Elimination Reactions of (*E*)-*O*-Pivaloylbenzaldoximes

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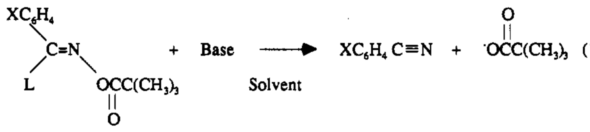
Elimination reactions of (*E*)-*O*-pivaloylbenzaldoximes promoted by Et_3N–MeCN, *t*-BuOK–*t*-BuOH, and *t*-BuOK–DMSO have been studied kinetically. The reactions produce benzonitrile quantitatively. The reactions are second-order and exhibit substantial values of ρ, β, and k_H/k_D and an E2 mechanism is evident. The rate of elimination from (*E*)-*O*-pivaloylbenzaldoxime increased with base–solvent system variation and gave relative rates of 1, 14.8, and 4.31×10^4 for Et_3N–MeCN, *t*-BuOK–*t*-BuOH, *t*-BuOK–DMSO, respectively. The k_H/k_D value increased, but the Hammett ρ value increased and then decreased, with this change in the base–solvent system. These results are compared with the predictions of the More O'Ferrall–Jencks reaction coordinate diagram to assess its scope and limitations in the interpretation of the elimination reactions.

Recently we have studied nitrile-forming eliminations of (*E*)-*O*-arylbenzaldoximes promoted by KOH–60% $DMSO_{(aq)}$, R_2NH–MeCN, R_3N–MeCN, and MeONa–MeOH.[2–5] The reactions proceeded via an E2-central type of transition state. The influence of base strength, base–solvent system, β-aryl substituent, and leaving group upon the transition state were thoroughly investigated. A most interesting result from these studies was the unusual leaving group effect observed for the R_3N promoted eliminations from (*E*)-*O*-arylbenzaldoximes. When the leaving group was changed from 2,4-dinitrophenoxide to picrate, the rate increased by 1800-fold, the ρ value decreased from 2.6 to 1.0, and the β value increased from 0.57 to 0.72.[2] These results are in conflict with the prediction of the More O'Ferrall–Jencks reaction coordinate diagram.[6a] However, when the same reactions were conducted with MeONa–MeOH as the base–solvent system, the rate difference diminished to 125-fold and a normal leaving group effect was observed.[5] This difference for the eliminations induced by R_3N–MeCN and MeONa–MeOH suggests a limitation of the More O'Ferrall–Jencks diagram in that it cannot explain the structure–reactivity relationship when the reactivity difference is too large, although it is very successful for reactions with modest difference in reactivity.

To further assess the scope and limitation for the use of reaction coordinate diagram in base-promoted 1,2-elimination reactions, we have investigated the reactions of (*E*)-*O*-pivaloylbenzaldoximes **1a–e** with Et_3N–MeCN, *t*-BuOK–*t*-BuOH, and *t*-BuOK–DMSO (eq 1). Since the pK_a values of pivaloate and 2,4-dinitrophenoxide in MeCN are estimated to be 21.0 and 16.0, respectively, the rates of elimination from **1** are expected to be much slower than those from corresponding (*E*)-*O*-2,4-dinitrophenylbenzaldoximes under the same conditions. On the other hand, variation of the base–solvent system from Et_3N–MeCN to *t*-BuOK–*t*-BuOH to *t*-BuOK–DMSO for eliminations from **1** should give rise to a modest-to-large rate enhancement. Therefore, the validity of the reaction coordinate diagram approach can be tested under a variety of conditions. The results of this study are reported below.



(1)

	L	X
1a	H	H
1b	D	H
1c	H	*p*-MeO
1d	H	*m*-Br
1e	H	*p*-NO_2

Base	Solvent
Et_3N	MeCN
t-BuOK	*t*-BuOH
t-BuOK	DMSO

Results

(*E*)-*O*-Pivaloylbenzaldoximes **1a–e** were prepared by the reactions of (*E*)-benzaldoximes with pivaloyl chloride. The NMR and IR spectra and combustion analysis data for these new compounds are consistent with the proposed structures.

