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Eliminations from Aryl bis(*p*-chlorophenyl)acetates Promoted by R_2NH in MeCN. Effects of Base-Solvent and β-Aryl Group[1]

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Abstract—Elimination reactions of $(4'\text{-}ClC_6H_4)_2CHCO_2C_6H_3\text{–}2\text{-}X\text{–}4\text{-}NO_2$ promoted by R_2NH in MeCN have been studied kinetically. The observed second-order kinetics, Brønsted $\beta = 0.44–0.86$ and $|\beta_{lg}| = 0.46–0.69$ are consistent with the E2 mechanism. The Brønsted β decreased as the leaving group was made more nucleofugic and the $|\beta_{lg}|$ increased with a weaker base. Comparison with existing data reveals that the structure of the transition state is relatively insensitive to the base-solvent and β- aryl substituent on the E2 transition state.

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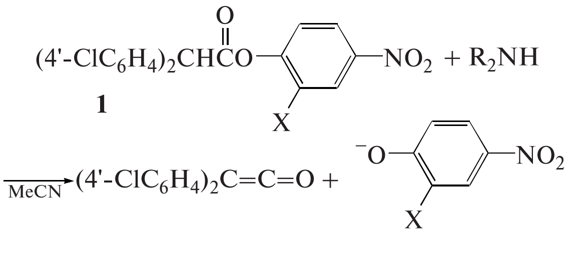
INTRODUCTION

Base catalyst reactions of aryl phenylacetates provide a rich mechanistic diversity ranging from hydrolysis to ketene-forming elimination reactions [1–14], whereas the former is the major reaction pathway in protic solvents with hydroxide or alkoxide as the base in protic solvents, the latter becomes predominant with amine bases in aprotic solvents. In protic solvents, the elimination reaction mechanism changes from E2 to E1cb as the good leaving group is made poorer and as the electron withdrawing ability of the β-aryl substituent increases. On the other hand, the E2 mechanism is the only mechanistic pathway in aprotic solvents.

In an earlier paper, we reported the ketene-forming elimination reactions from aryl diphenylacetates [$Ph_2CHCO_2C_6H_3\text{–}2\text{-}X\text{–}4\text{-}NO_2$, (**2**)] with $R_2NH/R_2NH_2^+$ buffer in 70 mol % MeCN(aq) and R_2NH in MeCN proceeded via an E2-central transition state, with similar extents of C_β–H and C_α–OAr bond cleavage [15, 16]. In this case, the reactions proceeded by the E2 mechanism despite the fact that the phenyl group is expected to increase the acidity of the C_β–H bond and the stability of the C=C bond, all of which favor the E1cb or E1cb-like transition state. On the other hand, a competing E2 and E1cb mechanism was observed in elimination from $(4'\text{-}ClC_6H_4)_2CHCO_2C_6H_3\text{–}2\text{-}X\text{–}4\text{-}NO_2$ promoted by $R_2NH/R_2NH_2^+$ buffer in 70 mol % MeCN(aq) [17]. The reaction proceeded by the E2 mechanism when X = Cl, CF_3, NO_2. As the leaving group was made poorer (X = H), the E2 transition state became more skewed toward the proton transfer and the E1cb mechanism competed. The mechanism changes from E2 to the concurrent E2 and E1cb mechanism by the introduction of the *p*-Cl substituent at the β-aryl group, probably because the carbanion intermediate was stabilized by the electron-withdrawing substituent. We thought that the effect of β-aryl group might be more pronounced in the ketene- than in the nitrile- and imine-forming eliminations for the following reason: the partial double bond character in the ketene-forming transition state may be better stabilized by the β-aryl group because the π-orbitals are composed of the *p*-orbitals of carbon atoms rather than those of carbon and nitrogen atoms. To assess the relative importance of this factor, we have investigated the reactions of aryl bis(*p*-chlorophenyl)acetates promoted by R_2NH in MeCN (Eq. (1)). Comparison with the existing data for the reactions of **1** with $R_2NH/R_2NH_2^+$ buffer in 70 mol % MeCN(aq) and **2** with R_2NH in MeCN reveal the effect of the base-solvent and β-aryl group on the ketene-forming eliminations.



