proceeds in a same reaction mechanism with a similar TS structure based on the magnitude of the β_{nuc} values. E1cB mechanism is not possible for the aminolysis of **2** due to the absence of an α-

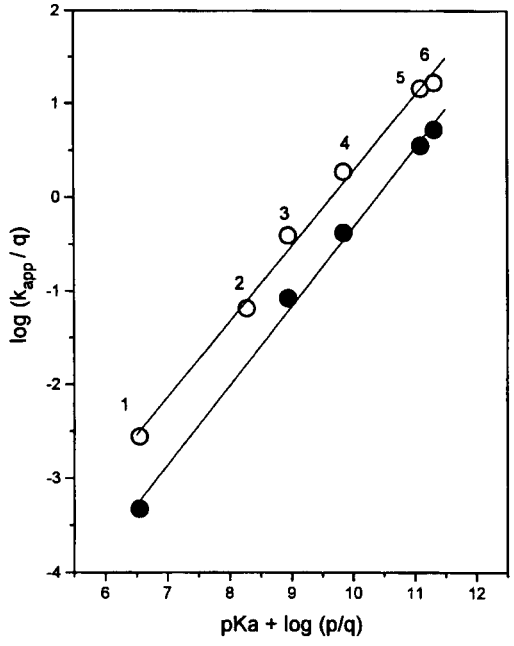


Figure 2. Brönsted-type plots for the aminolysis of *p*-nitrophenyl phenylacetate (○) and benzoate (●) in H_2O containing 20 mole % DMSO at 25.0±0.1 °C. The identity of the point is given in Table 2.

hydrogen in **2**. Besides, aminolysis of **2** has been suggested proceed *via* $B_{AC}2$ mechanism in which the rate-determining step is leaving group departure.[5a] Therefore, one can expect that the aminolysis of **1** in the present system also proceeds *via* $B_{AC}2$ mechanism with rate-determining leaving group departure but not *via* E1cB mechanism, and the nonlinear Brö nsted type plot observed by Lee and Yoh for the aminolysis of **1** is not due to a change in the reaction mechanism from $B_{AC}2$ to E1cB mechanism as the amine basicity increases.

It is also interesting that the reactivity of **1** toward a given amine is higher in 20 mole % DMSO at 25.0 °C than in H_2O at 40 °C. The reactivity difference becomes larger as the basicity of the amine increases. One might attribute the reactivity difference to solvent effect. It has been well known that the negative end of the dipole in dipolar aprotic solvents (*e.g.* DMSO, MeCN, DMF, etc) is exposed, whereas the positive end is buried in the middle of the molecule.[11] Consequently, the addition of dipolar aprotic solvent into the reaction medium (H_2O) would destabilize the ground state (GS) of anionic nucleophiles due to decreasing H-bonding and increasing repulsion between the negative dipole end and the anionic nucleophile. This argument can be nicely supported by the fact that anions are significantly more basic in dipolar aprotic solvents, *e.g.* phenoxide ion is known to be 6.4 and 17.2 pK_a units more basic in DMSO and MeCN, respectively, than in H_2O.[12] Therefore, one might expect significant rate enhancement upon solvent change from H_2O to dipolar aprotic solvent such as DMSO, MeCN, DMF, etc. In fact, Bruice observed rate enhancements of about 10^6 times upon solvent change from H_2O to 1 mole H_2O in DMSO for the reaction of *p*-nitrophenyl acetate (PNPA) with HO ion at 25 °C.[13] However, rate enhancements upon solvent change from H_2O to 20 mole % DMSO-H_2O mixture have been reported to be not larger than 4 folds for reactions of aryl acetates with various anionic nucleophiles.[14] In some cases, even rate retardations have been observed upon additions of DMSO (or MeCN) into H_2O up to near 30 mole %. Besides, solvent effect on rates would be smaller for the reaction with neutral amines than for the one with anionic nucleophiles, since neutral amines would not be destabilized as significantly as anionic nucleophiles in dipolar aprotic solvents. In fact, the basicity of the amines studied in the present system has been reported to be almost identical in H_2O and in 20 mole % DMSO.[5a] Therefore, rate enhancements would not be significant in the present system upon the addition of 20 mole % DMSO in the reaction medium. However, the lowering temperature from 40 to 25 °C would result in rate retardation over 2 folds. Accordingly, one might expect rate enhancement upon the solvent change would be compensated by rate retardation upon the lowering reaction temperature, and the difference in reaction conditions is not considered to be responsible for the difference in reactivity for the aminolysis of **1** in 20 mole % DMSO at 25 °C and in H_2O at 40 °C.

