Base-promoted elimination reactions of (*E*)- and (*Z*)-arylaldehyde *O*-benzoyloximes. Effects of stereochemistry, β-aryl group, and base-solvent on the nitrile-forming transition states

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This account is dedicated to Professor Richard A. Bartsch for his immense contribution to chemistry and education on the occasion of his retirement

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Abstract

This account summarizes the results of mechanism studies on the nitrile-forming eliminations from (*E*)- and (*Z*)-arylaldehyde *O*-benzoyloximes promoted by 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in MeCN, R_1R_2NH in MeCN, and $R_1R_2NH/R_1R_2NH_2^+$ in 70mol% MeCN(aq). The rate of *anti*-elimination was 36,000-fold faster than that of *syn*-elimination. The change of the β-aryl group from Ph to thienyl to furyl shifted the E2 transition state slightly towards product-like. When (*E*)-2,4-dinitrobenzaldehyde *O*-benzoyloxime was employed as the reactant and $R_1R_2NH/R_1R_2NH_2^+$ in 70mol% MeCN(aq) was used as the base-solvent, the $(E1cb)_{irr}$ was observed.

Keywords: Elimination, E2 mechanism, E1cb mechanism, transition state

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1. Introduction

Base-promoted elimination reactions forming C=C bonds have been extensively investigated for more than 50 years.[1-7] The results of the structure-reactivity relationships studies have led to a qualitative understanding of the relationship between the reactant structure and the transition state structure. One of the most important achievements from these studies is the development of the More-O'Ferrall-Jencks energy diagram, which has become a useful tool for the interpretation of not only elimination reactions, but also substitution reactions and the reactions of carbonyl compounds, and found its way in advanced organic chemistry textbooks.[8,9] In contrast, not much attention has been focused on the elimination reactions in which the π-bond is formed between carbon and a heteroatom, such as nitrogen, oxygen, or sulfur.

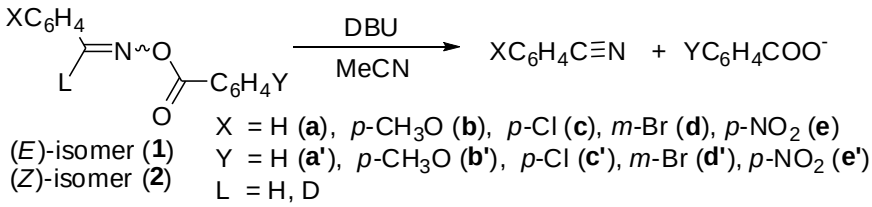
The imine-forming elimination reactions were thoroughly investigated by the groups of Hoffman, Bartsch, and subsequently by Cho and an account summarizing the results was jointly published by them.[11] Two decades ago, Cho group has initiated a systematic investigation on the nitrile-forming eliminations reactions. There are several differences between imine- and nitrile-forming eliminations. First, the energy difference between C-N and C=N bonds is significantly larger than that between C=N and C≡N bonds. Second, the β–carbon in the imine-forming elimination is sp^3 hybridized, whereas in the nitrile-forming elimination it is sp^2 hybridized. This is expected to stabilize the developing negative charge in the nitrile-forming transition state. Third, both the C_β–H bond and developing partial multiple bonds are parallel to the π–orbitals of the β–aryl group in the imine-forming transition state, whereas they are orthogonal to each other in the nitrile-forming transition state. Hence, the β–aryl group is expected to stabilize the developing negative charge more in the imine- than in the nitrile-forming transition state.[12] The combined effects would predict that the imine-forming eliminations would favor E1-like or E2 central transition state, whereas the nitrile-forming eliminations would favor E1cb-like transition state or an E1cb mechanism. Such predictions were borne out in the imine-forming eliminations, but not in the nitrile-forming eliminations until recently.[11-25] This account summarizes a systematic study on the nitrile-forming elimination reactions of (*E*)- and (*Z*)-arylaldehyde *O*-benzoyloxime derivatives.[12,23-25] This series of compounds provided unusual opportunities to study the effects of changing the stereochemistry, β–aryl group, leaving group, and base-solvent

on the nitrile-forming transition states. The results reveal a wide variation of the transition state structures ranging from E2-central to E1cb mechanism.

2. Base-promoted nitrile-forming eliminations from (*E*)- and (*Z*)-benzaldehyde *O*-benzoyloximes

An excellent understanding of electronic effects and the effects of changes in reactant structure and reaction conditions on the structure of the E2 transition state for alkene- and alkyne-forming *anti*-eliminations has evolved.[1,4,8,26] Similarly, the complementary *syn* eliminations have also been studied.[1,4,26] The results of these studies reveal that the *anti*-elimination is more facile and proceeds through the transition state with less carbanionic character and smaller extents of C_α–H bond cleavage than the corresponding *syn*-elimination reactions. In contrast, little was known about the differences between the *syn*- and *anti*-eliminations forming carbon-nitrogen triple bonds.

To provide an insight into the transition state differences between the *syn*- and *anti*-eliminations forming nitriles, we have investigated the reactions of (*E*)- and (*Z*)-benzaldehyde *O*-benzoyloximes with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in MeCN (Scheme 1).[23] We have determined the k_H/k_D, Hammett ρ, and Brönsted β and β_{lg} values for both reactions. The structure-reactivity parameters permitted a mapping of the transition state for these reactions on the More-O'Ferrall-Jencks reaction coordinate energy diagram. These results provided a complete picture of the transition state differences for the *syn*- and *anti*-eliminations forming nitriles.



Scheme 1

2.1 Mechanism of eliminations from 1 and 2 promoted by DBU in MeCN

Results of product studies and kinetic investigations revealed that the reactions of **1** and **2** with DBU in MeCN proceeded by the E2 mechanism.[23] Since the reactions produced only elimination products and exhibited second-order kinetics, all but bimolecular pathways could be ruled out. In addition, an E1cb mechanism could be negated by the substantial values of k_H/k_D and $|\beta_{lg}|$.[4,8,26]

2.2 Transition state differences for the *Syn*- and *Anti*-eliminations forming nitriles

The rate of *anti*-elimination reaction from **2** promoted by DBU in MeCN proceeded at approximately 36,000-fold faster rate than that of the *syn*-elimination from **1** (Table 1). An ab initio calculation with the 6-31G basis set revealed that **2** was less stable than the (*E*)-isomer by 3.734 kcal/mol due to the unfavorable steric interactions between the phenyl and the leaving group that distorted the structure. Hence, the much faster rate of anti-elimination was attributed to the steric strain in the (*Z*)-isomer and the greater extent of partial triple bond formation in the *anti*-transition state.

