Kinetics and Mechanism of the Aminolysis of Phenylacetyl Chlorides in Acetonitrile

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The aminolysis reactions of phenylacetyl chlorides with anilines and N,N-dimethylanilines (DMAs) in aceto-nitrile at -15.0 °C are investigated. The magnitude of ρ_X ($=-2.8\sim-2.9$) and ρ_Y ($=0.9\sim1.3$, after correcting for the fall-off), and the negative sign of ρ_{XY} ($=-0.12$) for the reactions with anilines suggest an associative S_N2 mechanism. For the reactions with DMAs, the magnitude of these Hammett coefficients increases so that tight-er bond making in the transition state (TS) is predicted. A nonlinear Hammett plots obtained for the DMAs with an electron acceptor substituent is interpreted to result from a more advanced degree of leaving group de-parture to assist closer approach of the bulky DMA in the TS. The normal secondary kinetic isotope effects ($k_H/k_D > 1.0$) involving deuterated anilines suggest partial deprotonation by hydrogen bonding to the departing chlo-ride ion.
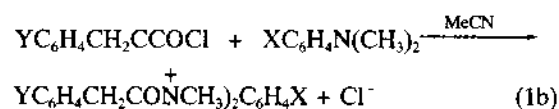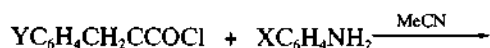
Introduction

The aminolysis of acyl compounds is in general known to proceed either through a stepwise mechanism with a tetrahedral intermediate,[1] or through a concerted, single step mechanism involving a tetrahedral transition state (TS) with no addition intermediate.[2] The aminolysis of acetyl chloride, MeCOCl,[3] and methyl chloroformate, MeOCOCl,[4] have been reported to proceed by rate-limiting departure of chlo-ride ion from a zwitterionic tetrahedral intermediate, $T^{\pm}$, for weakly basic amines with a change to rate-limiting addition for basic amines.

The aminolyses of benzoyl halides are mostly believed to proceed by a concerted displacement mechanism.[5] In con-trast, Song and Jencks[6] have shown that the reactions of benzoyl fluorides with primary amines in aqueous solution can be accommodated by an S_N2-like mechanism but a step-wise addition-elimination mechanism cannot be rigorously excluded. Satchell and coworkers[7] reported that the aminoly-sis of benzoyl fluorides in *non-hydroxylic* solvents proceeds by a stepwise mechanism involving rate-limiting expulsion of fluoride ion from a tetrahedral intermediate.

In previous works, we reported that the aminolysis mech-anism of phenyl chloroformates[8] (I, YC₆H₄OCOCl) and N-methyl-N-phenylcarbamoyl chlorides[9] (II, YC₆H₄N(CH₃)COCl) in acetonitrile, where Y is a substituent, is consistent with a single step, concerted displacement. Surprisingly, however, the reactions of cinnamoyl chlorides[10] (III, YC₆H₄-CH=CHCOCl) with anilines in acetonitrile are predicted to proceed by rate-limiting expulsion of chloride ion from the tetrahedral intermediate. These three acyl chlorides, I-III, differ only in an intervening group, R, in a general structure of YC₆H₄-R-COCl.

In this work, we extend this series of work to the amino-lysis of phenylacetyl chlorides (IV, YC₆H₄CH₂COCl) with anilines (ANs) and N,N-dimethylanilines (DMAs) in aceto-nitrile at -15.0 °C, eq 1.

$$YC_6H_4CH_2CCOCl \; + \; XC_6H_4NH_2 \xrightarrow{\text{MeCN}}$$

$$\overset{+}{YC_6H_4CONHC_6H_4X} \; + \; C_6H_4NH_3 \; + \; Cl^- \tag{1a}$$

$$YC_6H_4CH_2CCOCl \; + \; XC_6H_4N(CH_3)_2 \xrightarrow{\text{MeCN}}$$

$$YC_6H_4CH_2CO\overset{+}{N}(CH_3)_2C_6H_4X \; + \; Cl^- \tag{1b}$$

X = H, p-Cl, m-Cl, m-NO₂ or p-NO₂
Y = p-CH₃O, H, p-Cl or p-NO₂

The aims of this work are to investigate the effects of the in-tervening group R=CH₂ and of the bulky dimethyl group in DMAs on the mechanism of the aminolysis of phenylacetyl chlorides in acetonitrile.