Reactions of **1** with Et_3N–MeCN, *t*-BuOK–*t*-BuOH, and *t*-BuOK–DMSO produced benzonitrile quantitatively. The rates of reactions were followed by measuring the disappearance of absorption of the substrate at 254–282 nm. Pseudo-first-order conditions were employed for the kinetic studies. Reactions of **1a–d** with Et_3N–MeCN and *t*-BuOK–*t*-BuOH were only followed up to 20% reaction because they were too slow to follow to completion conveniently. However, the reactions of **1e** with Et_3N–MeCN and *t*-BuOK–*t*-BuOH and **1a–e** with *t*-BuOK–DMSO were more rapid and were followed for at least 2 half-lives. Excellent pseudo-first-order kinetic plots were obtained. The observed rate constants were divided by the base concentrations to obtain second-order rate constants, which remained constant for 5-fold variation in base concentration. The second-order rate constants are listed in Tables I and II.

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Table I. Rate Constants for Eliminations from (*E*)-$XC_6H_4CL{=}NOC(O)C(CH_3)_3$ Promoted by R_3N in MeCN

X	L	temp (°C)	base[a]	k_2, $M^{-1}\,s^{-1}$ [b] ($\times 10^7$)
H	H	25.0	Et_3N	1.82 ± 0.15
H	D	25.0	Et_3N	0.531 ± 0.079
H	H	25.0	$Et_2NCH_2CH_2OH$	0.647 ± 0.030
H	H	25.0	$EtN(CH_2CH_2OH)_2$	0.149 ± 0.030
H	H	25.0	$N(CH_2CH_2OH)_3$	0.108 ± 0.060
p-CH_3O	H	25.0	Et_3N	0.866 ± 0.02
m-Br	H	25.0	Et_3N	8.15 ± 0.38
p-NO_2	H	25.0	Et_3N	36.6 ± 0.2

[a] $[R_3N] = 6.53 - 8.65 \times 10^{-1}$ M. [b] Average and standard deviation for three or more kinetic runs.

Table II. Rate Constants for Eliminations from (*E*)-$XC_6H_4CH{=}NOC(O)C(CH_3)_3$ Promoted by *t*-BuOK–*t*-BuOH and *t*-BuOK–DMSO

			k_2, $M^{-1}\,s^{-1}$ [a]	
X	L	temp (°C)	*t*-BuOK–*t*-BuOH[b]	*t*-BuOK–DMSO[c]
H	H	25.0	$(2.70 \pm 0.85) \times 10^{-6}$	$(7.85 \pm 0.01) \times 10^{-3}$
H	D	25.0	$(6.53 \pm 0.55) \times 10^{-7}$	$(1.55 \pm 0.01) \times 10^{-3}$
p-CH_3O	H	25.0	$(1.48 \pm 0.46) \times 10^{-6}$	$(3.35 \pm 0.75) \times 10^{-3}$
m-Br	H	25.0	$(1.96 \pm 0.24) \times 10^{-4}$	$(1.38 \pm 0.00) \times 10^{-2}$
p-NO_2	H	25.0	$(1.59 \pm 0.32) \times 10^{-3}$	$(8.60 \pm 0.11) \times 10^{-2}$

[a] Average and standard deviation for three or more kinetic runs. [b] $[t\text{-BuOK}] = 1.19 \times 10^{-1}$ M. [c] $[t\text{-BuOK}] = 2.45 \times 10^{-2}$ M.

Table III. Transition State Parameters for Eliminations from (*E*)-$XC_6H_4CH{=}NOY$ Promoted by Et_3N–MeCN

	Y = pivaloyl	Y = 2,4-dinitrophenyl[a]
pK_{lg}	21.0	16.0
rel rate	1	4170
ρ	1.57 ± 0.02	2.6 ± 0.1
β	0.43 ± 0.05	0.57 ± 0.1

[a] Reference 2.

Table IV. Effects of Base–Solvent System Variation for Nitrile-Forming Eliminations from (*E*)-$XC_6H_4CH{=}NOC(O)C(CH_3)_3$

	base–solvent		
	Et_3N–MeCN	*t*-BuOK–*t*-BuOH	*t*-BuOK–DMSO
rel rate	1	14.8	4.31×10^4
ρ	1.57 ± 0.02	3.13 ± 0.09	1.27 ± 0.02
k_H/k_D	3.67 ± 0.31	4.15 ± 0.36	5.06 ± 0.01

The influence of β-aryl substituents upon the elimination rates gave excellent correlation with σ (plots not shown). Hammett ρ values for reactions of **1** with Et_3N–MeCN, *t*-BuOK–*t*-BuOH, and *t*-BuOK–DMSO are 1.57, 3.13, and 1.27, respectively (Tables III and IV).