The structures of the transition states were assessed by comparing the Hammett ρ, k_H/k_D, and $|\beta_{lg}|$ values. The Hammett ρ value for the *anti*-elimination was much smaller than that for the *syn*-elimination, indicating a smaller extent of negative charge developed at the β-carbon in the transition state. In addition, the k_H/k_D value was much larger for the former. Although this result could be interpreted with either a greater or a smaller extent of proton transfer in the transition state,[28] the latter interpretation was more compatible with the smaller ρ value observed for the *anti*-eliminations. Further, the $|\beta_{lg}|$ value was smaller for the *anti*- than for the *syn*-elimination, indicating a smaller degree of leaving group bond cleavage in the anti transition state. These results indicated that the transition state for the *anti*-eliminations from **2** appeared to be more symmetrical with a smaller degree of proton transfer, less negative charge development at the β-carbon, and a smaller extent of leaving group bond cleavage than that for the corresponding *syn* eliminations from **1**. The activation parameters were also consistent with this interpretation. The enthalpy of activation ($\Delta H^{\neq}$) was smaller for **2** probably because of the smaller extents of the C_β-H and N_α-OC(O)Ar bond cleavages and greater degree of partial triple bond formation in the transition state. The higher reactant energy of **2** should also decrease the $\Delta H^{\neq}$ (*vide supra*). Further, since the transition state for the anti-elimination was less associated with respect to the base-proton bond, the entropy of activation ($\Delta S^{\neq}$) should be less negative.

Table 1. Relative rate, k_H/k_D, Hammett ρ, and β_{lg} values for eliminations from (*E*)-and (*Z*)-$XC_6H_4CL{=}NOC(O)C_6H_4Y$[a] promoted by DBU in MeCN at 25.0 °C

Compound	(*E*)-isomer	(*Z*)-isomer
rel rate	1	36,000
k_H/k_D	3.3 ± 0.2	7.3 ± 0.2
ρ[b]	2.19 ± 0.05	1.21 ± 0.05
β_{lg}	-0.49 ± 0.01	-0.40 ± 0.01
$\Delta H^{\neq}$, kcal/mol[a]	10.4 ± 0.6	6.8 ± 0.5
$\Delta S^{\neq}$, eu[a]	-34.3 ± 2.6	-25.8 ± 1.9

[a]X = H, Y = H except otherwise noted. [b] Y = H. [c] X = H.

2.3 Mapping of the transition state

Changes in the structure-reactivity parameters provided additional evidences for the above conclusions. These changes can usually be described on the energy surface of More-O´Ferrall-Jencks diagram.[28] An energy surface for the elimination reactions of DBU-promoted eliminations from **1** and **2** is shown in Figure 1. Table 2 shows that the k_H/k_D values for **1** increased slightly as the leaving group was made less basic. Since the smaller isotope effect for the former had been attributed to an extensive proton transfer past halfway (*vide supra*), this result indicated a gradual decrease in the extent of proton transfer in the transition state. The result could be described by a positive p_{xy} interaction coefficient, $p_{xy} = \partial\beta/\partial pK_{lg} > 0$, which provided additional support for the concerted E2 mechanism.[26, 29]

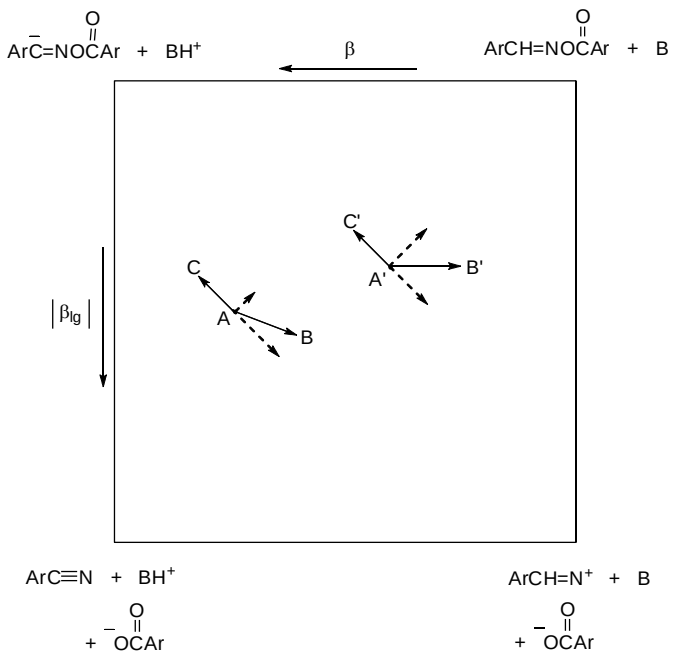


Figure 1. Reaction coordinate diagram for nitrile-forming eliminations. The effects of the change to a better leaving group and a stronger electron-withdrawing β-aryl substituent are shown by the shift of the transition state from A to B and A to C for the *E*-isomer and A´ to B´ and A´ to C´ for the *Z*-isomer, respectively.

