Kinetics and Mechanism of the Addition of Benzylamines to α-Cyano-β-phenylacrylamides in Acetonitrile

Hyuck Keun Oh,[*] Myoung Hwa Ku, and Hai Whang Lee[†]

Department of Chemistry, Research Center of Bioactive Materials, Chonbuk National University, Chonju 561-756, Korea
[*]E-mail: ohkeun@chonbuk.ac.kr
*[†]Department of Chemistry, Inha University, Incheon 402-751, Korea*
Received March 25, 2005

Nucleophilic addition reactions of benzylamines (BA; $XC_6H_4CH_2NH_2$) to α-cyano-β-phenylacrylamides (CPA; $YC_6H_4CH=C(CN)CONH_2$) have been investigated in acetonitrile at 25.0 °C. The rate is first order with respect to BA and CPA and no base catalysis is observed. The addition of BA to CPA occurs in a single step in which the addition of BA to $C_β$ of CPA and proton transfer from BA to $C_α$ of CPA take place concurrently with a four-membered cyclic transition state structure. The magnitude of the Hammett ($ρ_X$) and Brönsted ($β_X$) coefficients are rather small suggesting an early tansition state (TS). The sign and magnitude of the cross-interaction constant, $ρ_{XY}$ (= −0.26), is comparable to those found in the normal bond formation processes in the S_N2 and addition reactions. The normal kinetic isotope effect ($k_H/k_D > 1.0$) and relatively low $ΔH^{\neq}$ and large negative $ΔS^{\neq}$ values are also consistent with the mechanism proposed.

Key Words : Nucleophilic addition reaction, Single-step process, Cross-interaction constant, Kinetic isotope effect, Four-center cyclic transition state

Introduction

Nucleophilic additions of amines (RNH_2) to activated (by Z and/or Z' groups) olefins **1** in acetonitrile are found to proceed in a single step to neutral products,[1] eq. 1. In

$$(1)$$
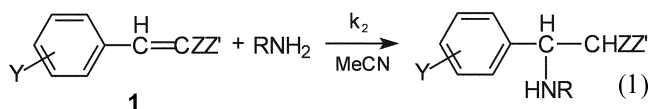
aqueous solution, however, the reactions are reported to occur through a zwitterionic intermediate, $T^{\pm}$, with imbalanced transition states (TSs) in which the development of resonance into the activating groups (Z,Z') lags behind charge transfer or C-N bond formation,[2] eq. 2. In most cases,

$$(2)$$
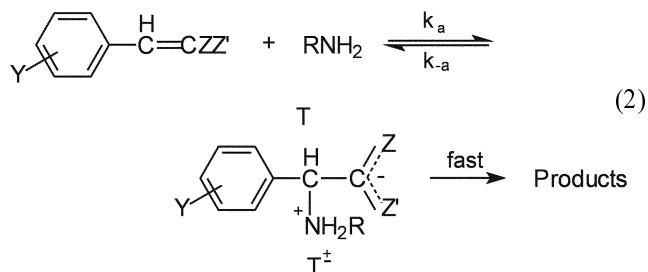
in aqueous solution the rapid acid-base equilibria, $T^{\pm} \rightleftharpoons T^- + H^+$, is established subsequently, and the initial addition, k_a, is the rate determining step.[2] The rates of amine additions in acetonitrile are in general extremely slower than in aqueous solution (k_a (aq) $\cong 10^4 k_2$ (MeCN)), due to much weak solvation by MeCN to stabilize the putative intermediate, $T^{\pm}$, but the relative order remains approximately

the same.[1] In the TS of the one step addition in acetonitrile, **2**, hydrogen bonding of the N-H(D) proton to negative

