

Elimination Reactions of Aryl Phenylacetates Promoted by $R_2NH/R_2NH_2^+$ in 70 mol % MeCN(aq). Effect of the β -Phenyl Group on the Ketene-Forming Transition State

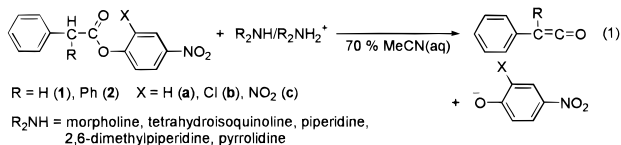
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It is well established that the base-catalyzed hydrolysis of aryl *p*-nitrophenylacetates and other activated esters proceed by an E1cb elimination to afford the ketene intermediate followed by the addition of water under various conditions.^{1–13} The reaction proceeded by the E2 mechanism when R_2NH in MeCN was employed as the base–solvent system.¹⁴ Concurrent E2 and E1cb mechanisms were noted for the reactions of *p*-nitrophenyl *p*-nitrophenylacetate with $R_2NH/R_2NH_2^+$ buffer in 70% MeCN(aq).¹⁴ These results demonstrate the mechanistic diversity of the ketene-forming eliminations in the E2 and E1cb borderline.

To further expand our understanding of ketene-forming eliminations, reactions of β -substituted aryl phenylacetates **1** and **2** with $R_2NH/R_2NH_2^+$ buffer in 70% MeCN(aq) have now been studied (eq 1). The phenyl



group is expected to increase the acidity of the C_β –H bond, the stability of the C=C bond, and the steric effect.

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The relative importance of these factors on the ketene-forming transition state is assessed.

Results

Aryl phenylacetates **1** and **2** were synthesized by the reaction between phenylacetic acid and diphenylacetic acids with substituted phenols, 2-chloro-1-methylpyridinium iodide, and Et₃N in CH₂Cl₂ as described previously.^{14,15} The reactions between **1** and **2** and $R_2NH/R_2NH_2^+$ buffers in 70% MeCN(aq) produced aryloxides in 92–99% yields.

To probe whether the aminolysis reaction may compete with the ketene-forming elimination reaction, the reactions of 4-nitro- and 2,4-dinitrophenyl butyrates with $R_2NH/R_2NH_2^+$ buffers in 70% MeCN(aq) were briefly examined. For reactions of the former with $R_2NH/R_2NH_2^+$ buffers, no trace of 4-nitrophenoxide could be detected by a UV–vis spectrophotometer after 10 h. On the other hand, the latter underwent slow aminolysis under the reaction conditions. The second-order rate constant for the reactions of 2,4-dinitrophenyl butyrates with $R_2NH/R_2NH_2^+$ buffers in 70% MeCN(aq) are summarized in the footnote in Table 1. The values are approximately 60–3000-fold smaller than the k_2 values for the corresponding ketene-forming eliminations from **1c** under the same conditions. Because the steric requirements of the propyl and benzyl groups are similar,¹⁶ the aminolysis of **1c**, if any, is expected to proceed at a rate comparable to that of 2,4-dinitrophenyl butyrate. Hence, it is highly unlikely that the aminolysis reaction would compete with the ketene-forming elimination of **1c**. Furthermore, since the steric requirement of the diphenylmethyl group is much larger than that of the propyl group, the aminolysis of **2c** should be even less important. Therefore, the possibility of competing aminolysis for the reactions of **1** and **2** is strongly negated by this result.

Rates of reactions between **1** and **2** and $R_2NH/R_2NH_2^+$ buffers in 70% MeCN(aq) were followed by monitoring the increase in the absorption of the aryloxides at 400–426 nm with a UV–vis spectrophotometer as described previously.¹⁴ Excellent pseudo-first-order kinetic plots, which covered at least 3 half-lives, were obtained. Dividing the pseudo-first-order rate constants by the base concentration provided the second-order rate coefficients k_2 presented in Table 1.