On the More-O'Ferrall-Jencks energy diagram in Figure 1, a change to better leaving group would raise the energy of the top edge of the diagram. The transition state with greater extent of proton transfer than N_α-OC(O)Ar bond cleavage would then move slightly toward the right as depicted by a shift from A to B on the energy diagram, resulting in a small increase in k_H/k_D (*vide supra*).[28] On the other hand, the k_H/k_D values for **2** decreased with the same variation of the leaving group. This could also be explained with a decrease in the extent of proton transfer by assuming less than half proton transfer in the former transition state, a positive p_{xy} interaction coefficient, $p_{xy} = \partial\beta/\partial pK_{lg} > 0$, and a shift of the transition state from A´ to B´ in Figure 1.[26,28,29]

Table 2. Primary isotope effect values for eliminations from (*E*)- and (*Z*)-$XC_6H_4CL{=}NOC(O)C_6H_4Y$[a] promoted by DBU in MeCN at 25.0 °C

	k_H/k_D	
Y	*E*-isomer	*Z*-isomer
p-MeO	3.4 ± 0.3(2.8 ± 0.1)[b]	-
H	3.3 ± 0.2	7.3 ± 0.2 (9.0 ± 0.3)[b]
m-Br	3.5 ± 0.3	6.7 ± 0.1
p-NO_2	3.6 ± 0.1	6.4 ± 0.3

[a]X = H except otherwise noted. [b]X = *p*-NO_2.

The k_H/k_D value decreased for **1** but increased for **2**, respectively, as the electron-withdrawing ability of the β-aryl substituent was increased (Table 2). Since the extent of proton transfer for the two reactions was assumed to be on different sides of the midpoint, these results indicated an increase in the extent of proton transfer in both transition states (*vide supra*). This effect could be described by a positive $p_{xy'}$ interaction coefficient, $p_{xy'} = \partial\beta/\partial\sigma > 0$, and the reaction coordinate that has large components of proton transfer and N_α-OC(O)Ar bond cleavage.[26,29] These changes in the k_H/k_D values could be described on the More-O'Ferrall-Jencks diagram (Figure 1). [28] An electron-withdrawing β-aryl substituent will lower the energy of the carbanion intermediate in the upper left corner of the diagram. The transition state will then move slightly toward the upper left corner, with more proton and larger or smaller k_H/k_D , as depicted by the shifts from A to C and A´ to C´ for **1** and **2**, respectively, on the energy diagram.

As shown in Table 3, there was a progressive decrease in the Hammett ρ values with a better leaving. This result could be described by a negative $p_{yy'}$ interaction coefficient, $p_{yy'} = -\partial\rho/\partial pK_{lg} = -\partial\beta_{lg}/\partial\sigma < 0$.[26,29] The decrease in the $|\beta_{lg}|$ values with a stronger electron-withdrawing β-aryl substituent (Table 4) provided additional evidence for this effect, i.e., $p_{yy'} = -\partial\beta_{lg}/\partial\sigma < 0$. The negative $p_{yy'}$ coefficients observed in these reactions were consistent with an E2 mechanism and the reaction coordinates that have large components of proton transfer and N_α-OC(O)Ar bond cleavage so that a better leaving group would shift the transition state from A to B and A´ to B´ for **1** and **2**, respectively, to decrease the extent of negative charge development and the ρ values (Figure 1). Moreover, an electron- withdrawing substituent would shift the transition state from A to C for **1** in the direction of decreased N_α-OC(O)Ar bond cleavage and smaller $|\beta_{lg}|$ values.[28]The nearly identical $|\beta_{lg}|$ values for **2** may be attributed to the relative insensitivity of anti-transition state to the variation of the β-aryl substituent. All of these results were consistent with a slightly E1cb-like transition state for **1** and a more symmetrical transition state for **2**, respectively, as depicted in Figure 1. For both reactions, the structures of the transition states changes only slightly with the variation of the β-aryl substituent and the leaving group.

In summary, the nitrile-forming *anti*-eliminations from **2** proceeded at a 36,000 fold faster rate than that of **1** *via* more symmetrical transition states with a smaller degree of proton transfer, less negative charge development at the β-carbon, and a smaller extent of leaving group bond

cleavage. The extent of proton transfer and negative charge density at the β-carbon decreased with a better leaving group, and the extent of the leaving group departure decreased as the electron-withdrawing ability of the β-aryl substituent was increased. Noteworthy was the relative insensitivity of both transition states to the structural variations in the reactants.

Table 3. Hammett ρ values for eliminations from (*E*)- and (*Z*)-$XC_6H_4CL{=}NOC(O)C_6H_4Y$[a] promoted by DBU in MeCN at 25.0 °C

	ρ	
Y	*E*-isomer	*Z*-isomer
p-MeO	2.2 ± 0.11	1.49[a]
H	2.19 ± 0.05	1.21 ± 0.05
m-Br	2.04 ± 0.07	1.12 ± 0.06
p-NO_2	1.90 ± 0.05	1.06 ± 0.04

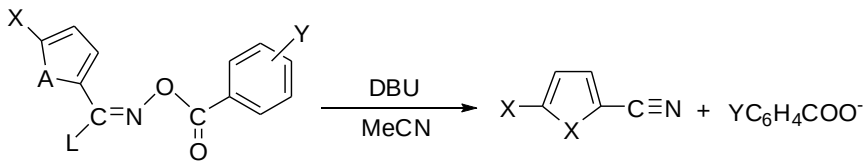
[a]Calculated with the rate data for **2cb'** and **2db'**.

Table 4. Values of β_{lg} for eliminations from (*E*)- and (*Z*)-$XC_6H_4CL{=}NOC(O)C_6H_4Y$[a] promoted by DBU in MeCN at 25.0 °C

	β_{lg}	
X	*E*-isomer	*Z*-isomer
p-MeO	-0.56 ± 0.03	-0.44 ± 0.01
H	-0.49 ± 0.02	-0.40 ± 0.01
m-Br	-0.49 ± 0.03	-0.44 ± 0.03
p-NO_2	-0.42 ± 0.04	-0.42 ± 0.04

3. Elimination reactions of (*Z*)-thiophene- and (*Z*)-furan-2-carbaldehyde *O*-benzoyloximes

It is well known that the aromatic resonance energies of thiophene and furan are much smaller than that of benzene. Since significant negative charge is developed at the β-carbon in the nitrile-forming transition state, it is conceivable that the heterocyclic rings could provide different stabilization of the respective transition states.[30] To assess this possibility, we have studied the elimination reactions of (Z)-thiophene- and (*Z*)-furan-2-carbaldehyde *O*-benzoyloximes promoted by DBU in MeCN (Scheme 2).[12] We have determined the k_H/k_D, Hammett ρ, and β_{lg} values and compared the results with those for **2** under the same conditions.



