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4 AUTHORS, INCLUDING:

Hyuck Keun Oh
Chonbuk National University

Dae Dong Sung
Dong-A University

Kinetics and Mechanism of the Addition of Benzylamines to β-Cyanostilbenes in Acetonitrile

Hyuck Keun Oh,* In Kon Kim, Dae Dong Sung,† and Ikchoon Lee†,‡,*

Department of Chemistry, Research Center of Bioactive Materials, Chonbuk National University, Chonju 560-756, Korea
**E-mail: ohkeun@chonbuk.ac.kr*
†Department of Chemistry, Dong-A University, Busan 604-714, Korea
*‡Department of Chemistry, Inha University, Incheon 402-751, Korea. *E-mail: ilee@inha.ac.kr*
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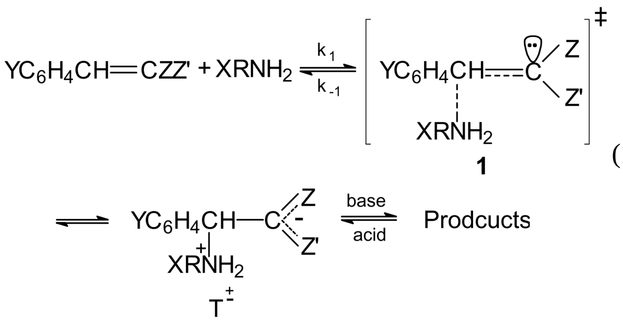
Nucleophilic addition reactions of benzylamines ($XC_6H_4CH_2NH_2$) to β-cyanostilbenes ($YC_6H_4CH{=}C(CN)C_6H_4Y'$) have been studied in acetonitrile at 30.0 °C. A greater degree of N-C_α bond formation (larger β_X) is obtained with a stronger electron-withdrawing substituent in either α- ($\delta\sigma_Y > 0$) or β-ring ($\delta\sigma_{Y'} > 0$). A stronger charge development is observed in the TS on C_β ($\rho_{Y'}$ = 1.06 for X=Y=H) rather than on C_α (ρ_Y = 0.62 for X=Y'=H) indicating the lag in the resonance development into the activating group (CN) on C_β in the transition state. Similarly, the magnitude of $\rho_{XY'}$ (–0.72) is greater than ρ_{XY} (–0.66) due to a stronger interaction of the nucleophile with β-ring than α-ring. The positive sign of $\rho_{YY'}$ correctly reflects π bond cleavage between the two rings in the TS. Relatively large kinetic isotope effects ($k_H/k_D \geq 2.0$) involving deuterated nucleophiles ($XC_6H_4CH_2ND_2$) suggest a four-membered cyclic TS in which concurrent N-C_α and H(D)-C_β bond formation occurs.

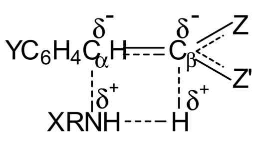
Key Words : Nucleophilic addition, β-Cyanostilbene, Cross-interaction constant, Kinetic isotope effects, Concerted mechanism

Introduction

In nucleophilic additions of amines ($XRNH_2$) to activated olefins ($YC_6H_4CH{=}CZZ'$), development of resonance and solvation of the incipient carbanion in the TS often lag behind C-N bond formation,[1] an exaggerated form of this can be given as **1** in eq. (1). In aqueous solution,


(1)

The reaction proceeds through a zwitterionic intermediate,[1] $T^\pm$, (eq. 1) whereas in acetonitrile the adduct was found to form in a single step,[2] **2**. The transition state imbalance, **1**, is far more pronounced for the reactions in aqueous solution than in acetonitrile. Due to weak solvation by MeCN to stabilize the carbanion in $T^\pm$ and hydrogen bonding by N-H proton to negative charge localized on C_β in the TS (**2**), the imbalance in the amine additions in acetonitrile becomes very weak. Nevertheless, the localized incipient anionic charge on C_β (**1**) due to the imbalance, albeit weak, was found to manifest itself in the strength of hydrogen bonding in the TS (**2**); thus a relatively strong imbalance has led to a stronger kinetic isotope effect ($k_H/k_D > 1.0$) involving deuterated amines ($XRND_2$).[3]