(1)

X = H (**a**), Cl (**b**), CF_3 (**c**), NO_2 (**d**)
R_2NH = morpholine, tetrahydroisoquinoline, piperidine, pyrrolidine

RESULTS

Aryl bis(4'-chlorophenyl)acetates **1a**–**1d** were synthesized by the reaction bis(4'-chlorophenyl)acetic acid with substituted phenols, 2-chloro–1-methylpy-

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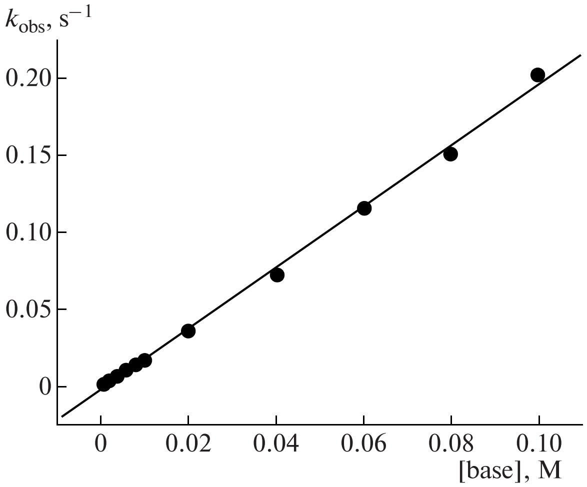

Fig. 1. Plot of k_{obs} vs. base concentration for elimination from *p*-nitrophenyl bis(4'-chlorophenyl)acetate (**1a**) promoted by piperidine in MeCN at 25°C.

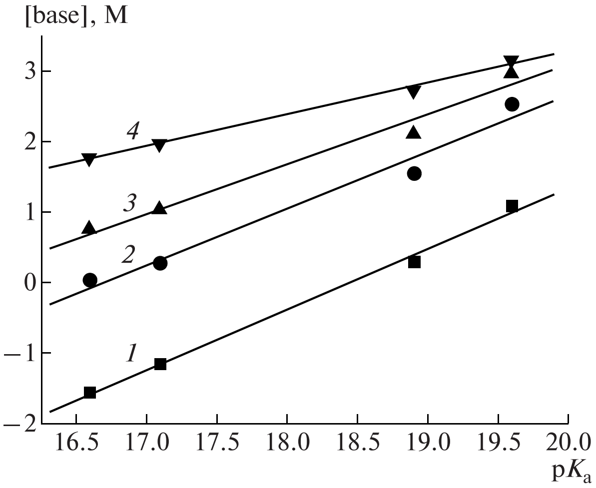

Fig. 2. Brønsted plots for the ketene-forming eliminations from $(4'\text{-ClC}_6\text{H}_4)_2\text{CHCO}_2\text{C}_6\text{H}_3$–2-X–4-$\text{NO}_2$ (**1a**–**1d**) promoted by R_2NH in MeCN at 25.0°C. [X = H (*1*), Cl (*2*), CF_3 (*3*), NO_2 (*4*)].

ridinum iodide, and Et_3N in CH_2Cl_2 as literature procedure [14, 15, 18, 19].

For reactions of **1a**–**1d** with R_2NH in MeCN, the yields of aryloxides as determined by comparison of the UV absorption of the infinity sample of the kinetic runs with those of the authentic samples were in the range 93–98%. The possibility of a competing aminolysis had been ruled out by a previous study [14]. The rates of elimination reactions were followed by monitoring the increase in the absorption at the λ_{max} for the aryloxides in the range of 404–434 nm. Excellent pseudo-first-order kinetics plots which covered at least three half-lives were obtained. The plots of k_{obs} versus base concentration for the reaction of **1a** were straight lines passing through the origin (Fig. 1). This result indicates that the reaction is over second order, first order to the substrate and first order to the base concentration, solvent-promoted elimination does not contribute to the observed rates, the slopes of the straight lines are the overall second-order rate constants k_2. Therefore, the rate constants for the base-promoted eliminations from **1a**–**1d** were determined at a single base concentration. The k_2 values were obtained by dividing the k_{obs} by the base concentration. For eliminations from **1a**–**1d** are summarized in Table 1.