Since general acid catalysis is not operative in the aminolysis of **1** with the present cyclic amines, the conjugate acid of these amines (>NH_2^+) would not participate in the reaction, and the contribution of >NH_2^+ to the k_{obs} values would be zero. Accordingly, the concentration of free amine (>NH) should be used to calculate apparent second-order rate constants (k_{app}) instead of total amine concentration (the free and the protonated amine). Therefore, the apparent second-order rate constants calculated by Lee and Yoh using the total amine concentration are considered to be smaller than they should be. Since the fraction of free amine becomes smaller for the more basic amine at a given pH, the error involved in the second-order rate constant becomes larger with increasing amine basicity. This explains the downward curvature observed in the Brönsted type plot by Lee and Yoh. Therefore, it is proposed that the aminolysis of **1** in the present system proceeds via a rate-determining leaving group departure without a change in the RDS for all the amines studied.

Acknowledgment. The authors are grateful for the financial support from Basic Science Research Instituted Program of Ministry of Education (BSRI-96-3422) and from Korea Science and Engineering Foundation (94-0501-09-3).

References

1. (a) March, J. *Advanced Organic Chemistry*; Willey: New York, 1985; Chapters 10 and 16. (b) Bruice, T. C. Benkovic, S. *Bioorganic Mechanisms*; Benjamin: New York, 1996; Vol. 1. (c) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1968; p 463.
2. (a) Castro, E. A.; Ibanez, F.; Santos, J. G.; Ureta, C. *J. Org. Chem.* **1993**, *58*, 4908. (b) Castro, E. A.; Ibanez, F.; Saitua, A. M.; Santos, J. G. *J. Chem. Res.* **1993**, (S) 56, (M) 317. (c) Castro, E. A.; Ureta, C. *J. Chem. Soc., Perkin Trans. 2* **1991**, 63. (d) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 3501.
3. Menger, F. M.; Smith, J. H. *J. Am. Chem. Soc.* **1972**,

94, 3824
4. (a) Oh, H. K.; Shin, C. H.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1169. (b) Koh, H. J.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1994**, 253. (c) Koh, H. J.; Lee, C. H.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **1995**, *16*, 839. (d) Oh, H. K.; Shin, C. H.; Lee, I. *Bull. Korean Chem. Soc.* **1995**, *16*, 657.
5. (a) Um, I. H.; Kwon, H. J.; Kwon, D. S.; Park, J. Y. *J. Chem. Res.* **1995**, (S) 301, (M) 1801. (b) Um, I. H.; Kim, M. J.; Min, J. S.; Kwon, D. S. *Bull Korean Chem. Soc.* **1997**, *18*, in press. (c) Um, I. H.; Shin, E. H.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1996**, *17*, 234. (d) Um, I. H.; Choi, K. E.; Kwon, D. S. *Bull. Korean Chem. Soc.* **1990**, *11*, 362.
6. Chapman, N. B.; Shorter, J., Eds. *Advances in Linear Free Energy Relationships*; Plenum: London, 1972.
7. Lee, J. P.; Yoh, S. D. *Bull. Korean Chem. Soc.* **1996**, *17*, 211.
8. Chandraseka, R.; Venkatasubramanian, N. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1625.
9. Um, I. H.; Hong, Y. J.; Kwon, D. S. *Tetrahedron* **1997**, *53*, 5073.
10. Bell, R. P. *The Proton in Chemistry*; Methuen: London, 1973; p 159.
11. Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 2nd Ed.; Harper and Row: New York, 1981.
12. Chantooni, M. K.; Kolthoff, I. M. *J. Phys. Chem.* **1976**, *80*, 1306.
13. Goitein, R.; Bruice, T. C. *J. Phys. Chem.* **1972**, *76*, 432.
14. Buncel, E.; Um, I. H. *J. Chem. Soc., Chem. Commun.* **1986**, 595.
15. (a) Buncel, E.; Um, I. H.; Hoz, S. *J. Am. Chem. Soc.* **1989**, *111*, 971. (b) Um, I. H.; Lee, G. J.; Yoon, H. W.; Kwon, D. S. *Tetrahedron Lett.* **1992**, *33*, 2023.