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In this work, we carried out kinetic studies of the benzylamine ($XC_6H_4CH_2NH_2$) addition in acetonitrile at 30.0 °C to β-cyanostilbenes (BCS : $YC_6H_4CH{=}C(CN)C_6H_4Y'$) where both substituents, Y and Y' in α- and β-rings respectively, are varied. By determining various selectivity parameters and the kinetic isotope effects, k_H/k_D, for the present reaction we hope to demonstrate that there is TS imbalance in the one step amine additions to olefins in acetonitrile, although it may be weak as noted above.

Results and Discussion

The kinetic law obeyed in the present reactions is given by eqs. (2) and (3). No catalysis by a second benzylamine (BA) molecule was detected. Plots of k_{obs} against [BA] were linear, and

$$\text{Rate} = k_{obs}\,[\text{BCS}] \tag{2}$$

$$k_{obs} = k_2\,[\text{BA}] \tag{3}$$

the second-order rate constants, k_2, determined from the slopes of these plots are summarized in Table 1. The Hammett coefficients, ρ_X, ρ_Y and $\rho_{Y'}$, together with Brönsted β_X values are shown in Table 2, and cross-interaction constants,[4] ρ_{ij} which are defined as eqs. (4), are given in Table 3, where i, j = X, Y, or Y'.

Table 1. The Second-Order Rate Constants, $k_2 \times 10^4$ dm^3 mol^{-1} s^{-1} for the Addition Reactions of β-Cyanostilbenes with X-Benzylamines in Acetonitrile at 30.0 °C

Y	Y'	X: *p*-OMe	*p*-Me	H	*p*-Cl
p-Me	*p*-Me	1.30	1.02	0.821	0.556
	H	2.03	1.60	1.20	0.824
	p-Cl	3.87	2.79	2.09	1.20
	p-Br	4.41	3.24	2.30	1.35
	p-NO_2	18.7	12.4	8.06	3.75
H	*p*-Me	1.97	1.49	1.06	0.693
	H	3.27	2.40	1.57	0.973
	p-Cl	6.17	4.27	2.78	1.50
	p-Br	7.07	4.83	2.91	1.66
	p-NO_2	33.1	19.5	10.7	5.17
p-NO_2	*p*-Me	7.59	5.58	3.11	1.64
	H	12.5	8.94	4.68	2.41
	p-Cl	25.5	16.1	8.71	3.72
	p-Br	30.9	18.8	9.51	4.21
	p-NO_2	177	87.9	39.4	14.2

$$\log(k_{ij}/k_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \quad (4a)$$

$$\rho_{ij} = \partial\rho_i/\partial\sigma_j = \partial\rho_j/\partial\sigma_i \quad (4b)$$

We can get three cross-interaction constants, ρ_{XY}, $\rho_{XY'}$, $\rho_{YY'}$. The β_X (β_{nuc}) values were determined by the plots of log k_2 (MeCN) versus pK_a(H_2O) of benzylamines. This procedure was found to be reliable[5] since the pK_a(MeCN) varies in parallel with the pK_a(H_2O) with a reasonably constant difference of Δ pK_a (= pK_a (MeCN)-pK_a (H_2O)) $\cong$ 7.5.