2
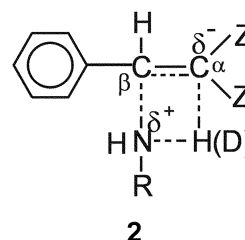
charge developed on $C_α$ was found to result in primary isotope effects, $k_H/k_D > 1.0$.[1] Another interesting observation is that the sign and magnitude ($ρ_{XY} \approx -0.6$ to -0.8) of the cross-interaction constant,[3] $ρ_{XY}$ in eqs. 3 where X and Y are substituents in the nucleophile and substrate, are in general agreement with those for bond formation in the concerted nucleophilic substitution (S_N2) reactions.[1,3b]

$$\log(k_{XY}/k_{HH}) = ρ_X σ_X + ρ_Y σ_Y + ρ_{XY} σ_X σ_Y \quad (3a)$$

$$ρ_{XY} = ∂ρ_Y/∂σ_X = ∂ρ_X/∂σ_Y \quad (3b)$$

In the present work, we carried out kinetic studies of benzylamine ($XC_6H_4CH_2NH_2$) additions to α-cyano-β-phenylacrylamides (CPA: Z = CN, Z' = $CONH_2$ in **1**) in acetonitrile at 25.0 °C. We aim to further explore the mechanistic differences between amine additions to olefin in aqueous and in acetonitrile solution. We are also interested in the effects of the activating groups, Z,Z', on the mechanism of the amine addition in MeCN by examining closely the trends of changes in the isotope effects, k_H/k_D, determined using the deuterated benzylamine nucleophiles ($XC_6H_4CH_2ND_2$).[4]

Results and Discussion

The reactions studied in this work (eq. 3) obeyed a simple rate law given by eqs. 4 and 5 where k_2 is the rate constant for the benzylamine (BA) addition to the α-cyano-β-phenyl-acrylamides (CPA). No catalysis by a second BA molecule was detected in the present studies. Plots of k_{obs} *vs* [BA] were

$$-d[CPA]/dt = k_{obs}[CPA] \qquad (4)$$

$$k_{obs} = k_2[BA] \qquad (5)$$

linear for *ca.* 10-fold increase in [BA]. The k_2 values obtained from the slopes of these plots are summarized in Table 1. The selectivity parameters, the Hammett ρ_X and ρ_Y values and the Brönsted β_X values, are also shown in Table 1 together with the corss-interaction constant ρ_{XY} (eq. 3). Although the β_X values are based on the plots of log k_2 (MeCN) against pK_a of the BAs in water, they are thought to be reliable since it was found both experimentally and theoretically that the absolute values of pK_a for conjugate

Table 1. The second order rate constants, $k_2 \times 10^2$ M^{-1} s^{-1} for the addition reactions of α-cyano-β-Y-phenylacrylamides with X-benzylamines in acetonitrile at 25.0 °C

| X | Y | | | | | $\rho_Y{}^a$ |
	p-OMe	*p*-Me	H	*p*-Cl	*p*-Br	
p-OMe	2.49	2.86	3.40	4.19	4.40	0.46 ± 0.02
	1.75^b				3.14	
	1.23^c				2.22	
p-Me	2.29	2.57	3.08	3.69	3.81	0.42 ± 0.02
H	1.94	2.14	2.49	2.95	3.05	0.38 ± 0.01
	1.57	1.72	1.95	2.28	2.33	0.33 ± 0.01
p-Cl	1.11				1.60	
	0.779				1.13	
$\rho_X{}^d$	−0.41	−0.45	−0.49	−0.53	−0.56	
	(±0.01)	(±0.01)	(±0.01)	(±0.01)	(±0.02)	$\rho_{XY}{}^e$ = −0.26
$\beta_X{}^f$	0.39	0.43	0.47	0.51	0.53	(±0.04)
	(±0.02)	(±0.02)	(±0.03)	(±0.02)	(±0.02)	

^{a}The σ values were taken from ref. 10. Correlation coefficients were better than 0.997 in all cases. ^{b}At 15.0 °C. ^{c}At 5.0 °C. ^{d}The source of s is the same as for footnote a. Correlation coefficients were better than 0.999 in all cases. ^{e}Correlation coefficients was 0.998. ^{f}The pKa values were taken from ref. 11. Correlation coefficients were better than 0.997 in all cases. pKa = 9.67 was used for X = *p*-CH$_3$O. (ref. 10c).