A = S (**3**); X = O (**4**); L = H, D
X = H (**a**), Me (**b**), MeO (**c**), Br (**d**), NO_2 (**e**); Y = H (**a'**), *m*-Br (**b'**), *p*-NO_2 (**c'**)

Scheme 2

3.1 Mechanism of elimination from 3 and 4 promoted by DBU in MeCN

The reactions of (*Z*)-thiophene- and (*Z*)-furan-2-carbaldehyde *O*-benzoyloximes **3** and **4** with DBU in MeCN produced elimination products quantitatively, exhibited second-order kinetics with substantial values of k_H/k_D and $|\beta_{lg}|$, indicating a common E2 mechanism for both reactions.[4,26] The conclusion was supported by the interaction coefficients. The k_H/k_D values for **3** and **4** decreased slightly as the leaving groups were made less basic (Table 5). Since smaller ρ values were observed for the better leaving groups, this result could be interpreted by a decrease in the extent of proton transfer in the transition state (Table 6). This could be described by a positive p_{xy} interaction coefficient, $p_{xy} = \partial\beta/\partial pK_{lg}$, that describes the interaction between the base catalyst and the leaving group.[26,29] On the More-O'Ferrall-Jencks energy diagram in Figure 2, a change to a better leaving group would raise the energy of the top edge of the diagram. The transition state on the vertical reaction coordinate would then move slightly toward the right as depicted by a shift from A to B on the energy diagram, resulting in a small increase in k_H/k_D (*vide supra*).[8,28] The positive p_{xy} coefficients provided additional support for the concerted E2 mechanism.[26,29]

For both reactions, the k_H/k_D value decreased as the electron-withdrawing ability of the β-aryl substituents were increased (Table 5). This was interpreted with an increase in the extent of proton transfer in the transition state because smaller $|\beta_{lg}|$ value was determined with a stronger electron-withdrawing β-aryl substituent (Table 7). This effect could be described by a positive $p_{xy'}$ interaction coefficient, $p_{xy'} = \partial\beta/\partial\sigma > 0$, which describes the interaction between the base catalyst and the β-aryl substituent.[26,29] Positive $p_{xy'}$ coefficients were in good agreement with an E2 mechanism and the reaction coordinate that has large components of proton transfer and N_α-OC(O)Ar bond cleavage.[26,29] These changes in the k_H/k_D values could be described on the More-O'Ferrall-Jencks energy diagram (Figure 2).[8,28] An electron-withdrawing β-aryl substituent would lower the energy of the carbanion intermediate in the upper left corner of the diagram. The transition state would then move slightly toward the upper left corner, with more proton transfer and smaller k_H/k_D, as depicted by the shift from A to C on the energy diagram.

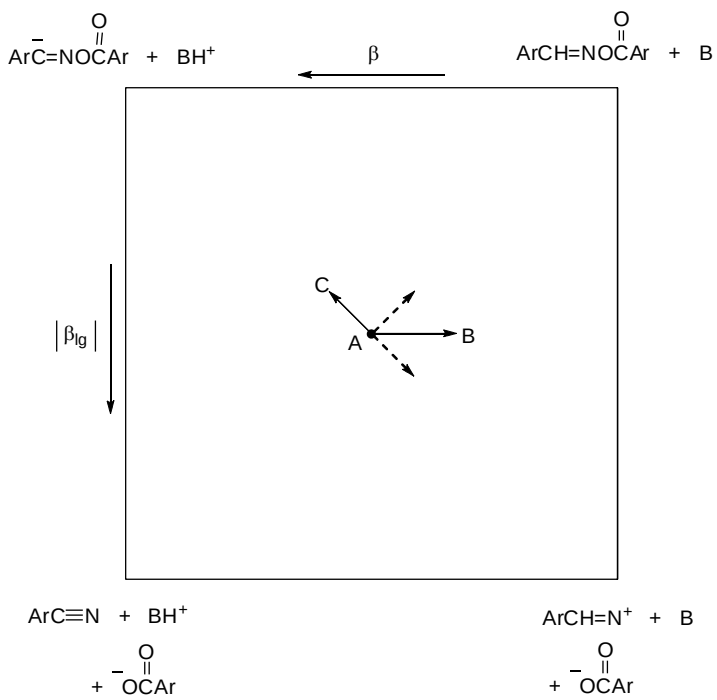


Figure 2. Reaction coordinate diagram for nitrile-forming eliminations. The effects of the change to a better leaving group and a stronger electron-withdrawing β-aryl substituent are shown by the shift of the transition state from A to B and A to C, respectively.

Table 5. Primary isotope effect values for eliminations from (*Z*)-XArCL=NOC(O)C_6H_4Y promoted by DBU in MeCN at 25.0 °C

		k_H/k_D	
X	Y	Ar = Thienyl	Ar = Furyl
H	H	8.2 ± 0.1	8.8 ± 0.2[b]
H	*m*-Br	7.9 ± 0.1	7.9 ± 0.2[b]
H	*p*-NO_2	7.5 ± 0.3	7.5 ± 0.2[b]
NO_2	H	7.7 ± 0.1	7.7 ± 0.1

[a]Substituents at 4- and 5-positions for phenyl and heterocyclic compounds, respectively, except otherwise noted. [b]X = 5-CH_3.

