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## Nonlinear Structure-Reactivity Correlations in the Aminolysis of *p*-Nitrophenyl Phenylacetates

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Structure-Reactivity relationships in the aminolysis[1~4] of aryl acetates have been important subjects of numerous kinetic studies since 1967. In the most of these studies, tetrahedral intermediate ($T^{\pm}$) by Hammett and Brønsted plots has been postulated in the reaction path. For instance, Jencks[4] reported the reaction of various amines with substituted-phenylacetates shows a change in the rate-determining step from break down to formation of $T^{\pm}$.

Castro[5] studied pyridinolyses of 2,4-dinitrophenyl acetate and methylphenyl-carbonate. The Brønsted plot obtained for the acetate system was curved but linear for carbonate system involving a $T^{\pm}$. The rate determining step of aminolysis[6] of arylthiol acetate, except the one for the reaction of *p*-nitrophenylthiol acetate with pipeidine, is decomposition of $T^{\pm}$ to product.

Recently, Castro[7] also studied aminolysis of O-ethyl-S(4-nitrophenyl) thiocarbonate, and found that Brønsted plot is nonlinear, *i.e.* $\beta_1=0.2$ and $\beta_2=0.8$ at high and low $pK_a$ values, respectively, indicating the presence of $T^{\pm}$ and a change in the rate-determinig step.

We[8] studied, one of these subjects, the pyridinolysis of substituted phenyl acetates in acetonitrile and interpreted the mechanism in terms of a dissociative $S_N2$ mechanism involving a metastable tetrahedral intermediate. However, there are only a few works with the simple acetate compounds. In order to investigate further, in this paper we study the reaction of the *p*-nitrophenyl phenylacetate with secondary alicyclic amines by means of the Brønsted plot. We compare it with that studied in the pyridinolysis of aryl acetates, in the aim of evaluating the transition state and rate determining step for the α-substituted phenyl phenylacetate.

Reagents for the preparation, which were obtained from commercial sources, were used without purification. Piperidine, piperazine, morpholine and 1-formylpiperazine as nucleophiles were used reagent grade of Aldrich and purified according to standard procedures.[6] *p*-Nitrophenyl phenylacetate (mp 60-61.5 ℃, lit[9]. 60.5-61.6 ℃) was prepared from the reaction of phenylacetyl chloride with *p*-nitrophenol. Phenylacetyl chloride was obtained from the reaction of phenyl acetic acid (13.6 g, 0.1 mole) with thionyl chloride (8.5 mL, 0.118 mol) at 0 ℃ for 30 minutes. The pH was maintained either with sodium borate from Mallinchrodt and hydrochloric acid from Junsei. Water was purified by distilling deionized water twice after oxidation by $KMnO_4$, and acetonitrile was purified according to references.[8]

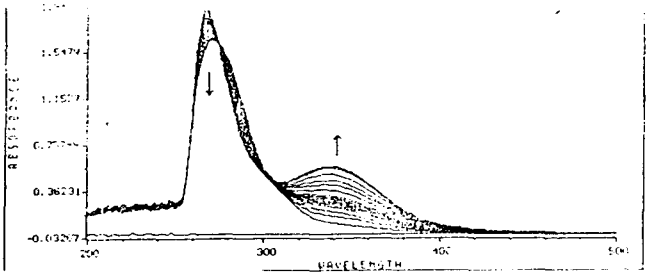



**Figure 1.** UV spectral change during the reaction of *p*-nitrophenyl phenylacetate(s) with 1-formyl piperazine(N) at pH=6.94. [S] $=2\times10^{-4}$ M, [N]=0.1 M.

**Table 1.** Experimental conditions and rate constants for the aminolysis of *p*-nitrophenyl phenylacetate in water at 40 ℃

| amine | $10^2[N]_{tot}\cdot M$ | pH | $10^3\ k_{obsd}\ (s^{-1})$ |
|---|---|---|---|
| piperidine | 0.300-1.30 | 8.40 | 2.21 - 3.69 |
| | 0.300-1.30 | 9.00 | 3.39 -97.5 |
| piperazine | 0.300-0.900 | 8.09 | 1.32 - 3.32 |
| | 0.300-1.30 | 8.45 | 2.42 - 5.18 |
| morpholine | 0.660-2.60 | 7.41 | 0.452- 1.47 |
| | 0.660-2.60 | 8.59 | 1.61 - 2.95 |
| 1-formylpiperazine | 0.660-2.60 | 7.51 | 0.326- 0.816 |
| | 0.660-2.60 | 7.00 | 0.222- 0.765 |

The reaction was carried out under pseudo-first-order conditions with amines over 100 folds excess at least over substrate and studied spectrophotometrically (8452A Diode Spectrophotometer, Hewlett Packed) by following the release of *p*-nitrophenol at 340 nm, 40 ℃ and ionic strength 0.2 M KCl in the reaction of 1-formylpiperazine. The rate constants were calculated with 89532 K kinetic software (Serial No. 3205 G00380 attached above the Spectrophotometer).

The UV spectra for the reaction of *p*-nitrophenyl phenyl acetate ($2\times10^{-4}$ M) with 1-formyl piperazine (0.1 M) are shown in Figure 1.