acids of amines in MeCN differ from those in water by a reasonably constant value of ΔpK_a (= $pK_{MeCN} - pK_{H2O}$) ≅ 7.5.[5] In the present work, aminolysis mechanism may be a possibility, but in our product analysis we found no aminolysis product. The leaving group in this work is NH$_2$ group which is a very poor nucleofuge and the reaction medium is also an aprotic one (MeCN) so that such possibility can be safely ruled out.[6]

In general, rates of amine additions to activated olefins are much faster in water (*ca.* > 10^2 fold) than those for the corresponding reaction in acetonitrile.[1] Although the rate-limiting steps in both media are believed to be the initial nucleophilic addition, k_a in water (eq. 2) and k_2 in aceto-nitrile (eq. 1), effects of the activating (electron-withdraw-ing) groups (Z,Z') on the rate are found to be different: In water the stabilization of the imbalance transition state (delocalization of which into the activating groups (Z,Z') lags behind the C$_\beta$-N bond formation) is important so that the rate (intrinsic rate) increases with the sum of electron accepting power of the activating groups, $\Sigma \sigma_p$.[1] In aceto-nitrile, however, the rate was found to increase with the sum of electron-accepting ability of Z,Z' through π-orbitals *i.e.*, the sum of through conjugative electron-accepting power, $\Sigma \sigma_p^-$or ΣR^-.[1] This is of course a manifestation of the mechanistic difference in the two media, *i.e.*, the amine addition reaction in water proceeds through an intermediate (eq. 2), whereas that in acetonitrile proceeds by a single step addition (eq. 1). The rates of amine additions to various activated olefins in water and in acetonitrile are compared in Table 2. The available rate data in aqueous solution show general parallelism between the intrinsic rate (log k_0)[7] and the sum of the normal substituent constants ($\Sigma \sigma_p$). For CPA the data in aqueous solution are not available, but we can predict that the log k_0 values will fall in between benzyl-idenemalononitrile (BMN) and benzylideneindanedione (BID). In acetonitrile, however, only the through conjugative electron shift, *i.e.*, the electron shift through π-orbital, is important, and β-nitrostyrene (NS) and β-nitrostilbene (NSB) have nearly the same rates since in the latter the benzene ring has negligible π-electron accepting effect due to non-coplanarity of the ring with the vinylic π-orbital.[3] Table 2 shows that the rate for CPA is slower than NS, which indicates that the through conjugative electron-withdrawing power of the CONH$_2$ group (σ_p^- = 0.61 and R^- = 0.35) is not fully operative.

Table 2. Comparisons of Reactivity Parameter for the Addition Reaction, YC$_6$H$_4$CH=CZZ' + XC$_6$H$_4$CH$_2$NH$_2$, in Acetonitrile at 25.0°C

| Entry	Z,Z'	$k_2{}^a$/M^{-1}s^{-1}	log $k_0{}^b$	$\rho_X{}^c$	$\rho_Y{}^c$	$\rho_{XY}{}^d$	$\Sigma \sigma^e$	$\Sigma \sigma^{-f}$
1 (BMN)^g	CN, CN	1.48	4.94	−1.62	−0.55	−0.31	1.32	2.00
2 (BID)^h	(CO)$_2$C$_6$H$_4$	1.48	4.20	−1.10	0.41	−0.33	0.83	2.08
3 (NS)^i	NO$_2$, H	2.63 × 10^{-2}	2.55	−1.22	1.73	−0.40	0.78	1.27
4 (BAA)^j	COCH$_3$, COCH$_3$	4.61 × 10^{-2}	0.30	−0.46	1.10	−0.49	1.00	1.68
5 (CPA)^k	CN, CONH$_2$	2.49 × 10^{-2}	−	−0.49	0.38	−0.26	1.02	1.61