Table 6 shows that there was a progressive decrease in the Hammett ρ value as the leaving group is made less basic. This result could be described by a negative $p_{yy'}$ interaction coefficients, $p_{yy'} = -\partial\rho/\partial pK_{lg} = -\partial\beta_{lg}/\partial\sigma < 0$, which describes the interaction between the leaving group and the β-aryl substituent.[26,29] The decrease in the $|\beta_{lg}|$ values with a stronger electron-withdrawing β-aryl substituent provided additional evidence for this effect, i.e., $p_{yy'} = -\partial\beta_{lg}/\partial\sigma < 0$ (Table 7). The negative $p_{yy'}$ coefficients observed in these reactions were consistent with an E2 mechanism and the reaction coordinates that have large components of proton transfer and N_α-OC(O)Ar

bond cleavage, so that a better leaving group would shift the transition state from A to B in Figure 2 to decrease the extent of negative charge development and the ρ values. In addition, an electron-withdrawing substituent would shift the transition state from A to C for both **3** and **4** in Figure 2 in the direction of decreased N_α-OC(O)Ar bond cleavage and smaller $|\beta_{lg}|$ values.[8,28] All of these results were very similar to those for closely-related eliminations from **2**.[23]

Table 6. Hammett ρ values for eliminations from (*Z*)-ArCL=NOC(O)C_6H_4Y promoted by DBU in MeCN at 25.0 °C

	ρ	
Y	Ar = Thienyl	Ar = Furyl
H	1.22 ± 0.19 (1.46[a])	1.87 ± 0.05 (1.84)[b]
m-Br	1.33[a]	1.79[b]
p-NO_2	1.31[a]	1.45[b]

[a]Calculated with the data for X = H and 5-NO_2. [b]Calculated with the data for X = 5-Me

Table 7. Values of β_{lg} for eliminations from (*Z*)-ArCL=NOC(O)C_6H_4Y promoted by DBU in MeCN at 25.0 °C

	β_{lg}	
X	Ar = Thienyl	Ar = Furyl
H	-0.43 ± 0.01	-0.55 ± 0.10[b]
p-NO_2	-0.37 ± 0.01	-0.37 ± 0.01[b]

[a]Substituents at 4- and 5-positions for phenyl and heterocyclic compounds, respectively, except otherwise noted. [b]X = 5-CH_3.

3.2 Effect of β-aryl group on the nitrile-forming transition state

Table 6 shows that the relative rate and transition state parameters for DBU-promoted eliminations from **2**, **3**, and **4** were similar. This revealed that the structures of the transition states were similar for all of the elimination reactions, despite the large difference in the aromatic resonance energy of the β-aryl group. Similar values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ provided additional evidence for this conclusion. However, a closer examination of the data revealed that there was small, but clear, trend in the transition state parameters. The k_H/k_D, Hammett ρ, and $|\beta_{lg}|$ values increased gradually as the β-substituent was changed in the order phenyl < thienyl < furyl. The transition state appeared to change slightly toward product-like with a larger degree of proton transfer, more negative charge development at the β-carbon, and a greater extent of the leaving group departure in the same order. The trend could not be explained with the aromatic resonance energy of the β-aryl group. An ab initio calculation had revealed that all of the three reactants are nearly planar. Hence, if the planarity was retained in the transition state, the π orbitals of the β-aryl groups should be nearly orthogonal to the developing negative charge at the β-carbon and

the partial triple bond character in the transition state. This would predict that the aromatic resonance energy of the β-substituent should have little influence on the transition state structures.

Table 8. Relative rate, k_H/k_D, Hammett ρ, and $|\beta_{lg}|$ values for eliminations from (*Z*)-XArCL=NOC(O)C_6H_4Y promoted by DBU in MeCN at 25 °C

	Ar = Phenyl[a] (**2**)	Ar = Thienyl (**3**)	Ar = Furyl (**4**)
Rel rate[b]	1	1.1	0.6
k_H/k_D[b]	7.3 ± 0.2	8.2 ± 0.1	8.8 ± 0.2[c]
ρ[d]	1.21 ± 0.05	1.22 ± 0.19	1.87 ± 0.05
β_{lg}[d]	–0.40 ± 0.01	–0.43 ± 0.01	–0.55 ± 0.10[c]
$\Delta H^{\neq}$[b]	6.8 ± 0.5	5.9 ± 0.1	6.5 ± 0.1[c]
$\Delta S^{\neq}$[b]	–25.8 ± 1.9	–28.5 ± 0.3	–29.0 ± 1.5[c]

[a]Reference 23. [b] X = H, Y = H unless otherwise noted. [c] X = 5-Me. Y = H.

On the other hand, the result could readily be attributed to the increased inductive effect of the β-substituent. Since the 5-thienyl and 5-furyl substituents were closer to the β-carbon than the phenyl substituents, the electronic effect of the former would be more efficiently transmitted to the reaction site.[31] Hence the negative charge density at the β-carbon and the partial triple bond character in the former transition states would be better stabilized by the electron-withdrawing substituents, which would in turn change the transition state structures more product-like.

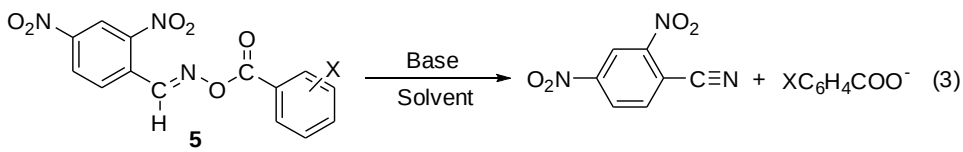
In summary, the nitrile-forming *anti*-eliminations from **3** and **4** proceeded by the E2 mechanism *via* symmetrical transition states. The structures of the transition states changed slightly towards more product-like with larger degree of proton transfer, more negative charge development at the β-carbon, and greater extent of the leaving group departure as the β-substituent is changed from phenyl to thienyl to furyl. Noteworthy was the negligible influence of the aromatic resonance energy the β-substituent upon the nitrile-forming transition state.

4. Elimination reactions of (*E*)-2,4-dinitrobenzaldehyde *O*-benzoyloximes

Previous studies have revealed that the nitrile-forming eliminations from the *E* and *Z* isomers of benzaldehyde *O*-pivaloyloximes with DBU in MeCN proceeded by the same E2 mechanism with similar transition state structures, despite the 36,000-fold difference in rate.[21,23] The results were somewhat surprising since the latter had *syn* stereochemistry, a poor leaving group, and a sp^2-hybridized β-carbon atom. It is well established that the transition state for the *syn*-elimination has more carbanion character than that for *anti*-elimination because of the poor overlap between the developing p-orbitals.[4,26,32,33] Moreover, carboxylates are poor leaving groups, which should

also increase the negative charge density at the β-carbon in the transition state.[26] Furthermore, an sp^2-hybridized β-carbon atom should stabilize the negative charge density more than an sp^3-hybridized carbon atom.[26,33] All of these factors favor an E1cb mechanism or E1cb-like transition state. However, such a transition state had never been observed in the nitrile-forming reactions until recently.