Results and Discussion

Solvolysis was not observed for all the phenylacetyl chlo-rides under the reaction conditions. The rates were measur-ed with excess amine concentrations, [N]=0.002-0.4 M, and [substrate] $\cong 1 \times 10^{-5}$ M, and pseudo-first order rate con-ditions, k_{obs}, were obtained at more than five amine con-centrations. The plots of k_{obs} versus amine concentration were linear with the slopes, k_N, for all the reactions, eq 2. The k_N

$$k_{obs} = k_N[N] \tag{2}$$

determined are summarized in Tables 1 and 2. The rate is faster with a stronger nucleophile ($\delta\sigma_X < 0$) and with a stronger electron withdrawing group on the substrate ($\delta\sigma_Y > 0$) as expected from a typical nucleophilic substitution reac-tion with a greater extent of bond making than leaving group departure in the TS. The rates of reactions with an-ilines are much faster than the corresponding rates with DMAs, $k_{AN}/k_{DMA} \cong 300$-900. This is in contrast to the slow-er rate of reactions with anilines than with DMAs in a step-wise mechanism with rate-limiting expulsion of the leaving group.[11] In such reactions, steric repulsion of dimethylamino group within the tetrahedral intermediate is thought to assist the departure of the leaving group. Therefore the stepwise

Table 1. Second-order rate constants, k_2 (M^{-1} S^{-1}), for the reactions of Y-phenylacetyl chlorides with X-anilines in acetonitrile at -15.0 °C

X \ Y	p-CH₃O	H	p-Cl	p-NO₂	$\rho_Y{}^c$
H	72.5	93.3	114	217	0.45
P-Cl	12.9	18.9 15.29^a 12.1^b	24.5	38.2	0.44
m-Cl	5.97	8.98 7.15 5.65	11.9	17.0	0.42
m-NO₂	0.831	0.918	1.01	1.83	0.33
p-NO₂	0.0190	0.0230 0.0183 0.0146	0.0280	0.0410	0.31
$\rho_X{}^d$	-2.77	-2.83	-3.01	-2.91	$\rho_{XY}{}'=-0.12$ $\pm0.04^g$
$\beta_X{}^e$	0.97	0.99	1.05	1.01	

^{a}At -20.0 °C. ^{b}At -25.0 °C. ^{c}The σ values were taken from: D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **1958**, *23*, 420. Correlation coefficients were better than 0.826 in all cases. ^{d}The σ⁻ values were taken from: D. H. Jaffe, *Chem. Rev.* **1953**, *53*, 191. Correlation coefficients were better than 0.999 in all cases. ^{e}The pK_a values were taken from: A. Streitwiser, Jr and C. H. Heathcock. *Introduction to Organic Chemistry*, 2nd ed.; Macmillan Publishing Co.; New York, 1981; p 737. ^{f}Correlaton coefficient was better than 0.999. ^{g}Standard deviation.

Table 2. Second-order rate constants, k_2 (M^{-1} S^{-1}), for the reactions of Y-phenylacetyl chlorides with X-N,N-dimethylanilines in acetonitrile at -15.0 °C

Y \ X	p-CH₃O	H	p-Cl	p-NO₂
p-CH₃	1.64	2.80	4.48	13.7
H	0.102	0.122	0.203	0.659
p-Br	0.0126	0.00785	0.0102	0.0216
m-NO₂	0.00212	0.00104	0.00127	0.00262

mechanism with rate-limiting breakdown of the intermediate can be eliminated for the reactions of phenylacetyl chlorides with anilines and DMAs. The considerably slower rates with DMAs suggest that there is a substantial steric inhibition to bond making by the bulky dimethylamino group of the DMA in a rate-limiting attack by the nucleophile.[12]

The secondary kinetic isotope effects (SKIEs), k_H/k_D, involving deuterated aniline nucleophiles (XC₆H₄ND₂) are summarized in Table 3. The normal SKIEs, $k_H/k_D > 1.0$, indicates that the rate-determining step is not a simple bond formation process since in such a case an inverse SKIE, $k_H/k_D < 1.0$, is expected due to an increase in the N-H vibrational frequency as a result of steric congestion of the N-H moiety in the bond formation step.[13] This suggests that the possibility of a stepwise mechanism with rate-limiting addition is small. The values of k_H/k_D (>1.0), however, attest to the possibility of partial deprotonation by hydrogen bonding to the departing chloride ion. The Hammett ρ_X and ρ_Y values are shown in Table 1 for the reactions with anilines. The magnitude of ρ_X (ρ_{nuc}) in MeCN ($\rho^X = -2.8$-2.9) is similar to or slightly greater than the corresponding

Table 3. Kinetic isotope effects on the second-order rate constants for the reactions of Y-phenylacetyl chlorides with deuterated X-anilines in acetonitrile at -15.0 °C