^{a}For X=Y=H at 25.0 °C unless otherwise noted in parentheses. *Extrapolated value. ^{b}Intrinsic rate constants, k_0, for carbanion forming reactions (k_a in eq. 2) in 50% DMSO-50% H$_2$O at 20.0 °C with amines.[2b] ^{c}For Y=H and X=H, respectively. ^{d}Correlation coefficients are better than 0.997 in all cases. ^{e}Normal Hammett substituent constant (σ_p). ^{f}Exalted substituent constant (σ_p^-) for direct conjugation with anionic functional center.[6] ^{g}Benzylidenemalononitrile.[1b] ^{h}Benzylidene-1,3-indandione.[1c] ^{i}b-Nitrostyrene.[1a] ^{j}Benzylideneacetylacetone.[1d] ^{k}This work.

The cross-interaction constant, ρ_{XY} in eqs. 3, are all negative for the five series in Table 2. This shows that the cross-interaction constants, ρ_{XY}, in the bond formation process is negative.[1c,3] It is also notable that the magnitude of ρ_{XY} (–0.26) as well as ρ_Y (+0.38) value for CPA is smaller than those for BMN ($\rho_{XY} = -0.31$),[1b] BID ($\rho_{XY} = -0.33$)[1c] and EAP ($\rho_{XY} = -0.38$).[8] These are consistent with somewhat lower degree of N-C_β bond formation in the TS than for the BA addition to other activated olefins listed in Table 2.

The kinetic isotope effects, k_H/k_D (Table 3), involving deuterated benzylamine nucleophiles[4] ($XC_6H_4CH_2ND_2$) are smaller than one, $k_H/k_D = 1.5$-2.0, suggesting a possibility of hydrogen-bond formation (**3** and/or **4**) as have been proposed for the BA additions in acetonitrile to other activated olefins listed in Table 2. The hydrogen bonding of the N-H proton toward one of the oxygen atoms in the $CONH_2$ group, **4**, (mostly toward the amide, since the trans C=C/C=O form is more stable and less steric hidrance) is also a possibility, albeit such hydrogen-bonding may involve a too long H-bond as the lone pair on N (n_N) of BA approaches to the $C_\beta = C_\alpha$ π-bond almost vertically from above (or below) the molecular plane of CPA. The k_H/k_D (> 1.0) values increase with an electron donor Y and an electron acceptor X, which is in line with the C_α-N bond formation in the TS with a greater degree of bond making by a stronger electron-acceptor X, $\delta\sigma_X > 0$ (with a larger positive Y, $\delta\rho_Y < 0$) and by a stronger electron-donor Y, $\delta\sigma_Y < 0$ (with a larger negative X, $\delta\rho_X > 0$) leading to a negative cross-interaction constant ρ_{XY}, eq. 3b.

3   **4**
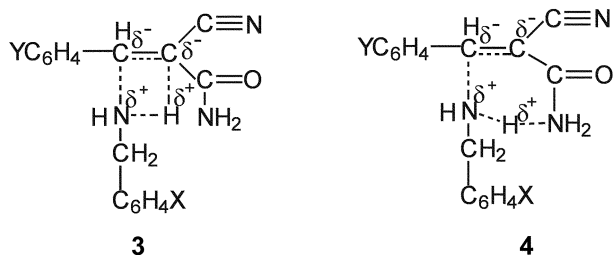
The activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$, for the benzylamine additions to CPA in Table 4 are quite similar those for the reactions of BMN and BID with low $\Delta H^{\neq}$ and large negative $\Delta S^{\neq}$ values. These are consistent with the concurrent bond formation of N-C_β and H-C_α in the TS, **3**. Since exclusion repulsion energy in the N-C_β bond making is partially offset by the bond energy of the bond formation and also by the proton transfer from N to C_α in the H-C_α bond formation, the barrier to bond formation is normally low showing little variation with substituents X and Y. This is because the higher barrier for a weaker nucleophile ($\partial\sigma_X > 0$) is partially offset by a stronger acidity of the N-H proton in the hydrogen bond formation. The large negative entropy of activation (–62 ∼ –63 eu) is consistent with a four-centered constrained TS structure, **3**.