To determine whether a change to the E1cb mechanism could be realized by introducing a more electron-withdrawing β-aryl substituent, we have studied the reactions of (*E*)-2,4-dinitrobenzaldehyde *O*-benzoyloxime promoted by R_1R_2NH in MeCN and $R_1R_2NH/R_1R_2NH_2^+$ in 70mol% MeCN(aq) (Scheme 3).[24] This substrate was the most strongly activated one studied so far in the (*E*)-benzaldehyde *O*-benzoyloxime series.



X = H (**a**), *p*-MeO (**b**), *m*-Br (**c**), *p*-NO_2 (**d**)
Base-Solvent =R_1R_2NH in MeCN; $R_1R_2NH/R_1R_2NH_2^+$ in 70 mol% MeCN(aq)
R_1R_2NH = Bz(i-Pr)NH, i-Bu_2NH, i-Pr_2NH, 2,6-DMP

Scheme 3

4.1 Mechanism of elimination from 5 promoted by R_2NH in MeCN

The reactions of **5** with R_1R_2NH in MeCN produced only elimination products, exhibited second-order kinetics and substantial values of β and $|\beta_{lg}|$, thereby indicating an E2 mechanism.[4,26] This conclusion was supported by the interaction coefficients.

Table 9 shows that the β value for **5** decreased slightly as the leaving group was made less basic. The result could be described by a positive p_{xy} interaction coefficient, $p_{xy} = \partial\beta/\partial pK_{lg} = \partial\beta_{lg}/\partial pK_{BH}$, that describes the interaction between the base catalyst and the leaving group.[26,29] The observed increase in the $|\beta_{lg}|$ values with a less basic catalyst was another manifestation of this effect, i.e., $p_{xy} = \partial\beta_{lg}/\partial pK_{BH} > 0$ (Table 10).

Table 9. Brönsted β values for elimination from (*E*)-2,4-$(NO_2)_2C_6H_3CH{=}NOC(O)C_6H_4X^a$ promoted by $R_1R_2NH/R_1R_2NH_2^+$ in 70 mol% MeCN(aq) at 25.0 °C

R_1R_2NH	X = *p*-Me	X = H	X = *m*-Cl	X = *p*- NO_2
pK_a^a	21.3	20.7	19.5	18.7
β_{lg}	0.55 ± 0.15	0.47 ± 0.04	0.45 ± 0.05	0.43 ± 0.04

[a]Reference 34.

Table 10. Brönsted β_{lg} values for elimination from (*E*)-2,4-$(NO_2)_2C_6H_3CH{=}NOC(O)C_6H_4X$ promoted by $R_1R_2NH/R_1R_2NH_2^+$ in 70 mol% MeCN(aq) at 25.0 °C

R_1R_2NH	Bz(*i*-Pr)NH	*i*-Bu_2NH	*i*-Pr_2NH	2,6-DMP[b]
pK_a[a]	16.8	18.2	18.5	18.9
β_{lg}	-0.24 ± 0.03	-0.36 ± 0.02	-0.35 ± 0.02	-0.32 ± 0.01

[a]Reference 35. [b]*cis*-2,6-Dimethylpiperidine.

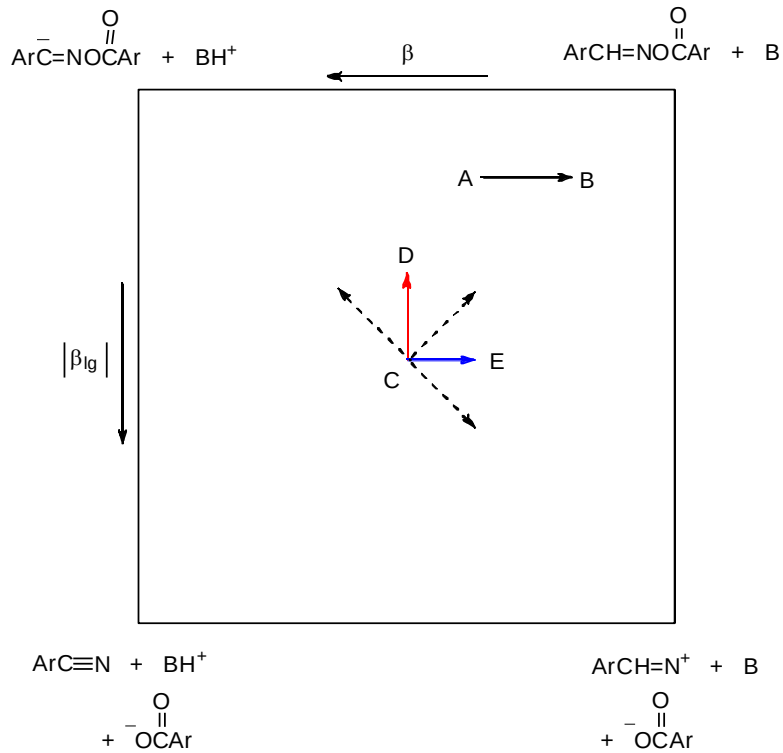


Figure 3. Reaction coordinate diagram for nitrile-forming eliminations from (*E*)-2,4-dinitrobenzaldehyde *O*-benzoyloximes. (top) The effect of the change to a stronger base on the horizontal reaction coordinate is shown by the shift of the transition state from A to B. The effect of the change to a 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 $p_{xy} > 0$.