The k_2 values showed excellent correlation with the pK_a values of the promoting base on the Brønsted plot (Figures 1 and 2). The β value decreases as the leaving group is made less basic (Table 2). Similarly, the k_2 values correlated satisfactorily with the leaving group pK_a values (Figures 3 and 4). The $|\beta_{lg}|$ value decreases with a stronger base (Table 3).

Discussion

Mechanism of Elimination from 1 and 2 Promoted by $R_2NH/R_2NH_2^+$ Buffers in 70% MeCN(aq). Results of kinetic investigations and product studies

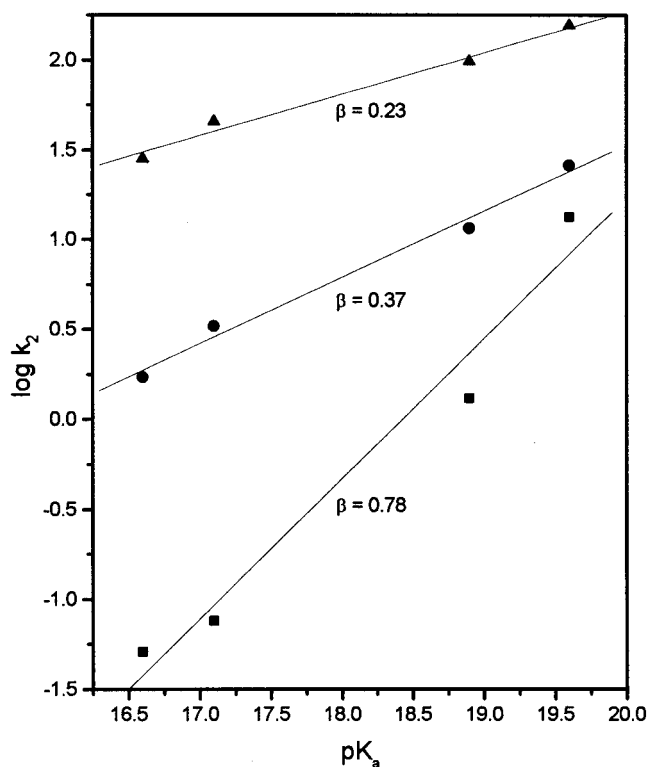
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Table 1. Rate Constants for Eliminations from PhCH(R)CO₂C₆H₄-2-X-4-NO₂^a Promoted by R₂NH/R₂NH₂⁺ Buffers in 70% MeCN(aq)^b

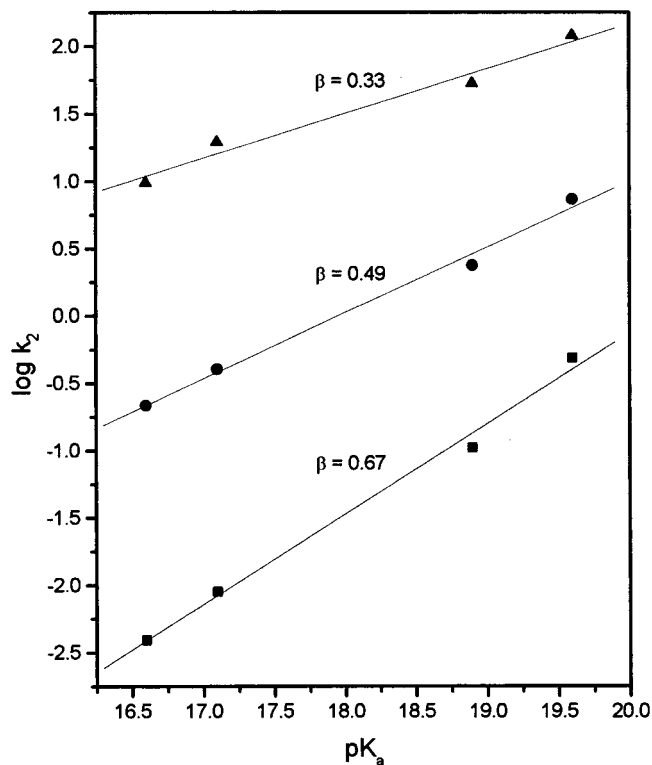
R ₂ NH ^{c,d}	pK _a ^e	<i>k</i> ₂ ^{f-h} M ⁻¹ s ⁻¹					
		1a	1b	1c	2a	2b	2c
morpholine	16.6	0.0510	1.71	28.0	0.00389	0.217	9.67
THIQ ⁱ	17.1	0.0759	3.29	45.3	0.00888	0.403	19.3
piperidine	18.9	1.31	11.5	97.5	0.104	2.36	52.5
2,6-DMP ^j	18.9	0.142 ^k		7.10 ^k	0.000937	0.00917	0.188
pyrrolidine	19.6	13.3	25.8	154	0.485	7.28	119

