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## Elimination Reactions of (*E*)-2,4-Dinitrobenzaldehyde *O*-Benzoyloximes Promoted by R<sub>2</sub>NH/R<sub>2</sub>NH<sub>2</sub><sup>+</sup> in 70 mol % MeCN(aq). Change of Reaction Mechanism

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Elimination reactions of (*E*)-2,4-(NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH=NOC(O)-C<sub>6</sub>H<sub>4</sub>X (1) promoted by R<sub>2</sub>NH/R<sub>2</sub>NH<sub>2</sub><sup>+</sup> in 70 mol % MeCN(aq) have been studied kinetically. The reactions are second-order and exhibit Brönsted  $\beta = 0.27-0.32$  and  $|\beta_{lg}| = 0.28-0.32$ . The result can be described by a negligible  $p_{xy}$  interaction coefficient,  $p_{xy} = \partial\beta/\partial pK_{lg} = \partial\beta_{lg}/\partial pK_{BH} \approx 0$ , which describes the interaction between the base catalyst and the leaving group. The negligible  $p_{xy}$  coefficients are consistent with the (E1cb)<sub>irr</sub> mechanism.

We have reported previously that elimination reactions of (E)and (Z)-YC<sub>6</sub>H<sub>3</sub>CH=NOC(O)C<sub>6</sub>H<sub>4</sub>X promoted by R<sub>2</sub>NH in MeCN proceed by the E2 mechanism.<sup>1</sup> The transition state for the syn-elimination from the (E)-isomer shifted slightly toward E1cb-like with greater extent of  $C_{\beta}$ -H bond cleavage, more negative charge development at  $\beta$ -carbon, and a smaller extent of triple bond formation than that of anti-elimination from the (Z)-isomer. To determine whether a change to an E1cb mechanism could be realized by introducing a more electronwithdrawing  $\beta$ -aryl substituent, we studied the elimination reactions of (E)-2,4- $(NO_2)_2C_6H_3CH=NOC(O)C_6H_4X$  (1a-d) with R<sub>2</sub>NH in MeCN.<sup>2</sup> However, only a modest change in the transition-state structure was observed. Moreover, an E2 mechanism was proposed for the reaction of 1a with i-Pr<sub>2</sub>NH/i- $Pr_2NH_2^+$  in 70 mol % MeCN(aq), a solvent capable of stabilizing the developing negative charge density at the  $\beta$ -carbon, and thereby additionally favoring the E1cb mecha-

TABLE 1.	Second-Order	Rate Constants	for Nitrile-Form	ning
Elimination	from (E)-2,4-(N	O <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH=N	OC(O)C <sub>6</sub> H <sub>4</sub> X <sup>a</sup>	Promoted
by R <sub>2</sub> NH/R <sub>2</sub>	NH <sub>2</sub> <sup>+</sup> in 70 mol	% MeCN(aq) <sup>b,c</sup>	at 25.0 °C	

		$10^2 k_2, \ \mathbf{M}^{-1} \mathbf{s}^{-1_{f,g}}$			
$R_2 NH^d$	$pK_a^e$	$\mathbf{X} = \mathbf{H}$	X = p-OMe	X = m-Cl	$X = p-NO_2$
Bz(i-Pr)NH	16.8	1.04	0.820	2.12	4.24
<i>i</i> -Bu <sub>2</sub> NH	18.2	3.20	1.86	7.40	12.8
<i>i</i> -Pr <sub>2</sub> NH	18.5	2.09	1.38	4.43	8.50
$2,6-DMP^{h}$	18.9	4.79	3.12	10.7	19.8

<sup>*a*</sup> [Substrate] =  $5.0 \times 10^{-5}$  M. <sup>*b*</sup> [R<sub>2</sub>NH]/[R<sub>2</sub>NH<sub>2</sub><sup>+</sup>] = 1.0. <sup>*c*</sup>  $\mu = 0.1$  (Bu<sub>4</sub>N<sup>+</sup>Br). <sup>*d*</sup> [R<sub>2</sub>NH] =  $2.0 \times 10^{-2}$ M. <sup>*e*</sup> Reference 4. <sup>*f*</sup> Average of three or more rate constants. <sup>*g*</sup> Estimated uncertainty,  $\pm 3\%$ . <sup>*h*</sup> *cis*-2,6-Dimethylpiperidine.

nism. However, the conclusion was based on the linear increase in  $k_{obs}$  with buffer concentration. Therefore, a detailed structure-reactivity relationship study seems necessary to provide a more convincing evidence for the proposed mechanism.