The rates are faster for a stronger nucleophile ($\delta\sigma_X < 0$) and for the substrate (BCS) with a stronger electron-withdrawing group in both rings ($\delta\sigma_Y > 0$ and $\delta\sigma_{Y'} > 0$) indicating that the reaction is a typical nucleophilic addition. For a given nucleophile, *eg*. X = H, the rate increase is greater for substitution of an electron-withdrawing group (*eg*. *p*-NO_2) in the β-ring than in the α-ring. This means that the effect of substituents on the rate is greater for the β- than α-ring. This is reflected in the greater magnitude of $\rho_{Y'}$ relative ρ_Y in Table 2. Negative charge development at C_α and C_β in the TS leads to positive ρ_Y and $\rho_{Y'}$ values. The fact that $\rho_{Y'}$ is greater than ρ_Y is a clear indication of a stronger anionic charge development at C_β rather than at C_α in the TS as a result of the lag (**1**) in the resonance development into the activating group, Z = CN in this case. If there were no lag in the resonance (and solvation) development, charge on C_β in the TS should be much smaller than that on C_α and the rate should have been more susceptible to the substituent changes in the α-ring rather than the β-ring, *i.e.*, $\rho_Y > \rho_{Y'}$. In fact when there is another carbon (C_β) in between the two rings, as in stilbene, the magnitude of $\rho_{Y'}$ for the β-ring should be attenuated and smaller compared to ρ_Y of the α-ring by a fall-off factor of approximately 3.8 (3.5 from bromination),[6] which was experimentally obtained by the ratio of $(\rho_Y/\rho_{Y'}) = 3.8$ from the dehydration of 1,2-diphenylethane.[6] Thus, the difference, $\Delta\rho = \rho_{Y'} - \rho_Y$, obtained in the present work should provide a measure of the imbalance, similarly with I $\equiv \alpha - \beta$ suggested by Bernasconi.[1]

The signs of ρ_{XY} and $\rho_{XY'}$ are negative, as observed in all the bond formation processes in nucleophilic substitution and addition reactions.[1,4] The magnitude of $\rho_{XY'}$ is again greater than that of ρ_{XY} reflecting a stronger interaction of

Table 2. The Hammett (ρ_X, $\rho_{Y'}$ and ρ_Y) and Brönsted (β_X) Coefficients for the Reactions of β-Cyanostilbenes with X-Benzylamines
(i) ρ_X and (β_X) values[a]

Y/Y'	*p*-Me	H	*p*-Cl	*p*-Br	*p*-NO_2
p-Me	−0.72 ± 0.05	−0.78 ± 0.04	−0.99 ± 0.07	−1.01 ± 0.05	−1.37 ± 0.07
p-Me	(0.69 ± 0.02)	(0.74 ± 0.02)	(0.94 ± 0.03)	(0.97 ± 0.01)	(1.31 ± 0.03)
H	−0.90 ± 0.05	−1.05 ± 0.06	−1.21 ± 0.06	−1.25 ± 0.08	−1.59 ± 0.12
H	(0.87 ± 0.03)	(1.00 ± 0.05)	(1.16 ± 0.02)	(1.19 ± 0.06)	(1.52 ± 0.08)
p-NO_2	−1.35 ± 0.04	−1.46 ± 0.06	−1.67 ± 0.05	−1.73 ± 0.08	−2.16 ± 0.14
p-NO_2	(1.28 ± 0.06)	(1.38 ± 0.08)	(1.58 ± 0.02)	(1.64 ± 0.06)	(2.06 ± 0.08)

[a]The correlation coefficients were better than 0.995 in all cases.

(ii) $\rho_{Y'}$ values[b]

Y/X	*p*-OMe	*p*-Me	H	*p*-Cl
p-Me	1.23 ± 0.03	1.14 ± 0.04	1.05 ± 0.02	0.87 ± 0.03
H	1.29 ± 0.03	1.18 ± 0.03	1.06 ± 0.01	0.92 ± 0.02
p-NO_2	1.45 ± 0.05	1.27 ± 0.04	1.17 ± 0.02	0.99 ± 0.03

[b]The correlation coefficients were better than 0.998 in all cases.