^a [Substrate] = 3.0 × 10⁻⁵ M. ^b μ = 1.0 M (Bu₄N⁺Br⁻). ^c [Base] = 8.0 × 10⁻⁴ to 1.0 × 10⁻¹ M. ^d [R₂NH]/[R₂NH₂⁺] = 1.0. ^e References 24 and 25. ^f Average of three or more rate constants. ^g Estimated uncertainty ± 3%. ^h The *k*₂ values for the aminolysis reactions of 2,4-dinitrophenyl butyrate with R₂NH/R₂NH₂⁺ buffers in 70% MeCN(aq) are 0.00985, 0.0174, 0.250, and 2.55 M⁻¹ s⁻¹ when R₂NH is morpholine, THIQ, piperidine, and pyrrolidine, respectively. ⁱ 1,2,3,4-Tetrahydroisoquinoline. ^j *cis*-2,6-Dimethylpiperidine. ^k Reference 14.

**Figure 1.** Brønsted plots for the ketene-forming eliminations from aryl phenylacetates [PhCH₂CO₂C₆H₃-2-X-4-NO₂] promoted by R₂NH/R₂NH₂⁺ buffers in 70% MeCN(aq) at 25.0 °C [X = H (■), Cl (●), NO₂ (▲)].

clearly establish that the reactions of aryl phenylacetates **1** and **2** with R₂NH/R₂NH₂⁺ buffers in 70% MeCN(aq) proceed by the E2 mechanism. Because the possibility of the competing aminolysis is ruled out and the ketene-forming elimination reactions exhibit second-order kinetics, all but bimolecular pathways can be ruled out. In addition, an E1cb mechanism is negated by the substantial values of β and |β_{lg}|.¹⁷⁻¹⁹

This conclusion is supported by the interaction coefficients. Table 2 shows that the β values for **1** decrease gradually as the leaving groups are made less basic.²⁰ The result can be described by a positive *p*_{xy} interaction coefficient, *p*_{xy} = ∂β/∂pK_{lg} = ∂β_{lg}/∂pK_{BH}, which describes the interaction between the base catalyst and the leaving

**Figure 2.** Brønsted plots for the ketene-forming eliminations from aryl diphenylacetates [Ph₂CHCO₂C₆H₃-2-X-4-NO₂] promoted by R₂NH/R₂NH₂⁺ buffers in 70% MeCN(aq) at 25.0 °C [X = H (■), Cl (●), NO₂ (▲)].**Table 2. Brønsted β Values for Ketene-Forming Eliminations from PhCH(R)CO₂C₆H₄-2-X-4-NO₂ Promoted by R₂NH/R₂NH₂⁺ Buffers in 70% MeCN(aq) at 25.0 °C**

X	pK _a ^a	β	
		R = H	R = Ph
H	20.7	0.78 ± 0.04	0.67 ± 0.04
Cl	18.6	0.37 ± 0.03	0.49 ± 0.03
NO ₂	16.0	0.23 ± 0.02	0.33 ± 0.04

^a Reference 24.