The experimental conditions and rate constants of the reactions are described in Table 1, in which the rate constants increase with incresing concentration of nucleophile. Therefore, the kinetic law obtained for the present reactions is given by Eq. 1, where $k_N$ is the rate constant for the aminolysis reaction, $[N]_{tot}$ is the concentration of amine. The values of $k_N$ obtained from slopes of linear plots of $k_{obsd}$ against $[N]_{tot}$ (free amine plus it's conjugated acid) at constant pH are shown in Table 2.

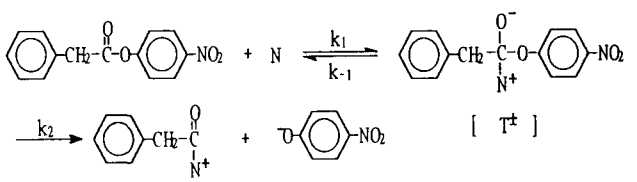
$$k_{obs}=k_N[N]_{tot} \quad (1)$$

Brønsted plot, logarithmic plot of $k_N$ *vs.* $pK_a$, obtained in this work is curved, with the center of curvature near 10

**Table 2.** $pK_a$ values of conjugate acid of the amines and second-order rate constants ($k_N$) for the aminolysis of *p*-nitrophenyl phenylacetate in water at 40 ℃

| amine | $pK_a$* | $k_N$ ($s^{-1}\cdot M^{-1}$) |
|---|---|---|
| piperidine | 11.2 | 0.186 |
| piperazine | 9.94 | 0.294 |
| morpholine | 8.78 | 0.0590 |
| 1-formyl piperidine | 7.98 | 0.0200 |

*values taken from reference 6.



**Scheme 1.**

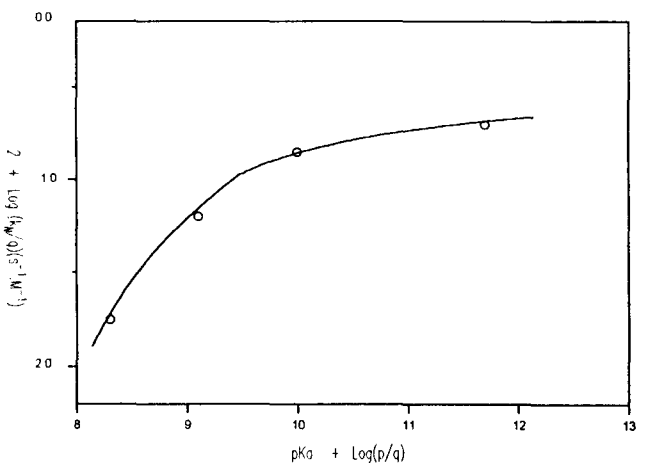



**Figure 2.** Brønsted plot for the nucleophilic reaction of *p*-nitrophenyl phenylacetate with secondary alicyclic amines against their basicity in water at 40 ℃, ionic strength 0.2 M. (the *q* and *p* values of amines were taken from reference 7.)

pKa of amine. The same results were found for the reactions of 2,4-dinitrophenyl acetate[10] and 2,4-dinitrophenylmethyl carbonate with secondary alicyclic amines.

The curved Brønsted plot obtained for the reaction of *N*-nitrophenyl phenylacetate with secondary alicyclic amine can be interpreted in terms of a tetrahedral intermediate ($T^{\pm}$ in Scheme 1, where *N* represents an amine) in the reaction path and a change in the rate determining step from $k_2$ to $k_1$ in Scheme 1 as the basicity of the amine increases..

Application of the steady state treatment to the tetrahedral intermediate leads to equation 2, where $k_N$ is the overall rate constant for the nucleophilic attack.

$$k_N = k_1k_2/(k_{-1}+k_2) \quad (2)$$

When the amine becomes more basic than the leaving group, $k_{-1} \ll k_2$, and according to equation 2 $k_N = k_1$, and the rate determining step should be formation of a tetrahedral intermediate. Where as, the nucleophilic amine is weakly basic, $k_{-1} \gg k_2$ and according to equation 2 $k_N = K_1k_2$, where $K_1$ is the equilibrium constant for the first step, and breakdown of a tetrahedral intermediate should be the rate determining step.

As we can see Figure 2, the slope in low $pK_a$ region ($\beta_2$) is 0.51 and in high $pK_a$ region ($\beta_1$) is 0.06 for breakdown and formation of a tetrahedral intermediate, respectively. These values are similar to the values found in the aminolysis of other reactive carbonyl compounds.[5-7]

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## Radical Cyclization of β-Aminoacrylates: Expedient Synthesis of (+)-Monomorine 1 and (+)-Indolizidine 195B

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Indolizidine alkaloids offer attractive targets for synthesis because of their scarcity, exotic origin, and interesting biological activity. For example, (+)-monomorine 1(**1**)[1,2] is a trail pheromone of Pharaoh's ant (*Monomorium pharaonis* L.) and its epimer (+)-indolizidine 195B (**2**, bicyclic gephyrotoxin 195B)[3,4] was found in the skin extracts of neotropical poison dart frogs of the dendrobatid species.

Recently we reported that radical cyclization reactions of β-alkoxyacrylates[5] and β-aminoacrylates[6] might be used in the stereoselective synthesis of heterocyclic compounds. We now wish to report that **1** and **2** can be synthesized *via*