On the More-O'Ferrall-Jencks energy diagram shown in Figure 3, a change to a better leaving group would raise the energy of the top edge of the diagram. The transition state on the vertical reaction coordinate would then move slightly toward the right as depicted by a shift from C to E on the energy diagram, resulting in a decrease in β (*vide supra*).[8,28] Similarly, a stronger base would raise the energy of the right side of the energy diagram and shift the transition state

from C to D to decrease the extent of N_α-OC(O)Ar bond cleavage. The positive p_{xy} coefficients were inconsistent with an E1cb mechanism for which p_{xy} = 0 was expected, but provided additional support for the concerted E2 mechanism.[26,29] All of these results were very similar to those for closely related eliminations from **1** and **2**.[23]

4.2 Effect of β-aryl group on the nitrile-forming transition state

Table 11 shows that the rate of elimination from **5a** is only 10-fold faster than that from the unsubstituted (*E*)-benzaldehyde *O*-benzoyloxime. Although this result may in part be attributed to the weaker basicity of *i*-Pr_2NH than DBU, the difference was surprisingly small considering the large difference in the electron-withdrawing ability of the β-aryl substituent.[21] Comparison of the transition-state parameters revealed that the structure of the transition states for these two reactions were also similar. It was previously reported that the DBU-promoted elimination from **1** proceed *via* a slightly E1cb-like transition state, in which the C_β-H bond cleavage has progressed to a greater extent than the N_α-OAr bond rupture.[21,23] Although a direct comparison between the k_H/k_D and β values was not possible, β = 0.47 for elimination from **5** appeared to indicate a smaller extent of proton transfer than the k_H/k_D = 3.3 value for the former since the latter was attributed to more than half proton transfer.[21,23] In addition, the smaller $|\beta_{lg}|$ value for the former could also be explained with a lesser degree of N_α-OAr bond cleavage. These results indicated that the transition state for elimination from **5** was slightly more reactant-like with lesser extents of C_β-H and N_α-OAr bond cleavage than that for **1**. However, it should be noted that the difference was remarkably small considering the large difference in the β-aryl substituent. The small difference in the transition-state structures may be attributed to the geometry of the reactant structure. It has been well established that the benzaldoxime esters have planar structures.[12,21,23] Hence, if the planarity was retained in the transition state, the π orbitals of the β-aryl groups should be nearly orthogonal to the developing negative charge at the β-carbon in the transition state.[12] This would predict that the electronic effect of the β-substituent should be transmitted to the reaction site only through an inductive effect. Further, the negative charge density developed on the β-carbon would be less sensitive to the substituent effect because it should be more stable than that on a sp^3 hybridized carbon atom. It appeared that the nitrile-forming transition states were intrinsically insensitive to the reactant structure variations because of the lack of resonance stabilization of charge density on the β-carbon and the increased carbanion stabilizing ability of the sp^2-hybridized β-carbon atom.

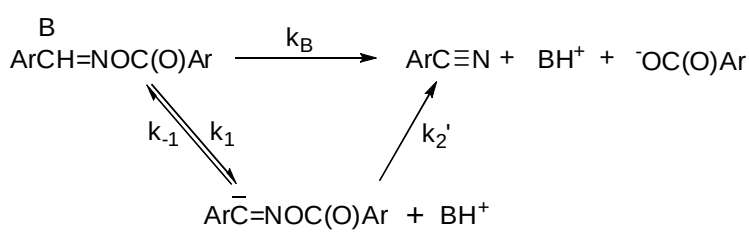
Table 11. Relative rate, Brönsted β, and β_{lg} values for eliminations from (*E*)-ArCH=NOC(O)C_6H_4X

	Ar =C_6H_5	Ar = $(NO_2)_2C_6H_3$
Base-solvent	DBU in MeCN	R_2NH in MeCN
pK_a	19.4	18.5
Rel rate	1	10
β	> 0.5	0.47 ±0.04
β_{lg}[c]	-0.49 ± 0.02	-0.35 ± 0.02

[a]Reference 23. [b] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [c] R_2NH = *i*-Pr_2NH. [d] X =H. [e] Estimated from k_H/k_D = 3.3 (see text).

4.3 Mechanism of elimination from 5 promoted by $R_1R_2NH/R_1R_2NH_2^+$ in 70mol% MeCN(aq)

The mechanism of elimination for **5** promoted by $R_1R_2NH/R_1R_2NH_2^+$ in 70 mol % MeCN(aq) have been elucidated by the results of kinetic investigations and product studies.[25] Because the reactions produced only elimination 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 β values ranging from 0.28 to 0.32 because these mechanisms would exhibit either a specific base catalysis or Brönsted β values near unity.[8,26] Hence, the most likely mechanism for this bimolecular process was either E2 or E1cb. If the reaction proceeded *via* a carbanion intermediate, the rate equation could be expressed as $k_{obs} = k_1k_2'[B]/(k_{-1}[BH^+] + k_2')$ (Scheme 4).[26] The $(E1cb)_R$ mechanism required that the first step must be reversible, i.e., $k_{-1}[BH^+] >> k_2'$, and the rate expression could be simplified to $k_{obs} = k_1k_2'[B]/(k_{-1}[BH^+])$. This would predict that the k_{obs} should remain constant regardless of the buffer concentration because $[B]/[BH^+]$ = 1.0 was maintained throughout the reaction. Therefore, the $(Elcb)_R$ mechanism was ruled out by the linear dependence of the k_{obs} values on the base concentration. On the other hand, the β = 0.28-0.32 and $|\beta_{lg}|$ = 0.28-0.32 were consistent with an E2 mechanism with limited cleavage of the C_β-H and N_α-OC(O)Ar bonds in the transition state, and a mechanism in which k_1 is the rate limiting $[(E1cb)_{irr}]$, for which a small or negligible leaving group effect is expected.[8]