Table 3. Kinetic Isotope Effects on the Second-Order Rate Constants for the Addition of Deuterated X-Benzylamines (XC_6H_4-CH_2ND_2) to α-cyano-β-Y-phenylacrylamides in Acetonitrile at 25.0 °C

X	Y	$k_H \times 10^2$/M^{-1}s^{-1}	$k_D \times 10^2$/M^{-1}s^{-1}	k_H/k_D
p-OMe	*p*-OMe	2.49(±0.02)	1.32(±0.01)	1.88 ± 0.02[a]
p-OMe	*p*-Me	2.86(±0.03)	1.63(±0.01)	1.75 ± 0.02
p-OMe	H	3.40(±0.05)	2.09(±0.02)	1.62 ± 0.03
p-OMe	*p*-Cl	4.19(±0.07)	2.79(±0.03)	1.50 ± 0.03
p-OMe	*p*-Br	4.40(±0.09)	3.09(±0.06)	1.42 ± 0.03
p-Cl	*p*-OMe	1.57(±0.01)	0.801(±0.004)	1.96 ± 0.02
p-Cl	*p*-Me	1.72(±0.01)	0.929(±0.006)	1.85 ± 0.02
p-Cl	H	1.95(±0.03)	1.12(±0.01)	1.73 ± 0.03
p-Cl	*p*-Cl	2.28(±0.04)	1.40(±0.02)	1.62 ± 0.03
p-Cl	*p*-Br	2.33(±0.05)	1.54(±0.02)	1.51 ± 0.03

[a]Standard deviations.

Table 4. Activation Parameters[a] for the Addition of X-Benzylamines to α-cyano-β-Y-phenylacrylamides in Acetonitrile

X	Y	$\Delta H^{\neq}$/kcal mol^{-1}	$-\Delta S^{\neq}$/cal mol^{-1}K^{-1}
p-OMe	*p*-OMe	5.2	62
p-OMe	*p*-Br	5.1	62
p-Cl	*p*-OMe	5.2	63
p-Cl	*p*-Br	5.2	62

[a]Calculated by the Eyring equation. The maximum errors calculated (by the method of Wiberg[11]) are ± 0.9 kcal mol^{-1} and ± 3 e.u. for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, respectively.

Conclusion

The reactions of benzylamine (BA) additions to α-cyano-β-phenylacrylamide (CPA) take place in a single step in which the C_β-N bond formation and proton transfer to C_α of CPA occur concurrently with a four-membered cyclic TS structure, **3**. The reaction center carbon, C_β, becomes more negative ($\rho_Y > 0$) on going from the reactant to TS, but the negative charge development is weaker than that for the reactions of NS. The sign and magnitude of the cross-interaction constant, ρ_{XY}, is comparable to those for the normal bond formation processes in the S_N2 and addition reactions. The normal kinetic isotope effects, k_H/k_D (> 1), involving deuterated benzylamine nucleophiles (XC_6H_4-CH_2ND_2), are somewhat smaller than those corresponding values for the reactions of BMN and NS due to the smaller extent of bond formation in the TS. The relatively low $\Delta H^{\neq}$ and large negative $\Delta S^{\neq}$ values are also consistent with the mechanism proposed.

Experimental Section

Materials. GR acetonitrile was used after three distillations. GR benzylamine nucleophiles, were used after recrystallization. Cyanoacetamide and benzaldehydes were GR grade.