group.^{19,23} The observed decrease in the |β_{lg}| values as the catalyst is made more basic is another manifestation of this effect, i.e., *p*_{xy} = ∂β_{lg}/∂pK_{BH} > 0 (Table 3). On the More–O'Ferall–Jencks energy diagram in Figure 5, a change to a better leaving group will raise the energy of the top edge of the diagram. The transition state on the diagonal reaction coordinate will then move slightly toward the right as depicted by a shift from A to B on the energy diagram, resulting in a small decrease in β (vide supra).^{19,23} Similarly, a stronger base will raise the energy of the right side of the energy diagram and shift

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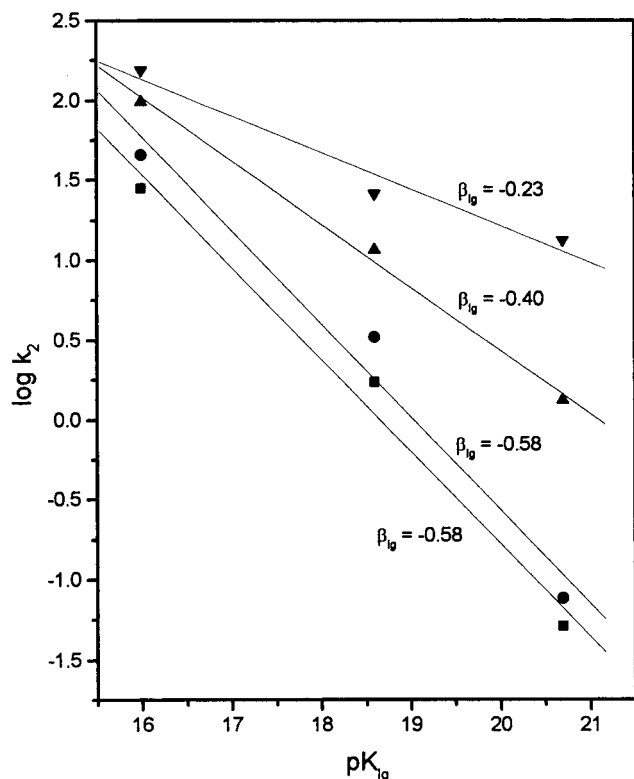


Figure 3. $\log k_2$ vs pK_{lg} values for the ketene-forming eliminations from aryl phenylacetates [$\text{PhCH}_2\text{CO}_2\text{C}_6\text{H}_3\text{-2-X-4-NO}_2$] promoted by $\text{R}_2\text{NH}/\text{R}_2\text{NH}_2^+$ buffers in 70% MeCN(aq) at 25.0 °C [R_2NH = morpholine (■), tetrahydroisoquinoline (●), piperidine (▲), pyrrolidine (▼)].

Table 3. Brönsted β_{lg} Values for Ketene-Forming Eliminations from $\text{PhCH(R)CO}_2\text{C}_6\text{H}_4\text{-2-X-4-NO}_2$ Promoted by $\text{R}_2\text{NH}/\text{R}_2\text{NH}_2^+$ Buffers in 70% MeCN(aq) at 25.0 °C

R_2NH	pK_a^a	β_{lg}	
		R = H	R = Ph
morpholine	16.6	-0.58 ± 0.07	-0.72 ± 0.06
THIQ	17.1	-0.58 ± 0.10	-0.71 ± 0.04
piperidine	18.9	-0.40 ± 0.03	-0.57 ± 0.04
2,6-DMP	18.9	-0.37^b	-0.49 ± 0.01
pyrrolidine	19.6	-0.23 ± 0.05	-0.51 ± 0.03

^a References 24 and 25. ^b Reference 14.

the transition state from A to C to decrease the extent of $\text{C}_\alpha\text{-OAr}$ bond cleavage. The positive p_{xy} coefficients are inconsistent with an E1cb mechanism for which $p_{xy} = 0$ is expected, but provide additional support for the concerted E2 mechanism.^{19,23}

A similar interpretation can be put forward for the changes in β and $|\beta_{lg}|$ values with the leaving group and base strength variations for **2**. However, it should be noted that the transition state for **2** is relatively insensi-