Brønsted plots for the eliminations from **1** promoted by R_2NH in MeCN are presented in Fig. 2. The rate data exhibit excellent correlation with the pK_a values of the promoting bases. The β value decreases as the leaving group is made less basic (Table 2). The β_{log} value was calculated from the rate constant for the

Table 1. Rate constants for ketene-forming eliminations from $(4'\text{-ClC}_6\text{H}_4)_2\text{CHCO}_2\text{C}_6\text{H}_3$–2-X–4-$\text{NO}_2^{\text{a}}$ (**1a**–**1d**) promoted by R_2NH in MeCN at 25.0°C

$\text{R}_2\text{NH}^{\text{b}}$	pK_a^{c}	k_2, M^{-1} s^{-1} $^{\text{d,e}}$			
		1a	**1b**	**1c**	**1d**
Morpholine	16.6	0.0280	1.04	5.58	60.7
THIQ$^{\text{f}}$	17.1	0.0690	1.87	10.7	98.1
Piperidine	18.9	1.96	34.3	126	526
Pyrrolidine	19.6	11.9	328	913	1393

[a] [Substrate] = 3.0×10^{-5} M.
[b] [Base] = $(3.0 \times 10^{-4} \sim 1.0 \times 10^{-1})$ M.
[c] References [16, 20].
[d] Average of three or more rate constants.
[e] Estimated uncertainty, ±5%.
[f] 1,2,3,4-Tetrahydroisoquinoline.

eliminations from **1** and the pK_{1og} values of aryloxides. The $|\beta_{1og}|$ value decreases with a stronger base (Table 3).

DISCUSSION

Reaction mechanism and transition state structure for eliminations from 1a–1d promoted by R_2NH in MeCN. Results of kinetic investigations and product studies clearly establish that the reaction of aryl bis(4'-chlorophenyl)acetates **1a–1d** with R_2NH in MeCN proceed via the *E*2 mechanism. Because the possibility of the competing aminolysis is ruled out [14] and the ketene-forming elimination reactions exhibit second-order kinetics, all but bimolecular pathways can be ruled out. In addition, an *E*1cb mechanism is negated by the substantial values of β and $|\beta_{\log}|$ [21–23].

The structure-reactivity coefficients provide additional support for the this conclusion. Table 2 shows that the Brønsted β values for **1** decrease gradually as the leaving groups are made less basic. The results can be described by a positive p_{xy} interaction coefficient, $p_{xy} = \partial\beta/\partial pK_{\log} = \partial\beta_{\log}/\partial pK_{BH}$, that describes the interaction between the base catalyst and the leaving group [21–23]. The observed decrease in the $|\beta_{\log}|$ values as the catalyst is made more basic is another manifestation of this effect, i.e., $p_{xy} = \partial\beta_{\log}/\partial pK_{BH} > 0$ (Table 3). These changes in the β and $|\beta_{\log}|$ values can be described on the More-O'Ferrall-Jencks reaction coordinate diagram (Fig. 4). A change to a better leaving group will raise the energy of the top edge of the diagram. The transition state on the vertical reaction coordinate will then move toward the right as depicted by a shift from A to B on the energy diagram, resulting in a decrease in β [21–23]. Similarily, a stronger base will raise the energy of the right side of the energy diagram and shift the transition state from *A* to *C* to decrease the extent of C_α-OAr bond cleavage [21–23]. The positive p_{xy} coefficients is not consist with an *E*1cb mechanism for which $p_{xy} = 0$ is expected, but provide additional support for the concerted *E*2 mechanism [21–23].

Effect of base-solvent. Table 4 shows the relative rates and transition state parameter for R_2NH-promoted eliminations of $(4'\text{-}ClC_6H_4)_2CHCO_2C_6H_3$–2-X–4-$NO_2$ (**1a–1d**). For eliminations from **1** promoted by pyrrolidine, the change of solvent-system from $R_2NH/R_2NH_2^+$ 70 mol % MeCN(aq) to R_2NH-MeCN increases the rate by approximately 5-fold, apparently because of the increased basicity of the promoting base in more aprotic solvent.

Table 2. Brønsted β Values for Elimination from Brønsted plots for the ketene-forming eliminations from $(4'\text{-}ClC_6H_4)_2CHCO_2C_6H_3$–2-X–4-$NO_2$ (**1a–1d**) promoted by R_2NH in MeCN at 25.0°C

X	H	Cl	CF_3	NO_2
$pK_{\log}^{a}$	20.7	20.6	18.1	17.0
β	0.86 ± 0.04	0.80 ± 0.09	0.70 ± 0.07	0.44 ± 0.02

[a] Reference [20].