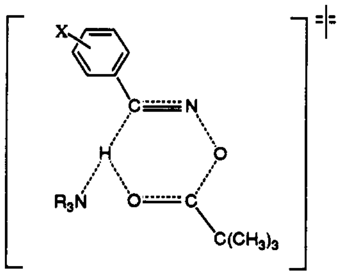
For elimination reactions of **1a** in MeCN, the rate constants were determined with Et_3N, $Et_2NCH_2CH_2OH$, $EtN(CH_2CH_2OH)_2$, and $N(CH_2CH_2OH)_3$ as the promoting bases. The rate increased linearly with the pK_a values of the base (plot not shown). The Bronsted β value is recorded in Table III.

From the rate constants for elimination from **1a** and its deuterated analogue **1b**, primary deuterium isotope effect values were calculated. The values are 3.7, 4.2, and 5.1 for eliminations induced by Et_3N–MeCN, *t*-BuOK–*t*-BuOH, and *t*-BuOK–DMSO, respectively (Table IV).

Discussion

Effect of Leaving Group upon the Nitrile-Forming Transition State. Earlier it was established that the elimination reactions of (*E*)-*O*-arylbenzaldoximes with KOH–60% $DMSO_{(aq)}$, Et_3N–MeCN, R_2NH–MeCN, and MeONa–MeOH proceeded by an E2 mechanism.[2–5] The results of product and kinetic studies reveal that the reactions of **1** with Et_3N–MeCN, *t*-BuOK–*t*-BuOH, and *t*-BuOK–DMSO also proceed by the same mechanism. Since the elimination reactions exhibit second-order kinetics and substantial values of β and k_H/k_D were determined (Tables III and IV), all but E2 and $(E1cb)_{irr}$ mechanisms can be ruled out.[6b,8] The $(E1cb)_{irr}$ mechanism requires the formation of a carbanionic intermediate in the rate-determining step. Hence the transition state for the $(E1cb)_{irr}$ mechanism should have more carbanionic character and a greater extent of C–H bond cleavage and thus exhibit greater values of ρ and β than those for an E2 mechanism. However, the values are comparable to those observed for eliminations from (*E*)-*O*-arylbenzaldoximes under similar conditions.[2] Therefore, it seems reasonable to ascribe an E2 mechanism to the reactions of **1** with Et_3N–MeCN, *t*-BuOK–*t*-BuOK, and *t*-BuOK–DMSO.

For Et_3N-promoted elimination, the change of the leaving group from 2,4-dinitrophenoxide to pivaloate decreases the rate by approximately 4000-fold (Table III). Both Hammett ρ and Bronsted β values are smaller for the latter, indicating a lesser extent of negative charge development at the β-carbon and reduced C_β–H bond cleavage in the transition state. The change in the transition state structure with this leaving group variation can be explained with a cyclic transition state **2** for eliminations from **1**. Since the developing negative charge in the transition state cannot be stabilized by the poorly anion-solvating MeCN, it should be delocalized as much as possible in order to minimize the transition state energy. Maximium charge dispersal can be accomplished by forming cyclic transition state **2** in which the negative charge is not only delocalized between the β-carbon and carbonyl oxygen atoms but is also partially cancelled by an intramolecular hydrogen bond. Therefore, Et_3N-promoted elimination from **1** should be less sensitive to change of the β-aryl substituent and the base than for Et_3N-promoted elimination from (*E*)-*O*-2,4-dinitrophenylbenzaldoximes for which a cyclic transition state is unlikely.



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The change in the transition state structure with the leaving group variation from 2,4-dinitrophenoxide to pivaloate cannot be interpreted with a More O'Ferrall–Jencks reaction coordinate diagram.[6a] A change to a poorer leaving group would increase the energy of the E1 intermediate and the product, shifting the transition state directly upward in the reaction coordinate diagram. This predicts an increase in negative charge development at the β-carbon and little change in the extent of proton transfer. The results shown in Table III are in conflict with this prediction. However, this dichotomy between the prediction and the experimental results should not be taken as an evidence for a limitation of the reaction coordinate diagram approach since the structures of the two transition states are entirely different.