Theoretical Studies on the Nucleophilic Substitution Reactions of 1-Phenylethyl Chlorides

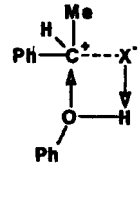
Wang Ki Kim, Wang Sun Ryu, Hyeong Yeoun Park[†], In-Suk Han[†], Chang Kon Kim[†], and Ikchoon Lee[*,†]

Department of Chemistry Education, Chonnam National University, Kwangju 500-757, Korea
[†]Department of Chemistry, Inha University, Inchon 402-751, Korea
Received May 27, 1997

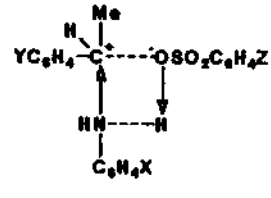
Nucleophilic substitution reactions of 1-phenylethyl chlorides (1-PEC; $YC_6H_4CH(CH_3)Cl$) with phenoxides ($XC_6H_4O^-$) and thiophenoxides ($XC_6H_4S^-$) are investigated theoretically using the PM3 method. The Brönsted α and β values are greater for the phenoxides indicating a more advanced reaction in the transition state (TS) than for the thiophenoxides. This is supported by a greater magnitude of ρ_X ($-6.4\sim-7.4$) and ρ_{XY} (-0.76) for the phenoxides than for the thiophenoxides ($\rho_X=-3.6\sim-4.4$ and $\rho_{XY}=-0.60$). The percentage bond order changes, $\%\Delta n^+$, suggest that the extents of bond making and breaking are similar for the phenoxides and hence the TS is symmetrical, but bond making is somewhat greater than bond cleavage for the thiophenoxides indicating an unsymmetrical TS. The reactions in the gas phase for both nucleophile series proceed by a S_N2 mechanism with a tight TS and negative charge development on the reaction center carbon, C_α. The reactions in water investigated with model systems of benzyl and 1-phenylethyl chlorides using the Cramer-Truhlar solvation model (PM3-SM3) indicate that the reactions of 1-PEC are far more complex due to enhanced stabilization of the carbocation by the methyl substitution for a benzylic hydrogen.

Introduction

Nucleophilic substitution reactions of 1-phenylethyl derivatives in solution have been stutied extensively.[1] The reactions are reported to display a variety of mechanisms depending on the substituent (Y) in the substrate, nucleophile and solvent. Tidwell *et al.*[1b,c] reported that solvolyses of 1-phenylethyl tosylates in protic solvents proceed by a stepwise mechanism in which nucleophilic solvent attack on an ion-pair plays a major role (S_N2C^+ mechanism), whereas Richard and Jencks[1g] showed that 1-phenylethyl derivatives react with azide ion through a concerted S_N2 mechanism. Okamoto *et al.*[2] observed products with retention of configuration in their phenolysis studies of 1-phenylethyl derivatives, which was rationalized by a mechanism involving a



I



II