X	Y	k_H ($M-1S^{-1}$)	k_D ($M^{-1}S^{-1}$)	k_H/k_D
H	p-CH₃O	72.5±2.1^a	70.4±2.0	1.03±0.04^a
H	H	93.3±2.7	90.5±2.4	1.03±0.04
H	p-NO₂	217±6	198±5	1.09±0.04
m-NO₂	p-CH₃O	0.831±0.025	0.762±0.020	1.09±0.04
m-NO₂	H	0.918±0.028	0.826±0.025	1.11±0.05
m-NO₂	p-NO₂	1.83±0.05	1.75±0.03	1.04±0.03

^{a} Standard deviation.

values for the reactions of anilines with benzoyl chlorides ($\rho_X = -2.1$-2.8)[14] and with phenyl chloroformates ($\rho_X = -2.2$-2.3)[8] suggesting that all react with anilines by an associative S_N2 mechanism. The ρ_Y values ($\rho_Y = 0.9$-1.3, after correcting for the fall-off) are also similar to those for benzoyl chlorides ($\rho_Y = 1.2$-2.2).[14] The $\beta_X(\beta_{nuc})$ values are relatively large, $\beta_X = 0.97$-1.05 (at -15.0 °C in MeCN), but these are again similar to the corresponding values for the reactions of anilines with benzoyl chlorides ($\beta_X = 0.75$ at 35.0 °C in MeOH)[14] and with benzoyl fluorides ($\beta_X = 1.14$ at 55.0 °C in MeOH).[15] All of these reactions are believed to proceed by an associative S_N2 mechanism.

The Hammett plots for the reactions of DMAs with electron acceptor substituents ($\sigma_X > 0$) were nonlinear as shown in Figures 1 and 2. Examination of Figure 1 reveals positive deviations of the rates against σ_X for the electron acceptor substituent ($\sigma_X > 0$). Again in Figure 2 we note that for the electron acceptor X, an electron donor substituent in the substrate ($\sigma_Y < 0$) deviate positively with a concave upward (U-shape) type curves in the log k_N versus σ_Y plots. Exclusion of X=m-NO₂ led to the ρ_X values ranging from *ca.* -5 to -7 with satisfactory linearities ($r \geq 0.98$). These are greater in magnitude by two times of the corresponding ρ_X values for the reactions with anilines in Table 1. The ρ_Y
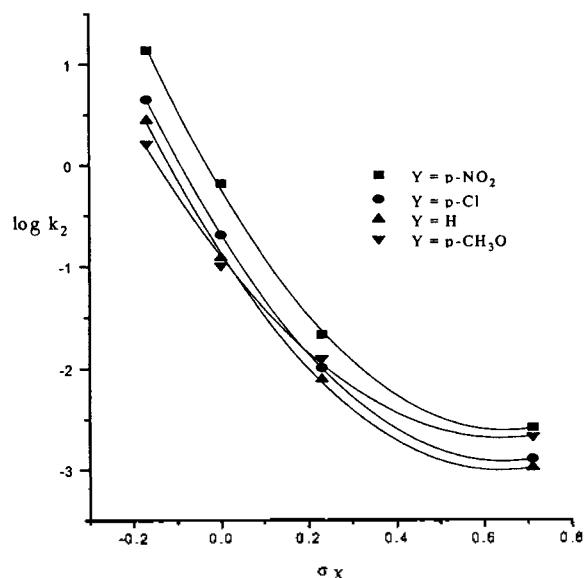
Figure 1. Hammett plots (ρ_X) for the reactions of Y-phenylacetyl chlorides with X-N,N-dimethylanilines in acetonitrile at -15.0 °C.
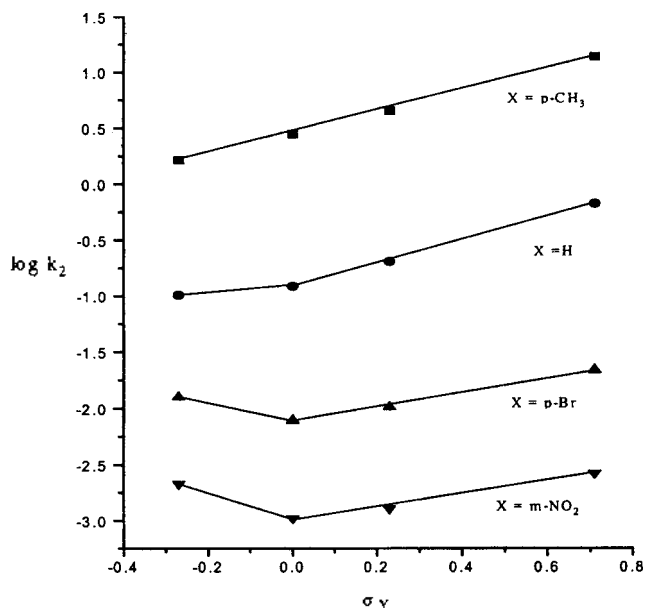
Figure 2. Hammett plots (ρ_Y) for the reactions of Y-phenyla-cetyl chlorides with X-N,N-dimethylanilines in acetonitrile at -15.0 °C.