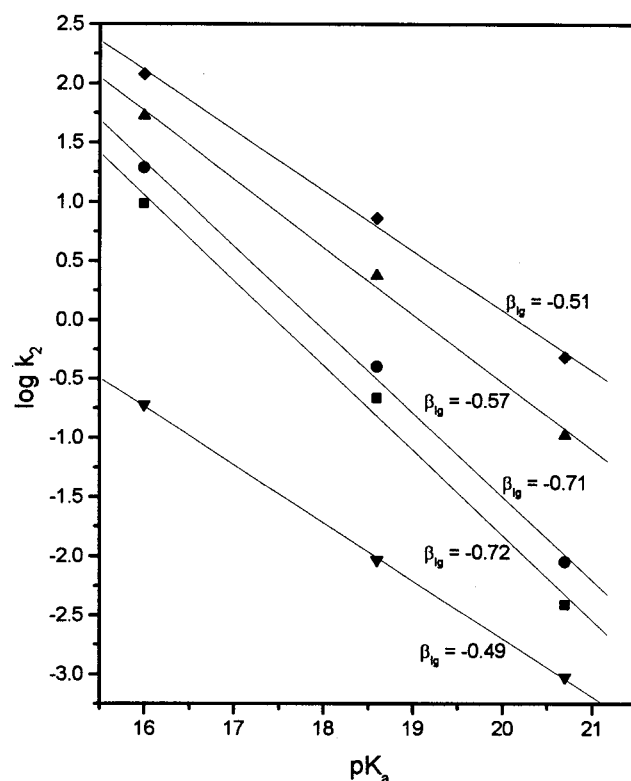


Figure 4. $\log k_2$ vs pK_{lg} values for the ketene-forming eliminations from aryl diphenylacetates [$\text{Ph}_2\text{CHCO}_2\text{C}_6\text{H}_3\text{-2-X-4-NO}_2$] promoted by $\text{R}_2\text{NH}/\text{R}_2\text{NH}_2^+$ buffers in 70% MeCN(aq) at 25.0 °C [R_2NH = *cis*-2,6-dimethylpiperidine (▼), morpholine (■), tetrahydroisoquinoline (●), piperidine (▲), pyrrolidine (◆)].

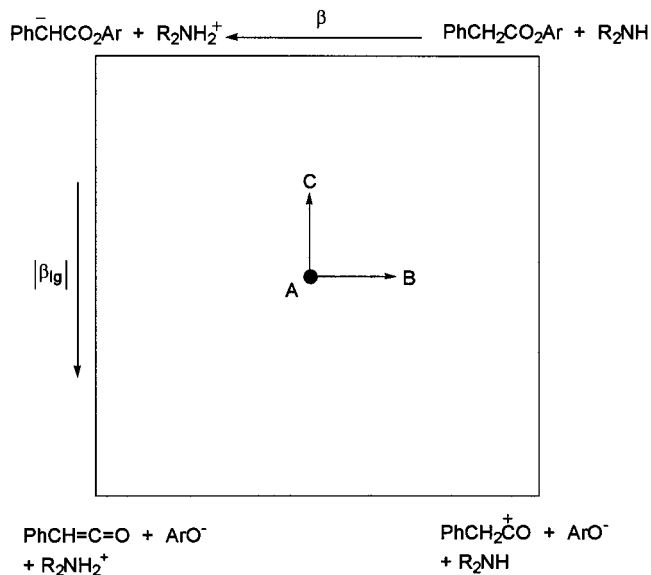


Figure 5. Reaction coordinate diagram for ketene-forming eliminations. The effects of the change to a better leaving group and a stronger base are shown by the shift of the transition state from A to B and from A to C, respectively.

tive to the variations of the leaving group and base (Tables 2 and 3).