To gain a better insight into the nitrile-forming eliminations, we have now studied the reactions 1a-d with  $R_2NH/R_2NH_2^+$  in 70 mol % MeCN(aq) (eq 1). By comparing with the existing data for 1a-d with  $R_2NH$  in MeCN, the effects of the base-solvent on the nitrile-forming elimination was assessed.



**Product Study.** (*E*)-2,4-Dinitrobenzaldehyde *O*-benzoyl oximes **1a**-d were available from a previous study.<sup>2</sup> The reactions of **1a** with *i*-Bu<sub>2</sub>NH/*i*-Bu<sub>2</sub>NH<sub>2</sub><sup>+</sup> in 70 mol % MeCN(aq) produced 2,4-dinitrobenzonitrile and benzoate. The isolated yield of 2,4dinitrobenzonitrile from a large-scale reaction was 94%. No trace of (*E*)-2,4-dinitrobenzaldehyde oxime could be detected by TLC, negating the possibility of the hydrolysis reaction.

Kinetic Study. The rates of elimination reaction were followed by monitoring the decrease in the absorption at the  $\lambda_{\rm max}$  for the substrates in the range of 258–280 nm as described.<sup>1,3</sup> In all cases, the ionic strength was maintained to be 0.1 M with Bu<sub>4</sub>N<sup>+</sup>Br<sup>-</sup>. Excellent pseudo-first-order kinetics plots, which covered at least 3 half-lives, were obtained. Plots of  $k_{obs}$  for the reactions of **1a** and **1d** with *i*-Bu<sub>2</sub>NH/*i*-Bu<sub>2</sub>NH<sub>2</sub><sup>+</sup> and *i*-Pr<sub>2</sub>NH/*i*-Pr<sub>2</sub>NH<sub>2</sub><sup>+</sup> in 70 mol % MeCN(aq) against base concentration were straight lines passing through the origin, indicating that the reactions are second order, first order to the substrate, and first order to the base.<sup>2</sup> Moreover, the  $k_2$  values calculated from the slopes of the plots were in excellent agreement (within  $\pm 3\%$ ) with the  $k_2$  calculated by using a single data point. Hence, the rate constants for the base-promoted eliminations from 1a-dwere determined at a single base concentration. The  $k_2$  values were obtained by dividing the  $k_{obs}$ by the base concentration. Values of  $k_2$  for eliminations from 1a-d are summarized in Table 1. Except for the rate data

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**FIGURE 1.** Brönsted plots for the elimination from (*E*)-2,4- $(NO_2)_2C_6H_3CH=NOC(O)C_6H_4X$  promoted by  $R_2NH/R_2NH_2^+$  in 70 mol % MeCN(aq) at 25.0 °C [X = H (1a,  $\bullet$ ), *p*-OMe (1b,  $\blacksquare$ ), *m*-Cl (1c,  $\blacktriangle$ ), *p*-NO<sub>2</sub> (1d,  $\checkmark$ )].



**FIGURE 2.** Plots of log  $k_2$  versus p  $K_{lg}$  values of the leaving group for the elimination from (E)-2,4- $(NO_2)_2C_6H_3CH$ =NOC $(O)C_6H_4X$  (**1a-d**) promoted by R<sub>2</sub>NH/R<sub>2</sub>NH<sub>2</sub><sup>+</sup> in 70 mol % MeCN(aq) at 25.0 °C [R<sub>2</sub>NH = Bz(i-Pr)NH( $\blacksquare$ ), *i*-Bu<sub>2</sub>NH(•), *i*-Pr<sub>2</sub>NH( $\blacktriangle$ ), 2,6-DMP( $\triangledown$ )].