On the other hand, the values of β and $|\beta_{\log}|$ remained nearly the same within experimental error by the variation of the base-solvent system, indicating that similar transition-state structures.

The similar values of β and $|\beta_{\log}|$ indicate the relatively insensitive of the ketene-forming transition state to the base-solvent variation. Because the developing negative density at β-carbon can be stabilized either by the β-Ph group (in MeCN) or by the oxygen atoms of carbonyl and leaving group ($R_2NH/R_2NH_2^+$ 70 mol % MeCN(aq)), the anion solvating ability of the solvent appears to be less important. In 70 mol % MeCN(aq), where the negative charge on the leaving group oxygen atom can be stabilized by forming a stronger hydrogen bonding with water and $R_2NH_2^+$, a significant amount of charge density could be transferred toward the C_β–C_α bond to enhanced the double bond character and increase the charge density on the leaving group oxygen atom. However, in MeCN, the charge density at β-carbon may be stabilized by the β-Ph group rather than to transfer toward C_β–C_α the bond to form the partial double bond because the leaving group oxygen atom cannot be stabilized by the hydrogen bonding. This would predict that the transition state structure would not be significantly altered and the extents of C_β–H and C_α–OAr bond cleavage would remained nearly the same.

Effect of β-aryl substituent on the ketene-forming transition-state. For ketene-forming eliminations from $(4'\text{-}YC_6H_4)_2CHCO_2C_6H_3$–2-X–4-$NO_2$ promoted by R_2NH–MeCN, the change of the β-aryl substituent from Y = H to Y = Cl increased the rate by approximately 3-fold, despite the difference in the electron-withdrawing ability of the β-aryl substituent (Table 4). It is conceivable that an increase in the elec-

Table 3. Values of $\beta_{\log}$ for elimination from $(4'\text{-}ClC_6H_4)_2CHCO_2C_6H_3$–2-X–4-$NO_2$ (**1a–1d**) promoted by R_2NH in MeCN at 25.0°C

R_2NH	Morpholine	THIQ[a]	Piperidine	Pyrrolidine
$\beta_{\log}$	–0.69 ± 0.05	–0.65 ± 0.05	–0.51 ± 0.02	–0.46 ± 0.05

[a] 1,2,3,4-Tetrahydroisoquinoline.

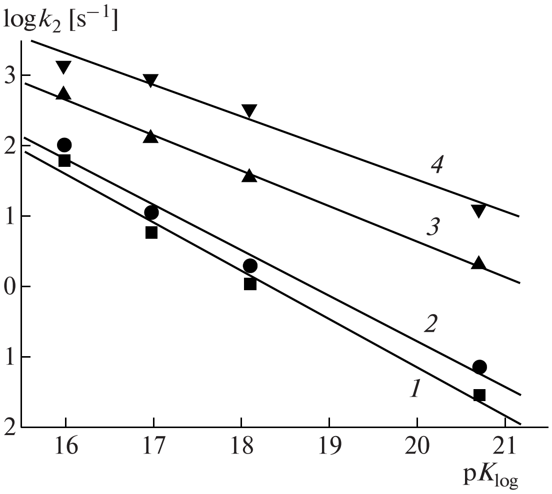

Fig. 3. Plots of $\log k_2$ vs. p$K_{\log}$ values of the leaving group for eliminations reactions of $(4'\text{-}ClC_6H_4)_2CHCO_2C_6H_3$–2-X–4-$NO_2$ promoted by R_2NH in MeCN at 25.0°C. [R_2NH = morpholine (*1*), tetrahydroisoquinoline (*2*), piperidine (*3*), pyrrolidine (*4*)].