Effect of the β -Phenyl Group on the Ketene-Forming Transition State. Table 4 shows that the rate of piperidine-promoted elimination from **2a** is 12.5-fold slower than that from **1a** probably because of the steric effect by the β -phenyl group (vide supra). The β value is

(20) A reviewer argued that the 500-fold difference in rate for the reactions of **1a-c** is relatively small and would not result in such changes in the β values. However, we have previously observed a large change of the k_{11}/k_D values from 7.8 to 1.6 by the change in the N-R group in the imine-forming eliminations from $\text{ArCH}_2\text{N(Cl)R}$ promoted by Et_2NH in MeCN, even though the rate difference was only 30-fold.²¹ A similar result was observed for MeONa-promoted eliminations from the same substrates.²²

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Table 4. Effect of the β -R Group and Amine Bases on the Ketene-Forming Eliminations from $\text{PhCH(R)CO}_2\text{C}_6\text{H}_4\text{-2-X-4-NO}_2$ Promoted by $\text{R}_2\text{NH/R}_2\text{NH}_2^+$ Buffers in 70% MeCN(aq) at 25.0 °C

R_2NH	R = H		R = Ph	
	piperidine	2,6-DMP	piperidine	2,6-DMP
relative rate ^a	1	0.1	0.08	0.0008
β	0.78 \pm 0.04		0.67 \pm 0.03	
β_{lg}	-0.40 \pm 0.03	-0.37 ^b	-0.57 \pm 0.04	-0.49 \pm 0.01

^a X = H. ^b Reference 14.

smaller and $|\beta_{\text{lg}}|$ is larger for the latter, indicating a smaller extent of proton transfer and a larger degree of $\text{C}_\alpha\text{-OAr}$ bond rupture in the transition state. The transition state for **2** appears to be more symmetrical than that for **1**, with similar extents of $\text{C}_\beta\text{-H}$ and $\text{C}_\alpha\text{-OAr}$ bond cleavage.

The transition-state differences for **1** and **2** can most reasonably be interpreted with the substrate steric effect and the stability of the C=C bond. The bulky phenyl substituent at the β -carbon may hinder the approach of the base to the $\text{C}_\beta\text{-H}$ bond to decrease the extent of the $\text{C}_\beta\text{-H}$ bond cleavage in the transition state. The prediction is borne out by the smaller β value observed for **2**. In addition, because the phenyl group can stabilize the C=C bond, more of the electron density on the β -carbon would be transferred between C_β and C_α to increase the transition-state double bond character, to obtain a maximum stabilization. This would predict a greater extent of $\text{C}_\alpha\text{-OAr}$ bond rupture and a larger $|\beta_{\text{lg}}|$ value for **2**, as observed. Similar results were observed for the imine-forming eliminations from $\text{ArCH}_2\text{N(X)R}$.^{21,22} Thus, the extent of the $\text{C}_\beta\text{-H}$ bond cleavage decreased and the degree of double bond character increased as the steric requirements of the R group and the base were increased.

It is interesting to note that the rate of the ketene-forming transition state is significantly influenced by the base steric effect. Thus, the rate of elimination from **1** is decreased by approximately 10-fold when the base is changed from piperidine to more bulky *cis*-2,6-dimethylpiperidine. The corresponding difference in rate is much larger for **2**, apparently because of the increased steric requirement of the substrate. For both substrates, the $|\beta_{\text{lg}}|$ values decrease slightly, indicating a decrease in the extent of $\text{C}_\alpha\text{-OAr}$ bond cleavage, as the steric effect of the promoting base increases. However, due to the lack of data for the degree of proton transfer, it is difficult to assess the change in the transition-state structure caused by the base steric effect.

In conclusion, the ketene-forming elimination reactions from **1** and **2** promoted by $\text{R}_2\text{NH/R}_2\text{NH}_2^+$ buffer in 70% MeCN(aq) proceed by the E2 mechanism. The rate is retarded and the transition-state structure becomes more symmetrical with similar extents of $\text{C}_\beta\text{-H}$ and $\text{C}_\alpha\text{-OAr}$

bond cleavage by the β -Ph group. A significant base steric effect was noted for the reaction of **2** with 2,6-DMP buffer.