TABLE 2. Brönsted  $\beta$  Values for Elimination from (*E*)-2,4-(NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH=NOC(O)C<sub>6</sub>H<sub>4</sub>X (1a-d)<sup>*a*</sup> Promoted by R<sub>2</sub>NH/R<sub>2</sub>NH<sub>2</sub><sup>+</sup> in 70 mol % MeCN(aq) at 25.0 °C

	X = p-OMe	X = H	X = m-Cl	$X = p-NO_2$
$egin{array}{c} { m p}{K_{ m lg}}^a \ eta \end{array} eta \ eta \end{array}$	$21.3 \\ 0.27 \pm 0.01$	$20.7 \\ 0.32 \pm 0.02$	${}^{19.5}_{0.34\pm0.04}$	$18.7 \\ 0.32 \pm 0.02$
<sup><i>a</i></sup> Reference 4.				

determined with *i*-Pr<sub>2</sub>NH, the rate increased with the base strength of the promoting base and the leaving group ability. The slower rate of eliminations from 1a-d with *i*-Pr<sub>2</sub>NH than with *i*-Bu<sub>2</sub>NH as the base can be attributed to the greater steric requirement of the former.

The plots of  $k_2$  values for  $1\mathbf{a}-\mathbf{d}$  against the  $pK_a$  values of the base are depicted in Figure 1. The plots are linear with excellent correlations, if the data for *i*-Pr<sub>2</sub>NH is excluded. Therefore, the  $\beta$  values were calculated from the straight lines without the data for *i*-Pr<sub>2</sub>NH. Similarly, the elimination rates determined with different leaving groups correlated reasonably well with the leaving group  $pK_{1g}$  values (Figure 2). The  $\beta$  and  $|\beta_{1g}|$  values are in the range of 0.27–0.32 and 0.28–0.32, respectively. The  $\beta$  and  $|\beta_{1g}|$  values remained nearly the same within experimental error for all leaving groups and bases employed in this study (Tables 2 and 3).

**Mechanism of Elimination.** The mechanism of elimination for 1a-d promoted by  $R_2NH/R_2NH_2^+$  in 70 mol % MeCN(aq) have been elucidated by the results of kinetic investigations and product studies. Because the reactions produced only elimination

TABLE 3. Brönsted  $\beta_{lg}$  Values for elimination from (*E*)-2,4-(NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH=NOC(O)C<sub>6</sub>H<sub>4</sub>X Promoted by R<sub>2</sub>NH/R<sub>2</sub>NH<sub>2</sub><sup>+</sup> in 70 mol % MeCN(aq) at 25.0 °C

R <sub>2</sub> NH	Bz (i-Pr)NH	<i>i</i> -Bu <sub>2</sub> NH	<i>i</i> -Pr <sub>2</sub> NH	2,6-DMP <sup>b</sup>
$pK_{a}^{a}$ $\beta_{lg}$	$16.8 - 0.28 \pm 0.02$	$     \begin{array}{r}       18.2 \\       -0.32 \pm 0.01     \end{array} $	$     18.5 \\     -0.30 \pm 0.01   $	$     \begin{array}{r}       18.9 \\       -0.31 \pm 0.01     \end{array} $
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<sup>*a*</sup> Reference 5. <sup>*b*</sup> *cis*-2,6-Dimethylpiperidine.