Effect of Base–Solvent System Variation upon the Nitrile-Forming Transition State. Comparison of the transition state parameters presented in Table IV reveals that the structure of the transition state varies significantly with a change of the base–solvent system from Et_3N–MeCN to *t*-BuOK–*t*-BuOH, despite only a moderate difference in rate. Both the Hammett ρ and k_H/k_D values increase, indicating enhancement in the negative charge density at the β-carbon and the extent of C_β–H bond cleavage in the transition state. The result may be attributed to a solvation effect. Since *t*-BuOH is a better anion-solvating solvent than MeCN, it is no longer necessary for the transition state to form a cyclic structure. Therefore, more negative charge can be developed at the β-carbon, and the C_β–H bond can be broken to a greater extent in the transition state. The result for this base–solvent system variation cannot be interpreted with a More O'Ferrall–Jencks reaction coordinate diagram because the effect of changing the energy of each corner of the reaction coordinate diagram upon the transition state will be different for the cyclic and syn-elimination transition states.

For *t*-BuOK-promoted eliminations from 1, the change of solvent from *t*-BuOH to DMSO increases the rate by 3000-fold. The Hammett ρ value decreases from 3.13 to 1.27 indicating a decrease in the negative charge development at the β-carbon in the transition state. The increase in k_H/k_D value from 4.2 to 5.1 can be interpreted as either an increase or a decrease in the C_β–H bond rupture in the transition state.[9] However, since the maximum k_H/k_D is expected for 0.4 proton transfer[10] and the k_H/k_D values of 3.1–4.0 observed for MeONa-promoted elimination from (*E*)-*O*-arylbenzaldoximes have been interpreted as more than 0.4 proton transfer in the transition state,[4] the k_H/k_D value of 4.2 for *t*-BuOK-promoted elimination from 1 should also indicate a proton transfer that is past the midpoint. Therefore, the change in k_H/k_D value from 4.2 to 5.1 for solvent variation from *t*-BuOH to DMSO is interpreted as arising from a decrease in transition state proton transfer in DMSO.

These results may be rationalized by considering relative effects of parallel and perpendicular motion in the reaction coordinate diagram. Since DMSO is a poorer anion-solvating solvent than *t*-BuOH, *tert*-butoxide ion and the carbanion will be much better solvated in *t*-BuOH than in DMSO. Hence, although the neutral reactant molecules may be slightly more stable in DMSO, the overall effect for the change in the solvent would be to increase the energy of the reactant, and the E1 and E1cb intermediates compared to that of the product in the reaction coordinate diagram. Moreover, the free energy of activation for elimination from 1 should be decreased significantly with the change of the solvent as indicated by the large rate enhancement. Therefore, the curvature of the potential energy surface should decrease along the reaction coordinate but increase in the perpendicular direction when the solvent is changed from *t*-BuOH to DMSO. This would predict that the parallel effect should be predominant and the transition state should move toward the reactant since the transition state will move easier in the direction where curvature of the surface is smaller.[11] The observed decrease in ρ and the increase in k_H/k_D value for the solvent change from *t*-BuOH to DMSO are consistent with this interpretation.

In an earlier paper,[2] we proposed that the More O'Ferrall–Jencks reaction coordinate diagram may fail to interpret the structure–reactivity relationship for elimination reactions when the reactivity difference is too large. For a large difference in reactivity there may be a profound change in the potential energy surface which prevents one from starting at one transition state and predicting the structure of another. The present results indicate that the More O'Ferrall–Jencks diagram may be successfully employed for reactions with reactivity difference of 3000-fold when the structures of the transition states are closely-related, but fails to interpret results for reactions with only modest difference in reactivity when the transition state structures are very different. The results demonstrate the usefulness of the reaction coordinate diagram in the interpretation of the elimination reactions which proceed via closely-related transition state.