Scheme 4

The distinction between the two mechanisms had been made by the interaction coefficients. Table 12 shows that the β values for **5a** remained almost the same within experimental error regardless of the base strength. The result could be described by a negligible p_{xy} interaction coefficient, $p_{xy} = \partial\beta/\partial pK_{lg} \approx 0$, which described the interaction between the base catalyst and the leaving group.[26,28,29,36,37] The similar $|\beta_{lg}|$ values for all bases was another manifestation of this effect, $p_{xy} = \partial\beta_{lg}/\partial pK_{BH} \approx 0$ (Table 13). On the More-O'Ferrall-Jencks energy diagram shown in Figure 3, a change to a better leaving group would raise the energy of the top edge of the diagram. The transition state on the horizontal coordinate would remain at nearly the same position because there is no diagonal character. This would predict negligible change in $|\beta_{lg}|$.[28] Similarly, a change to a stronger base would raise the energy of the right side of the diagram. The transition state on the horizontal coordinate would then move toward the right as depicted by a shift from A to B, resulting in little change in $|\beta_{lg}|$.[28] The negligible p_{xy} coefficients were inconsistent with the E2 mechanism for which $p_{xy} > 0$ is expected (Figure 3) but provided a strong evidence for the $(E1cb)_{irr}$ mechanism.[26,28,29,36,37]

Table 12. Brönsted β values for elimination from (*E*)-2,4-$(NO_2)_2C_6H_3CH{=}NOC(O)C_6H_4X$[a] promoted by $R_1R_2NH/R_1R_2NH_2^+$ in 70 mol% MeCN(aq) at 25.0 °C

	X = *p*-Me	X = H	X = *m*-Cl	X = *p*-NO_2
pK_{lg}[a]	21.3	20.7	19.5	18.7
β	0.27 ± 0.01	0.32 ± 0.02	0.34 ± 0.04	0.32 ± 0.02

[a]Reference 34.

Table 13. Brönsted β_{lg} values for elimination from (*E*)-2,4-$(NO_2)_2C_6H_3CH{=}NOC(O)C_6H_4X$ promoted by $R_1R_2NH/R_1R_2NH_2^+$ in 70 mol% MeCN(aq) at 25.0 °C

R_1R_2NH	Bz(*i*-Pr)NH	*i*-Bu_2NH	*i*-Pr_2NH	2,6-DMP[b]
pK_a[a]	16.8	18.2	18.5	18.9
β_{lg}	-0.28 ± 0.02	-0.32 ± 0.01	-0.30 ± 0.01	-0.31 ± 0.01

[a]Reference 35. [b]*cis*-2,6-Dimethylpiperidine.

4.4 Effect of base-solvent

Table 14 shows that the rate of elimination from **1a** decreased slightly as the base-solvent was changed from i-Bu_2NH in MeCN to i-Bu_2NH/i-$Bu_2NH_2^+$ in 70 mol% MeCN(aq), presumably due to the decreased basicity in more protic solvent.[38] The extent of C_β-H and N_α-OC(O)Ar bond cleavage decreased remarkably as revealed by the large decrease in the Brönsted β and $|\beta_{lg}|$ values by the same variation of the base-solvent system (Table 14). The change in the transition-state structure with the base-solvent variation could be attributed to a solvent effect. If the partial negative charge developed at the β-carbon in the transition state was 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 β value, as observed. Moreover, the negative charge should be transferred from the β-carbon toward the α-nitrogen to form partial triple bond and to break the N_α-OC(O)Ar bond. If a smaller amount of negative charge was transferred from the β-carbon, the extent of N_α-OC(O)Ar bond cleavage should be smaller too. The most interesting result from this study was 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 14). The change in the elimination reaction mechanism had been realized by the combined effects of strongly electron-withdrawing β-aryl substituents, intrinsically carbanion stabilizing sp^2-hybridized β-carbon, *syn*-stereochemistry and enhanced anion-solvating ability of more protic solvent.

Table 14. Effect of the base-solvent on the nitrile-forming eliminations from (*E*)-2,4-$(NO_2)_2C_6H_3CH{=}NOC(O)C_6H_5$

Base-solvent	R_1R_2NH in MeCN [a]	$R_1R_2NH/R_1R_2NH_2^+$ in 70 mol% MeCN(aq)
rel. rate (k_2)[b]	1.0	0.6
β	0.47 ±0.04	0.32 ± 0.02
β_{lg}[c]	-0.41 ± 0.01	-0.28 ± 0.02
p_{xy}	> 0	0

[a]Reference 24. [b] R_1R_2NH = i-Bu_2NH. [c] R_1R_2NH = Bz(i-Pr)NH.

5. Conclusions

We have studied the nitrile-forming elimination reactions from a series of (*E*)- and (*Z*)-arylaldehyde *O*-benzoyloxime derivatives promoted by DBU in MeCN, R_1R_2NH in MeCN and $R_1R_2NH/R_1R_2NH_2^+$ in 70mol% MeCN(aq). The rate of *anti*-elimination from **2a** was 36,000-fold faster than that of *syn*-elimination from **1a** due to the steric strain in **2a** and the greater extent of partial triple bond formation in the anti-transition state. The change of the β-aryl group from Ph **2** to thienyl **3** to furyl **4** shifted the transition state structures slightly towards product-like without altering the reaction rate. A further change in the β-aryl group from phenyl **1** to 2,4-dinitrophenyl **5** resulted in little change in the transition state structure except for the 10-fold increase in the reaction rate. The change of reaction mechanism from E2 to $(E1cb)_{irr}$ was realized only when most activated **5** was employed as the reactant and $R_1R_2NH/R_1R_2NH_2^+$ in 70mol% MeCN(aq) was used as the base-solvent. To change the reaction mechanism from E2 to E1cb, the combined effects of strongly electron-withdrawing β-aryl group, intrinsically carbanion stabilizing sp^2-hybridized β-carbon, *syn*-stereochemistry, and enhanced anion-solvating ability are necessary.

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Bong Rae Cho was born in Sanchung, Kyungnam in 1949. He obtained his B.S. degree from Seoul National University in 1971. His Ph.D. degree was awarded by Texas Tech University in 1980, where he studied the mechanism of imine-forming eliminations under the guidance of Professor Richard A. Bartsch. After postdoctoral research at UCLA with Prof. John Gladysz and SRI International with Dr. Richard M. Laine, he joined the faculty of Chemistry Department of Korea University in 1982. His research interest ranges from mechanistic organic chemistry to the synthesis of organic nonlinear optical materials, two-photon materials, and two-photon probes for biological imaging.

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