products and exhibited second-order kinetics, all but bimolecular elimination pathways can be negated. The (E1cb)ip and internal return mechanisms were ruled out by the observed general base catalysis with the Brönsted  $\beta$  values ranging from 0.28 to 0.32 because these mechanisms would exhibit either a specific base catalysis or Brönsted  $\beta$  values near unity.<sup>6,7</sup> Hence, the most likely mechanism for this bimolecular process is either E2 or E1cb. If the reaction proceeds via a carbanion intermediate, the rate equation can be expressed as  $k_{obs} = k_1 k_2' [B] / (k_{-1} [BH^+] +$  $k_2'$ ) (Scheme 1).<sup>6</sup> The (E1cb)<sub>R</sub> mechanism requires that the first step must be reversible, i.e.,  $k_{-1}[BH^+] \gg k_2'$ , and the rate expression can be simplified to  $k_{obs} = k_1 k_2' [B] / (k_{-1} [BH^+])$ . This would predict that the  $k_{obs}$  should remain constant regardless of the buffer concentration because  $[B]/[BH^+] = 1.0$  is maintained throughout the reaction. Therefore, the (Elcb)<sub>R</sub> mechanism is ruled out by the linear dependence of the  $k_{obs}$ values on the base concentration. On the other hand, the  $\beta =$ 0.28-0.32 and  $|\beta_{lg}| = 0.28-0.32$  are consistent with an E2 mechanism with limited cleavage of the  $C_{\beta}$ -H and  $N_{\alpha}$ -OC(O)Ar bonds in the transition state, and a mechanism in which  $k_1$  is the rate limiting [(E1cb)<sub>irr</sub>], for which a small or negligible leaving group effect is expected.<sup>7</sup>

The distinction between the two mechanisms has been made by the interaction coefficients. Table 2 shows that the  $\beta$  values for **1a** remain almost the same within experimental error regardless of the base strength. The result can be described by a negligible  $p_{xy}$  interaction coefficient,  $p_{xy} = \partial\beta/\partial pK_{lg} \approx 0$ , which describes the interaction between the base catalyst and the leaving group.<sup>6,8–11</sup> The similar  $|\beta_{lg}|$  values for all bases is another manifestation of this effect,  $p_{xy} = \partial\beta_{lg}/\partial pK_{BH} \approx 0$  (Table 3). On the More–O'Ferrall–Jencks energy diagram shown in Figure 3, a change to a better leaving group will raise the energy of the top edge of the diagram. The transition state on the horizontal coordinate will remain at nearly the same position because there is no diagonal character. This would predict negligible change in  $\beta$ .<sup>8</sup> Similarly, a change to a stronger base will raise the energy of the right side of the diagram. The

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**FIGURE 3.** Reaction coordinate diagram for nitrile-forming eliminations from (*E*)-2,4-dinitrobenzaldehyde *O*-benzoyloximes. (Top) The effect of the change to a stronger base on the horizontal reaction coordinate is shown by the shift of the transition state from A to B. The effect of the change to a better leaving group is omitted because there will be little shift. (Center) The effects of the change to a stronger base and a better leaving group on the diagonal reaction coordinate are shown by the shifts from C to D and C to E, respectively. These effects can be described by  $p_{xy} > 0$ .

TABLE 4.Effect of the Base-Solvent on the Nitrile-FormingEliminations from (E)-2,4- $(NO_2)_2C_6H_3CH=NOC(O)C_6H_5$ 

base-solvent	R <sub>2</sub> NH-MeCN <sup>a</sup>	R <sub>2</sub> NH/R <sub>2</sub> NH <sub>2</sub> <sup>+</sup> -70 mol % MeCN(aq)	
rel rate $(k_2)^b$	1.0	0.6	
β	$0.47 \pm 0.04$	$0.32 \pm 0.02$	
$\beta_{lg}^{c}$	$-0.41\pm0.01$	$-0.28\pm0.02$	
$p_{xy}$	$0.040\pm0.005$	$\sim 0$	
<sup><i>a</i></sup> Reference 2. <sup><i>b</i></sup> $R_2NH = i$ -Bu <sub>2</sub> NH. <sup><i>c</i></sup> $R_2NH = Bz(i$ -Pr)NH.			

transition state on the horizontal coordinate will then move toward the right as depicted by a shift from A to B, resulting in little change in  $|\beta_{1g}|^{.8}$  The negligible  $p_{xy}$  coefficients are inconsistent with the E2 mechanism for which  $p_{xy} > 0$  is expected (Figure 3) but provide a strong evidence for the (E1cb)<sub>irr</sub> mechanism.<sup>6,8-11</sup>