(iii) ρ_Y values[c]

X/Y'	*p*-Me	H	*p*-Cl	*p*-Br	*p*-NO_2
p-OMe	0.79 ± 0.05	0.81 ± 0.07	0.84 ± 0.06	0.87 ± 0.06	1.00 ± 0.08
p-Me	0.71 ± 0.03	0.77 ± 0.05	0.78 ± 0.05	0.79 ± 0.04	0.88 ± 0.05
H	0.61 ± 0.01	0.62 ± 0.01	0.65 ± 0.01	0.65 ± 0.01	0.73 ± 0.01
p-Cl	0.49 ± 0.01	0.50 ± 0.01	0.52 ± 0.01	0.52 ± 0.01	0.60 ± 0.04

[c]The correlation coefficients were better than 0.998 in all cases.

Table 3. Cross-interaction Constants, ρ_{XY}, $\rho_{XY'}$ and $\rho_{YY'}$ for the Reactions of β-Cyanostilbenes with X-Benzylamines in Acetonitrile at 30.0 °C (i) ρ_{XY} values[a]

Y'	ρ_{XY}
p-Me	–0.64 ± 0.08
H	–0.66 ± 0.10
p-Cl	–0.67 ± 0.10
p-Br	–0.71 ± 0.10
p-NO_2	–0.78 ± 0.21

[a]The correlation coefficients were better than 0.995 in all cases.

(ii) $\rho_{XY'}$ values[b]

Y	$\rho_{XY'}$
p-Me	–0.71 ± 0.09
H	–0.72 ± 0.10
p-NO_2	–0.87 ± 0.12

[b]The correlation coefficients were better than 0.998 in all cases.

(ii) $\rho_{YY'}$ values[c]

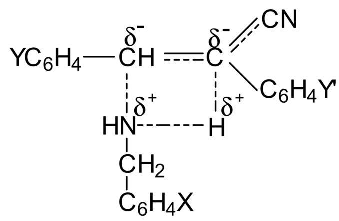
X	$\rho_{YY'}$
p-OMe	0.15 ± 0.01
p-Me	0.10 ± 0.02
H	0.08 ± 0.01
p-Cl	0.08 ± 0.01

[c]The correlation coefficients were better than 0.998 in all cases.

the substituents in the nucleophile with those in the β-ring than in the α-ring. Another important result is that the sign of $\rho_{YY'}$ is positive. The positive ρ_{ij} is normally obtained between substituents *i* and *j* in the bond cleavage process between them.[4] Thus the ρ_{YZ} values are positive for the bond cleavage between the substrate nonleaving (substituent Y) and the leaving group (substituent Z) in the direct displacement (S_N2) reactions.[4,7] For example, in the S_N2 nucleophilic substitution reactions of anilines ($XC_6H_4NH_2$) with benzyl benzenesulfonates ($YC_6H_4CH_2OSO_2C_6H_4Z$) in methanol at 35.0 °C,[4a] the cross-interaction constants were : $\rho_{XY} = -0.62$, $\rho_{YZ} = 0.11$ and $\rho_{XZ} = -0.10$. In the present reaction, as the nucleophile (benzylamine) attacks C_α, the π-bond between C_α (linked to Y-ring) and C_β (linked to Y'-ring) is partially broken in the TS so that the sign of $\rho_{YY'}$ becomes positive. The positive $\rho_{YY'}$ also indicates that a stronger electron acceptor Y ($\delta\sigma_Y > 0$) or Y' ($\delta\sigma_{Y'} > 0$) will result in a greater charge development, $\delta\rho_Y > 0$ or $\delta\rho_{Y'} > 0$, since $\rho_{YY'} = \delta\rho_{Y'}/\delta\sigma_Y = \delta\rho_Y/\delta\sigma_{Y'} > 0$. This is supported by the greater magnitude of ρ_X (and β_X) for the stronger acceptor Y and Y' as can be seen in Table 2; the greater the magnitude of ρ_X (and β_X), the greater is the degree of bond formation and hence the greater becomes the π-bond cleavage in the TS with a stronger anionic charge development on C_α as well as on C_β in the TS.