Experimental Section

Materials. Aryl esters of phenylacetic acid **1a–c** and 4-nitro- and 2,4-dinitrophenyl butyrates were available from a previous study.¹⁴ Diphenylacetic acid derivatives **2a–c** were synthesized by reacting diphenylacetic acid, substituted phenols, 2-chloro-1-methylpyridinium iodide, and triethylamine in CH_2Cl_2 under nitrogen as described previously.^{14,15} The spectral and analytical data of the compounds were consistent with the proposed structures. The yield (%), melting point (°C), IR (KBr, $\text{C}=\text{O}$, cm^{-1}), NMR (CDCl_3), and combustion analysis data for the new compounds are as follows.

(C₆H₅)₂CHCO₂C₆H₄-*p*-NO₂ (2a**):** yield 51%; mp 88–89; IR 1760 (C=O); NMR δ 8.25 (d, 2H, J = 9.0), 7.41–7.32 (m, 10H), 7.25 (d, 2H, J = 9.0), 5.28 (s, 1H). Anal. Calcd for $\text{C}_{20}\text{H}_{15}\text{NO}_4$: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.23; H, 4.68; N, 4.05.

(C₆H₅)₂CHCO₂C₆H₃-2-Cl-4-NO₂ (2b**):** yield 77%; mp 87–88; IR 1770 (C=O); NMR δ 8.26 (d, 1H, J = 2.4), 8.07 (dd, 1H, J = 8.9, 2.6), 7.37–7.25 (m, 10H), 7.21 (d, 1H, J = 9.0), 5.29 (s, 1H). Anal. Calcd for $\text{C}_{20}\text{H}_{14}\text{ClNO}_4$: C, 65.31; H, 3.84; N, 3.81. Found: C, 65.42; H, 4.02; N, 3.60.

(C₆H₅)₂CHCO₂C₆H₃-2,4-(NO₂)₂ (2c**):** yield 42%; mp 88–89; IR 1774 (C=O); NMR δ 8.88 (d, 1H, J = 2.7), 8.41 (dd, 1H, J = 9.0, 2.7), 7.33–7.25 (m, 11H), 5.33 (s, 1H). Anal. Calcd for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_6$: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.63; H, 3.77; N, 7.13.

Buffer solutions were prepared by dissolving equivalent amounts of R_2NH and R_2NH_2^+ in 70% MeCN(aq). In all cases, the ionic strength was maintained to be 0.1 with $\text{Bu}_4\text{N}^+\text{Br}^-$.

Kinetic Studies. Reactions of **1** and **2** with $\text{R}_2\text{NH/R}_2\text{NH}_2^+$ in 70% MeCN(aq) were followed by monitoring the increase in absorption of the aryloxides at 400–426 nm with the reaction time with a UV–vis spectrophotometer as described previously.¹⁴

Product Studies. The products of the reactions between **2a–c** and $\text{R}_2\text{NH/R}_2\text{NH}_2^+$ in 70% MeCN(aq) were identified with a UV–vis spectrophotometer. For all reactions, the absorbance corresponding to the reactant decreased at 240–300 nm and those for the aryloxides increased at 300–480 nm as the reaction proceeded. Clean isosbestic points were observed at 310, 320, and 310 nm for **2a**, **2b**, and **2c**, respectively. The yields of aryloxides determined by comparing the absorbance of the infinity samples from the kinetic studies with those of the authentic aryloxides were in the range 92–99%.

To determine whether **1** and **2** may undergo aminolysis reaction, solutions of 4-nitro- and 2,4-dinitrophenyl butyrates (3.0×10^{-5} M) and $\text{R}_2\text{NH/R}_2\text{NH}_2^+$ buffers (2.0×10^{-2} M, buffer ratio 1.0) in 70 mol % MeCN(aq) were allowed to react in a cuvette at 25.0 °C. The former did not undergo any reaction for 10 h. However, the latter underwent slow aminolysis under the reaction conditions. The rate constant for the aminolysis was determined by monitoring the increase in the 2,4-dinitrophenoxide concentration with time with a UV–vis spectrophotometer as described previously.¹⁴

Control Experiments. The stability of **2a–c** was determined as reported earlier.¹⁴ They were stable for 6 months in the solid state. However, the solutions of **2a–c** decomposed after 2 days at room temperature.

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