Preparartions of α-cyano-β-phenylacrylamides. The α-cyano-β-phenylacrylamides were prepared by the literature method of Zabicky.[9] A 0.1 M ethanolic solution of both

benzaldehyde and cyanoacetamide with few drops of piperidine was refluxed for 4-6 hours. The solvent was quickly evaporated, and the residue cooled, filtered off, and purified by repeated recrystallizations from ethanol (yield > 85%). Melting point, 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.[9]

Kinetic measurement. The reaction was followed spectrophotometrically by monitoring the decrease in the concentration of α-cyano-β-phenylacrylamide, [CPA], at λ_{max} of the substrate to over 80% completion. The reaction was studied under pseudo-first-order condition, [CPA] = 6.0 × 10^{-5} M and [BA] = 0.04-0.10 M at 25.0 ± 0.1 °C. The pseudo first-order rate constant, k_{obs}, was determined form the slope of the plot (r > 0.994) ln[CPA] (2.303 log [CPA]) *vs* time. Second-order rate constants, k_N, were obtained from the slope of a plot (r > 0.995) of k_{obs} *vs*. benzylamine with more than six concentrations of more than three runs and were reproducible to within ± 3%.

Product analysis. The analysis of final products 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 MeCN at 25.0 °C. Initially we found a peak for CH in the reactant, p-ClC$_6$H$_4$CH=C(CN)CONH$_2$, at 8.27 ppm, which was gradually reduced, and a new two peaks for CH-CH in the product, p-ClC$_6$H$_4$(MeOC$_6$H$_4$CH$_2$-NH)CH-CH(CN)CONH$_2$, grew at 3.78 and 4.77 ppm as the reaction proceed. No other peaks or complecations were found during the reaction except the 3 peak height changes indicating that the reaction proceeds with no other side reactions.

References

1. (a) Oh, H. K.; Yang, J. H.; Sung, D. D.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **2000**, 101. (b) Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2000**, *65*, 2188. (c) Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2000**, *65*, 5391. (d) Oh, H. K.; Lee, J. M. *Bull. Korean Chem. Soc.* **2002**, *23*, 1459; (e) Oh, H. K.; Kim, I. K.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2004**, *69*, 3806.

2. (a) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301.

3. (a) Lee, I. *Adv. Phys. Org. Chem.* **1992**, *27*, 57. (b) Lee, I.; Lee, H. W. *Coll. Czech. Chem. Commun.* **1999**, *64*, 1529. (c) Lee, I. *Chem. Soc. Rev.* **1990**, *19,* 317. (d) Oh, H. K.; Kim, T. S.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **2003**, *24*, 193.

4. (a) Lee, I. *Chem. Soc. Rev.* **1995**, *24*, 223. (b) Song, H. B.; Choi, M. H.; Koo, I. S.; Oh, H. K.; Lee, I. *Bull. Korean Chem. Soc.* **2003**, *24*, 91 (c) Oh, H. K.; Lee, J. M.; Sung, D. D.; Lee, I. *Bull. Korean Chem. Soc.* **2004**, *25*, 557. (d) Oh, H. K.; Park, J. E.; Lee, H. W. *Bull. Korean Chem. Soc.* **2004**, *25*, 1041.

5. Lee, I.; Kim, C. K.; Han, I. S.; Lee, H. W.; Kim, W. K.; Kim, Y. B. *J. Phys. Chem. B* **1999**, *103*, 7302.

6. Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc.* **2002**, *23*, 221.

7. Bernasconi, C. F.; Ketner, R. J. *J. Org. Chem.* **1998**, *63*, 6266.

8. Oh, H. K.; Kim, I. K.; Lee, H. W.; Lee, I. *Org. Biomol. Chem.* **2004**, *2*, 1213.

9. Zabicky, J. *J. Chem. Soc.* **1961**, 683.

10. (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. (b) Fischer, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588. (c) Oh, H. K.; Lee, J. Y.; Lee, I. *Bull. Korean Chem. Soc.* **1988**, *19*, 1198.

11. Wiberg, K. B. *Physical Organic Chemistry*; Wiley: New York: 1964; p 378.