It is interesting to test the reliability of the cross-interaction constant values (ρ_{XY}, $\rho_{XY'}$ and $\rho_{YY'}$) listed in Table 3 by confirming that the third derivative values ($\rho_{XYY'} = \partial\rho_{XY}/\partial\sigma_{Y'} = \partial\rho_{XY'}/\partial\sigma_Y = \partial\rho_{YY'}/\partial\sigma_X$), which can be estimated from Table 3, are indeed constant. The estimated values were –0.10 ± 0.01 (r = 0.970, n = 4), –0.11 ± 0.01 (r = 0.999, n = 3) and –0.12 ± 0.06 (r = 0.810, n = 4) in the order listed, and are reasonably constant as required., although admittedly the last value has a rather large uncertainty.

The kinetic isotope effects involving deuterated benzylamine nucleophiles[8] ($XC_6H_4CH_2ND_2$) are quite large with k_H/k_D = 1.88-2.25 (Table 4) indicating that strong hydrogen bonding of the N-H(D) proton toward the anionic center, C_β, in the TS. Thus the reaction proceeds in a single step with concurrent formation of N-C_α and H-C_β bonds, **3**.



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The k_H/k_D values are, however, smaller for Y = *p*-NO_2 than for Y = H, which is rather unexpected since for Y = *p*-NO_2 the degree of bond formation is greater than for Y = H. A greater degree of bond formation should lead to a stronger hydrogen bonding with a larger k_H/k_D value. The reasons for this lower k_H/k_D values with Y = *p*-NO_2 than with Y = H are not clear, but the greater contribution of heavy-atom motion to the reaction coordinate and the nonlinear hydrogen transfer may well be the cause.[9]

The relatively low activation enthalpies, $\Delta H^{\neq}$, and large negative entropies of activation, $\Delta S^{\neq}$, in Table 5, are consistent with a four-centered constrained TS structure, **3**, proposed.

Experimental Section

Materials. GR grade acetonitrile was used after three distillations. The benzylamine nucleophiles, GR grade were used after recrystallization. Phenylacetonitrile and benzaldehydes were commercial reagents.

Table 4. Kinetic Isotope Effects on the Second-Order Rate Constants (k_2) for the Reactions of β-Cyanostilbenes with Deuterated X-Benzylamines in Acetonitrile at 30.0 °C

X	Y	Y'	$k_H \times 10^4$ ($M^{-1}s^{-1}$)	$k_D \times 10^4$ ($M^{-1}s^{-1}$)	k_H/k_D
p-OMe	H	*p*-Me	1.97 (± 0.03)	0.875 (± 0.008)	2.25 (± 0.04)[a]
p-Cl	H	*p*-Br	1.66 (± 0.02)	0.775 (± 0.007)	2.14 (± 0.03)
p-OMe	*p*-NO_2	*p*-Me	7.59 (± 0.07)	3.75 (± 0.03)	2.02 (± 0.03)
p-Cl	*p*-NO_2	*p*-Br	4.21 (± 0.05)	2.24 (± 0.02)	1.88 (± 0.03)

[a]Standard deviation.

Table 5. Activation Parameters[a] for the Reactions of β-Cyanostilbenes with X-Benzylamines in Acetonitrile

X	Y	Y’	t (°C)	k_2 ($\times 10^4$ $M^{-1}s^{-1}$)	$\Delta H^{\neq}$ (kcal mol^{-1})	$-\Delta S^{\neq}$ (cal $mol^{-1}K^{-1}$)
p-OMe	H	*p*-Me	30.0	1.97	6.3	55
			20.0	1.33		
			10.0	0.878		
p-Cl	H	*p*-Br	30.0	1.66	6.1	56
			20.0	1.11		
			10.0	0.755		
p-OMe	*p*-NO_2	*p*-Me	30.0	7.59	6.7	51
			20.0	5.01		
			10.0	3.21		
p-Cl	*p*-NO_2	*p*-Br	30.0	4.21	6.3	53
			20.0	2.86		
			10.0	1.89		

[a]Calculated by using the Eyring equation. The maximum errors calculated (by the method of K. B. Wiberg, *Physical Organic Chemistry*; Wiley, New York, 1964, p 378) are ± 0.5 kcal mol^{-1} and ± 2 e.u. for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, respectively.