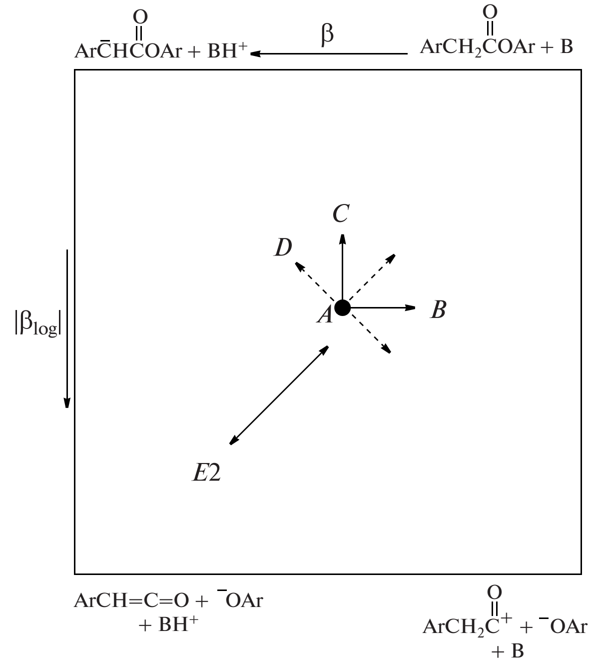

Fig. 4. Reaction coordinate diagram for the ketene-forming elimination. The effect of the change to a better leaving group and a stronger base are shown by the shift of the transition state from *A* to *B* and *A* to *C*, respectively.

tron-withdrawing ability of the β-aryl substituent would lower the energy of the carbanion intermediate, shifting the transition state from *A* to *D* as depicted in Fig. 4. This corresponds to an increase in C_β–H bond cleavage and a decrease in C_α–OAr bond rupture. However, this prediction is in conflict with our result. Comparison of the transition-state parameters reveals that the structure of the transition states for these two reactions are very similar, although the $|\beta_{\log}|$ values increase slightly for **2**. Because the developing negative density at the β-carbon cannot be stabilized by the Ph-group compared to *p*-chlorophenyl group, the transition state structure of **2** became more symmetrical with similar extents of C_β–H and C_α–OAr bond cleavage. This result can be attributed to a solvent effect. Since the negative charge density developed at the β-carbon and aryloxide in the transition state cannot be stabilized by solvation in MeCN, *E*1- or *E*1cb-like transition state would be destabilized and a symmetric transition state with maximum charge dispersal becomes the favored alternative. However, it should be noted that the difference is remarkably small consider the large difference in the electron-withdrawing ability of β-aryl substituent. Noteworthy is the relative insensitivity of the ketene-forming transition state to the base-solvent and β-aryl substituent.

EXPERIMENTAL SECTION

Materials. Aryl bis(*p*-chlorophenyl)acetates (**1a**–**1d**) were available from previous studies [14, 15, 18, 19]. Reagent grade acetonitrile and secondary amines were fractionally distilled from CaH_2. The solutions of R_2NH in MeCN were prepared by dissolving R_2NH in MeCN.

Table 4. Effect of the solvent and β-aryl group on the ketene-forming *E*2 reaction of $(4'\text{-}YC_6H_4)_2CHCO_2C_6H_3$–2-Cl–4-$NO_2$ promoted by R_2NH in MeCN at 25.0°C

Parameter	Y = Cl[a]	Y = Cl	Y = H[b]
Base-solvent	$R_2NH/R_2NH_2^+$ in 70 mol % MeCN (aq)	R_2NH-MeCN	R_2NH-MeCN
Rel. rate (k_2)[c]	1	5	3
β	0.67 ± 0.07	0.80 ± 0.09	0.79 ± 0.09
$\beta_{\log}$	−0.41 ± 0.02	−0.46 ± 0.05	−0.51 ± 0.07

[a] Reference [17].
[b] Reference [16].
[c] R_2NH = pyrrolidine.

Kinetic studies. Reactions of **1** with R_2NH in MeCN were followed by monitoring the increase in the absorbance of the aryl oxides at 404–434 nm with a UV-vis spectrophotometer as described before [14, 16, 24]. Due to the instability of **1d** in MeCN, freshly prepared solutions of **1d** was used in all kinetic runs.

Product studies. The products of eliminations from **1** promoted by R_2NH in MeCN were identified as described previously [14]. The yields of the aryloxides determined by comparing the UV absorptions of the infinity samples with those for the authentic aryloxides were in the range of 93–98%.

Control experiments. The stabilities of **1a**–**1d** were measuring the melting point and periodical scanning of their solutions in MeCN with the UV spectrophotometer as reported earlier [14, 24, 25]. Solutions of aryl bis(*p*-chlorophenyl)acetates **1a**–**1c** were stable for at least 2 months in MeCN solution at room temperature. However, the solution of **1d** was stable for only several hours.

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