values were also larger ($\rho_Y \cong 0.7$ for X=H) than those for the aniline reactions. These larger magnitude of ρ_Y as well as ρ_X values suggest that the TS is much tighter with much more advanced bond making for the reactions with DMAs than with anilines. The larger magnitude of the cross-interaction constant, ρ_{XY} ($\cong -1.5$) also support this conclusion[15] (*vide infra*). The tighter bond formation with sterically congested nucleophiles is in fact consistent with the Bell-Evan-Polanyi (BEP) principle[16]: Since the product will be highly unstable due to the steric effect, the TS will be not only later along the reaction coordinate with tighter bond formation but also higher in the activation barrier with slower rate[17] (*vide supra*). The upward shift of the ρ_Y curves (*i.e.*, $\rho_Y < 0$) for an electron donor Y (Y=p-CH$_3$O) with the DMAs of electron acceptor substituent appears to indicate development of an electron deficient reaction center in the TS due to more advanced bond cleavage of the chloride ion than bond formation for the DMAs with electron acceptor substituent ($\sigma_X > 0$). This means that the closer approach of the nucleophile is made possible by developing a stronger positive charge center by expulsion of the leaving group to a greater extent. Thus the tighter bond formation in the TS is assisted by the greater degree of bond cleavage in a concerted process.

The magnitude of ρ_X increases with a more electron acceptor substituent (Y) in the substrate, $\delta\rho_X < 0$ (or $\delta|\rho_X| > 0$) with $\delta\sigma_Y > 0$. Likewise, for a stronger acceptor substituent (X) in the nucleophile leads to a smaller ρ_Y value, $\delta\sigma_X > 0$ $\rightarrow$ $\delta\rho_Y < 0$. In accordance with these interrelationships, ρ_{XY} is negative ($= -0.12 \pm 0.04$; $r = 0.9997$) as its definition requires, eqs. 3.[15] It has been shown that the sign

$$\log(k_{XY}/k_{HH}) = \rho_X \, \sigma_X + \rho_Y \, \sigma_Y + \rho_{XY} \, \sigma_X \, \sigma_Y \qquad (3a)$$

$$\rho_{XY} = \frac{\partial\rho_Y}{\partial\sigma_X} = \frac{\partial\rho_X}{\partial\sigma_Y} \qquad (3b)$$

of ρ_{XY} is negative for a concerted nucleophilic displacement

Table 4. Activation parameters[a] for the reactions of Y-phenyla-cetyl chlorides with X-anilines in acetonitrile

X	$\Delta H^{\neq}$ (Kcal · mol^{-1})	$-\Delta S^{\neq}$ (cal · mol^{-1}
p-Cl	5.20 ± 0.01	32 ± 1
m-Cl	5.41 ± 0.02	33 ± 1
p-NO$_2$	5.30 ± 0.01	45 ± 2

[a] Calculated by the Eyring equation. Errors shown are standard deviations.

reaction, whereas it is positive for a stepwise mechanism with rate-limiting breakdown of the tetrahedral intermediate.[18] The aminolysis of benzoyl chlorides and phenyl chloroformates are reported to proceed by the direct displacement mechanism, and the ρ_{XY} values were -0.85[18] and -0.04[8] respectively, whereas for the reactions of cinnamoyl chlorides for which a stepwise mechanism was predicted, ρ_{XY} was positive ($\rho_{XY}=0.88$).[10] Thus the negative ρ_{XY} value obtained supports the $S_N 2$ mechanism for the reactions of phenylacetyl chlorides with anilines. A rough estimate of ρ_{XY} ($\cong -1.5$) for the reactions with DMAs also support the $S_N 2$ mechanism but exceptionally large magnitude suggests a much tighter, nearly complete, bond formation in the TS.

The activation parameters, ($\Delta H^{\neq}=5\text{-}6$ kcal mol^{-1} and $\Delta S^{\neq}$ $= -32\sim-45$ cal deg^{-1}mol^{-1}), shown in Table 4 are again similar to those for the reactions of phenyl chloroformates with anilines[8] in acetonitrile at 25.0 °C ($\Delta H^{\neq}=5\text{-}8$ kcal mol^{-1} and $\Delta S^{\neq}= -34\sim-39$ cal deg^{-1} mol^{-1}).