Preparations of β-Cyanostilbene. The β-cyanostilbenes were prepared by the literature method of Schonne, Braye and Bruylants.[10] A solution of phenylacetonitrile (10 mmol) and benzaldehyde (10 mmol) in absolute ethanol was treated with a few drops of sodium ethoxide and refluxed for 3 h. The solution was cooled, some of the ethanol was evaporated, and the dark-colored solid was removed by filteration to yield (85%) crude material. This was recrystallized from ethanol. Melting points, IR (Nicolet 5BX FT-IR) and ^{1}H and ^{13}C NMR (JEOL 400 MHz) data were found to agree well with the literature values.[11]

Kinetic Measurement. The reaction was followed spectrophotometrically by monitoring the decrease in the concentration of β-cyanostilbenes, [BCS], at λ_{max} of the substrate to over 80% completion. The reaction was studied under pseudo-first-order condition, [BCS] = 6.0×10^{-5} M and [BA] = $(3.0\sim4.5) \times 10^{-1}$ M at 30.0 ± 0.1°C. The pseudo first-order rate constant, k_{obs}, was determined from the slope of the plot (r > 0.993) of ln[BCS] vs time. Second-order rate constants, k_2, were obtained from the slope of a plot (r > 0.995) of k_{obs} *vs* [BA] with more than four concentrations of benzylamine, carried out more than three runs, and were reproducible to within ± 3%.

Product Analysis. The analysis of final product was difficult due to partial decomposition during product separation and purification. We therefore analysed the reaction mixture by NMR (JEOL 400 MHz) at appropriate intervals under exactly the same reaction conditions as the kinetic measurement in CD_3CN at 30.0 °C using larger amount of reactants. Initially we found a peak for CH in the reactant, *p*-$NO_2C_6H_4CH{=}C(CN)C_6H_4NO_2$-*p*, at 8.04 ppm, which was gradually reduced, and two new peaks for CH-CH in the product, *p*-$NO_2C_6H_4$(*p*-$ClC_6H_4CH_2NH$)CH-CH(CN)$C_6H_4NO_2$-*p*, grew at 3.98 and 4.81 ppm as the reaction proceeded. No other peaks or complications were found during the reaction except the three peak height changes, indicating that the reaction proceeds with no other side reactions (Figure 1).

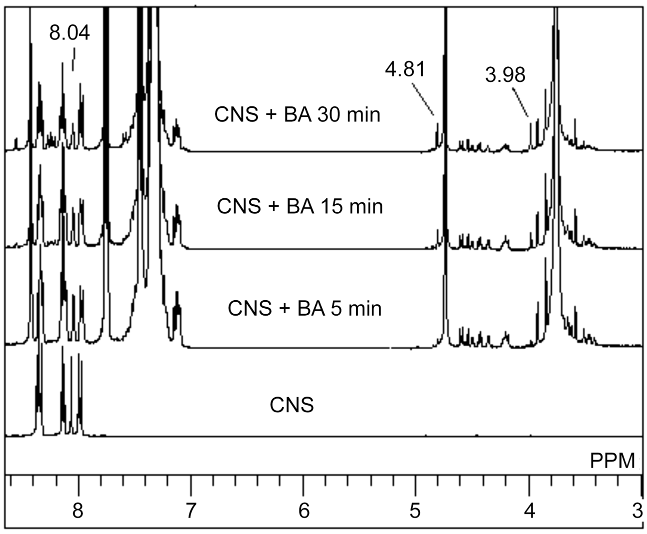

Figure 1. ^{1}H NMR spectrum for the reaction *p*-$NO_2C_6H_4CH{=}C(CN)C_6H_4NO_2$-*p* with *p*-$ClC_6H_4CH_2NH_2$ in CD_3CN at 30.0 °C.

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