Effect of Base-Solvent. Table 4 shows that the rate of elimination from 1a decreases slightly as the base-solvent is changed from *i*-Bu<sub>2</sub>NH-MeCN to *i*-Bu<sub>2</sub>NH/*i*-Bu<sub>2</sub>NH<sub>2</sub><sup>+</sup> in 70 mol % MeCN(aq), presumably due to the decreased basicity in more protic solvent.<sup>12</sup> The extent of  $C_{\beta}$ -H and  $N_{\alpha}$ -OC(O)Ar bond cleavage decreased remarkably as revealed by the large decrease in the Brönsted  $\beta$  and  $|\beta_{lg}|$  values by the same variation of the base-solvent system (Table 4).

The change in the transition-state structure with the base—solvent variation can be attributed to a solvent effect. If the partial

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negative charge developed at the  $\beta$ -carbon in the transition state is better stabilized by solvation in more protic 70 mol % MeCN(aq), the transition state should be less sensitive to the base strength. This would predict a smaller  $\beta$  value, as observed. Moreover, the negative charge should be transferred from the  $\beta$ -carbon toward the  $\alpha$ -nitrogen to form partial triple bond and to break the  $N_{\alpha}$ -OC(O)Ar bond. If a smaller amount of negative charge is transferred from the  $\beta$ -carbon, the extent of  $N_{\alpha}$ -OC(O)Ar bond cleavage should be smaller too. The most interesting result from this study is the change of the reaction mechanism from E2 to (E1cb)irr by the base-solvent variation as revealed by the interaction coefficients  $(p_{xy} > 0 \rightarrow p_{xy} \sim 0)$ (Table 4). It appears that the change in the elimination reaction mechanism has been realized by the combined effects of strongly electron-withdrawing  $\beta$ -aryl substituents, intrinsically carbanion stabilizing sp<sup>2</sup>-hybridized  $\beta$ -carbon, syn-stereochemistry and enhanced anion-solvating ability of more protic solvent.

#### **Experimental Section**

**Materials.** (*E*)-2,4-Dinitrobenzaldehyde *O*-benzoyloximes 1a-d were available from previous investigations.<sup>2</sup> Reagent-grade acetonitrile and secondary amine were fractionally distilled from CaH<sub>2</sub>. Buffer solutions were prepared by dissolving equivalent amounts of R<sub>2</sub>NH and R<sub>2</sub>NH<sub>2</sub><sup>+</sup> in 70 mol % MeCN(aq). In all cases, the ionic strength was maintained to be 0.1 with Bu<sub>4</sub>N<sup>+</sup>Br<sup>-</sup>.

**Kinetic Studies.** All of the reactions were followed using a UV-vis spectrophotometer with thermostated cuvette holders. Reactions were monitored by the decrease in the absorption of the substrate at 258-280 nm under pseudo-first-order condition employing at least 400-fold excess of the base. The pseudo-first-order rate constants were divided by the base concentration to afford the second-order rate constants,  $k_2$ .

**Product Studies.** The product from the reaction of **1a** with *i*-Bu<sub>2</sub>NH/*i*-Bu<sub>2</sub>NH<sub>2</sub><sup>+</sup> in 70 mol % MeCN(aq) was identified by using more concentrated solution as described previously.<sup>2</sup> A solution of 0.5 g (1.59 mmol) of **1a** and an excess amount of base in the appropriate base (15 mL) was stirred for 7 h at room temperature. The solvent was removed in vacuo and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> and washed thoroughly with water until all of the amine, ammonium salt, and the benzoate were completely removed. The product was 2,4-dinitrobenzonitrile with mp 103 °C (lit.<sup>13</sup> mp 104–105 °C). The yield of 2,4-dinitrobenzonitrile was 0.29 g (94%).

**Control Experiments.** The stabilities of 1a-d were determined as reported.<sup>1,2</sup> The solutions of 1 in MeCN were stable for at least 5 weeks when stored in the refrigerator.

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