We conclude that the reactions of phenylacetyl chlorides with anilines in acetonitrile proceed by a direct displacement ($S_N 2$) mechanism and those with DMAs are characterized by a TS with rather tight bond formation of the sterically crowded nucleophiles which is assisted by a more advanced degree of leaving group departure.

Experimental

Material. Merck GR acetonitrile was used after three distillations. Anilines and N,N-dimethylanilines were purified as described previously.[19] Preparations of deuterated anilines were as described previously.[20] The analysis H-NMR spectroscopy of the deuterated anilines showed more than 98% deuterium content, so that no corrections to kinetics isotope effects for a complete deuteration were made. The substrates Y-phenylacetyl chlorides (Y=p-CH$_3$O, H) were Aldrich G.R. purchased, which were redistilled before used. Y-Phenylacetyl chlorides (Y=p-NO$_2$, p-Cl) were prepared by reacting p-nitrophenylacetic acid and p-chlorophenylacetic acid with thionyl chloride at 70 °C for 1-3 hr in an oil bath, respectively. The physical constants after column chromatography were:

p-NO$_2$-C$_6$H$_4$CH$_2$-C(=O)Cl: mp 44-45 °C. δ_H (CDCl$_3$), 7.2-7.8 (Ph-H, 4H, m), 4.2 (CH$_2$, 2H, s). v$_{max}$ (KBr), 3100 (C-H, aromatic), 1790 (C=O). m/z, 199 (M$^+$).

p-Cl-C$_6$H$_4$CH$_2$-C(=O)Cl: liquid. δ_H (CDCl$_3$), 7.4-8.0 (Ph-H, 4H, m), 4.2 (CH$_2$, 2H, s). v$_{max}$ (neat), 3000 (C-H, aromatic), 1780 (C=O). m/z, 188 (M$^+$).

Rate Constants. Rates were measured conductimetrically at -15.0 ± 0.05 °C. The conductivity bridge used in this work was a self-made computer automatic A/D converter conductivity bridge. Pseudo-first order rate constants, k_{obs}, were determined by the Guggenheim method.[21] Second-ord-

er rate constants, k_2, were obtained from the slope of a plot of k_{obs} versus amine with more than five concentrations of more than three runs and were reproducible to within ±3%.

Product analysis. p-Nitrophenylacetyl chloride was reacted with excess p-chloroaniline with stirring for more than 15 half-lives at −15.0 °C in acetonitrile, and the products were isolated by evaporating the solvent under reduced pressure. The physical constants after recrystallization were:

p-NO₂·C₆H₄CH₂·C(=O)NHC₆H₄·p·Cl: mp 158-160 °C; δ_H (CDCl₃), 6.6-7.4 (Ph-H, 8H, m), 3.6 (NH, 1H, s), 4.3 (CH₂, 2H, s). v_{max}, (KBr), 3400 (N-H). 1760 (C=O). m/z, 290 (M⁺).

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New pH-Sensitive Liposomes Using Bis(6-hemisuccinyloxyhexyl) Fumarate

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In order to develop pH-sensitive liposomes that are stable in plasma, liposomes containing membrane-spanning bipolar amphiphiles as protonatable components were studied. Sonicated small unilamellar liposomes composed of dioleoylphosphatidylethanolamine (DOPE), dioleoylphosphatidylcholine (DOPC) and bis(6-hemisuccinyloxyhexyl) fumarate (BHF) in a 3:1:1 molar ratio are stable at neutral pH, but destabilized at weakly acidic pH with 50% leakage of entrapped materials at about pH 5.5. The liposomes are relatively stable in plasma such that only a few percent entrapped calcein was released in 50% plasma within 1.5 h incubation at 37 °C, while about 10% entrapped calcein was released from sonicated liposomes composed of DOPE , DOPC, and oleic acid (OA) in a 3:1:1 molar ratio under the identical conditions. The aqueous contents mixing and lipid components mixing experiments suggest that the protonation of BHF may induce fusion between the liposomes, followed by the release of the entrapped materials.

Introduction

Immunoliposomes are taken up by cells through the endocytic pathway, and many drugs, especially the macromolecular drugs, are hydrolyzed in the lysosome, thus resulting in poor biological activities of the delivered drug.[1] The pH-sensitive liposomes have been designed to circumvent the lysosomal catabolic degradation by delivering

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