Experimental Section

Materials. (*E*)-*O*-Pivaloylbenzaldoximes 1 were prepared by stirring a mixture of (*E*)-benzaldoximes with pivaloyl chloride in 2 N aqueous NaOH solution for 1 h at 0 °C. IR and ^1H NMR (300 MHz) spectral data and the results of combustion analysis for these compounds were consistent with the proposed structures. The melting point (°C), NMR ($CDCl_3$, ppm), IR (KBr, C=N, C=O, cm^{-1}), and combustion analysis data for the new compounds are as follows. $C_6H_5CH{=}NOC(O)C(CH_3)_3$ (**1a**): mp 31–32; IR 1605, 1740; NMR δ 8.38 (s, 1H), 7.75 (d, 2 H), 7.43 (m, 3H), 1.32 (s, 9H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.44; H, 7.51. $C_6H_5CD{=}NOC(O)C(CH_3)_3$ (**1b**): mp 36–37; IR 2220 (C–D), 1605, 1740; NMR δ 7.77 (d, 2 H), 7.45 (m, 3H), 1.32 (s, 9H). Anal. Calcd for $C_{12}H_{14}DNO_2$: C, 69.88; H, 6.84. Found: C, 69.85; H, 7.21. *p*-$CH_3OC_6H_4CH{=}NOC(O)C(CH_3)_3$ (**1c**): mp 70–71; IR 1615, 1760; NMR δ 8.33 (s, 1H), 7.70 (d, 2 H), 6.93 (d, 2H), 3.83 (s, 3H), 1.31 (s, 9H). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.22; H, 7.21. *m*-$BrC_6H_4CH{=}NOC(O)C(CH_3)_3$ (**1d**): mp 78–79; IR 1620, 1750; NMR δ 8.34 (s, 1H), 7.95 (s, 1 H), 7.68 (d, 1 H), 7.60 (d, 1 H), 7.32 (t, 1H), 1.32 (s, 9H). Anal. Calcd for $C_{12}H_{14}NO_2Br$: C, 50.72; H, 4.97. Found: C, 50.69; H, 4.75. *p*-$NO_2C_6H_4CH{=}NOC(O)C(CH_3)_3$ (**1c**): mp 172–173; IR 1600, 1750; NMR δ 8.50 (s, 1H), 8.31 (d, 2 H), 7.97 (d, 2H), 1.32 (s, 9H). Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64. Found: C, 57.64; H, 5.58.

Tertiary amines, MeCN, and *t*-BuOH were purified as reported previously.[2,12] *t*-BuOK–*t*-BuOH was prepared by a known method.[12] The solutions of *t*-BuOK in DMSO were prepared by adding freshly prepared *t*-BuOK to DMSO in a glove box.

Kinetic Studies. All of the reactions were followed by measuring the decrease in absorption of the substrate at 254–282 nm under pseudo-first-order conditions employing at least a 10-fold excess of base. The reactions of 1 with R_3N–MeCN and *t*-BuOK–*t*-BuOH were monitored by periodically removing samples from a reaction flask immersed in a constant temperature bath maintained at 25.0 ± 0.1 °C. On the other hand, the reactions of 1 with *t*-BuOK in DMSO were followed using a UV-vis spectrophotometer with thermostated cuvette holders by injecting 5–10 μL of an ca. 10^{-2} M solution of substrate as reported previously.[2–5] The reactions of **1a–d** with R_3N–MeCN and *t*-BuOK–*t*-BuOH were followed up to 20% reaction because they were too slow to follow to completion conveniently. However, the reactions of **1e** with R_3N–MeCN and *t*-BuOK–*t*-BuOH and **1a–e** with *t*-BuOK–DMSO were followed at least for 2 half-lives. In all cases plots of ln $(A_t - A_\infty)$ against time with linear with

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excellent correlation. The slope was the observed rate constant. The observed rate constants were divided by the base concentration to obtain the second-order rate constant. The average second-order rate constant and standard deviation were calculated from three or more kinetic runs.

Product Studies. The yield of PhC≡N from the reactions were determined using a more concentrated solution and higher temperatures than employed in the kinetic runs. A solution of 1.0 g of **1a** and an excess amount of base in the appropriate solvent (15 mL) was refluxed for 1–3 days. A large amount of water was added and the solution was extracted with CH_2Cl_2. The CH_2Cl_2 solution was analyzed by gas chromatography on a 25-m capillary column of 5% phenylmethylsilicon with *m*-nitrotoluene as an internal standard. For reactions of **1a** with Et_3N–MeCN, *t*-BuOK–*t*-BuOH, and *t*-BuOK–DMSO, the yields of PhC≡N were 90, 88, and 92%, respectively.

Control Experiments. The stabilities of **1a–e** were determined as reported earlier.[2-5]

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