Kinetics and Mechanism of the Addition of Benzylamines to Ethyl-α-cyanocinnamates in Acetonitrile

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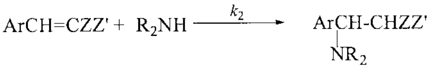
Nucleophilic addition reactions of benzylamines (BA; $XC_6H_4CH_2NH_2$) to ethyl-α-cyanocinnamates (ECC; $YC_6H_4CH{=}C(CN)COOEt$) have been investigated in acetonitrile at 30.0 °C. The rate is first order with respect to BA and ECC. The rate is slower than that expected from the additive effect of σ^- or R^- for the activating groups (CN and COOEt). Natural bond orbital $\pi^*_{c=c}$ calculations show that the contribution of COOEt group may not be fully effective despite the coplanar molecular structure. The selectivity parameters including the cross-interaction constant (ρ_{XY} = -0.22) indicate that the addition occurs in a single step. The kinetic isotope effects (k_H/k_D= 2.5-2.8) involving deuterated BA ($XC_6H_4CH_2ND_2$) nucleophiles and activation parameters ($\Delta H^{\neq}$=4~6 kcal mol^{-1}; $\Delta S^{\neq}$= -45~ - 52 e.u.) suggest a cyclic transition state in which N-C$_\alpha$ and H-C$_\beta$ bonds are formed concurrently.

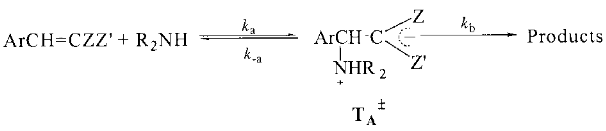
Keywords : Nucleophilic addition reaction, Natural bond orbital calculation, Cross-interaction constant, Kinetic isotope effect.

Introduction

Nucleophilic additions of amines to activated olefins in acetonitrile (eq. 1) are found to proceed in a single step to neutral products.[1] This is in striking contrast to the mechanism of addition in aqueous solution through zwitterionic intermediate[2] (eq. 2).



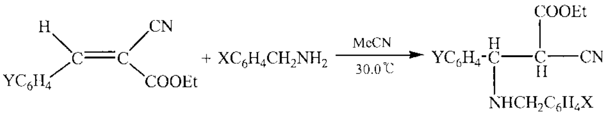
$$\mathrm{ArCH{=}CZZ' + R_2NH \xrightarrow{k_2} \underset{\displaystyle NR_2}{ArCH}\text{-}CHZZ'} \qquad (1)$$



(2)

In most cases in aqueous solution the acid-base equilibria, $T_A^{\pm} \rightleftarrows T_A^-$, is rapidly established subsequently and hence nucleophilic addition, k_a, is rate limiting.[2] In this mechanism, the development of resonance into the activating (electron-acceptor) group (Z,Z′) lags behind charge transfer or bond formation and hence the transition state (TS) becomes imbalanced.[2] Thus the ease of the initial attack by amines on C$_\alpha$ and hence the polar electron-withdrawing effect of Z,Z′, is the rate determining factor for the reaction in aqueous solution. This means that the greater the electron-withdrawing power ($\Sigma\sigma$) of the activating group (Z,Z′), the faster becomes the rate. In contrast the rate in acetonitrile (eq. 1) increases with the sum of exalted substituent constants $\Sigma\sigma_p^-$, since the addition step, k_2, involves π-orbitals through an sp^2 carbon center, C$_\alpha$.

In the present work, we aim to further investigate the mechanistic difference of the amine addition to olefins between in water and in acetonitrile by conducting kinetic studies of benzylamine (BA) additions to ethyl-α-cyanocinnamates (ECC) in acetonitrile at 30.0 °C, eq. 3. We have determined various selectivity parameters including cross-interaction constant ρ_{XY},[3] eqs. 4 where X and Y are the substituents in the nucleophile (X) and substrate (Y), respectively.



(3)

$$\log (k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \qquad (4a)$$

$$\rho_{XY} = \partial\rho_Y/\partial\sigma_X = \partial\rho_X/\partial\sigma_Y \qquad (4b)$$

Results and Discussion

The reactions studied in this work (eq. 3) obeyed a simple rate law given by eqs. 5 and 6 where k_2 is the rate constant

$$-\frac{d[\mathrm{ECC}]}{dt} = k_{\mathrm{obs}}[\mathrm{ECC}] \qquad (5)$$

$$k_{\mathrm{obs}} = k_2[\mathrm{BA}] \qquad (6)$$

for the benzylamine (BA) addition to the ethyl-α-cyanocinnamates (ECC). No catalysis by a second BA molecule was detected in the present studies. Plots of k_{obs} *vs.* [BA] were 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

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Table 1. The second order rate constants, $k_2 \times 10^2$ M^{-1} s^{-1} for the addition reactions of X-benzylamines to ethyl-α-cyano-Y-cinnamates in acetonitrile at 30.0 °C

X	Y					$\rho_Y{}^a$
	p-Me	H	*p*-Cl	*p*-Br	*p*-NO$_2$	
p-OMe	2.79 2.14^b 1.61^c	3.34	4.36	4.65	7.63 5.38 3.77	0.46±(0.03)
p-Me	2.25	2.73	3.38	3.54	5.59	0.41±(0.02)
H	1.47	1.62	2.01	2.16	3.32	0.38±(0.02)
p-Cl	0.828 0.591 0.418	0.929	1.11	1.16	1.75 1.19 0.801	0.35±(0.01)
$\rho_X{}^d$	-1.07 (±0.02)	-1.15 (±0.05)	-1.21 (±0.03)	-1.22 (±0.01)	-1.29 (±0.02)	$\rho_{XY}{}^e$= -0.22 (±0.05)
$\beta_X{}^f$	1.02 (±0.05)	1.09 (±0.08)	1.15 (±0.06)	1.416 (±0.05)	1.23 (±0.04)	

[a] The σ values were taken from reference 11. Correlation coefficients were better than 0.995 in all cases. [b] At 20.0 °C. [c] At 10.0 °C. [d] The source of σ is the same as for footnote *a*. Correlation coefficient were better than 0.998 in all cases. [e] Correlation coefficient was 0.999. [f] The pK_a values were taken from Fischer, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588. Correlation coefficient were better than 0.995 in all cases. The pK_a = 9.67 was used for X = *p*-CH$_3$O. (Oh, H. K.; Lee J. Y.; Lee, I. *Bull. Korean. Chem. Soc.* **1998**, *19*, 1198.)

values and the Brønsted β_X values, are also shown in Table 1 together with the cross-interaction constant ρ_{XY} (eqs. 4). 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 acids of amines in MeCN differ from those in water by a reasonably constant value of ΔpK_a (= pK_{MeCN}-pK_{H20}) ≅ 7.5.[4] Bruice and cowoker[5] have investigated ester hydrolysis mechanism using *p*-nitrophenyl-2-cyano-3-(*p*-methoxyphenyl) propenoate (p-CH_3O-C_6H_4CH=$C(CN)COOC_6H_4$-p-NO_2). They found that the ester hydrolysis occurs with the expulsion of *p*-NO$_2$-phenoxide leaving group in aqueous solution. This step was found to have a substantially high activation barrier, $\Delta H^{\neq}$ = 26.9 ± 1.0 kcal mol^{-1} with $\Delta S^{\neq}$ = -6.0 ± 3.1 e.u. In the present work, such ester aminolysis mechanism may also be a possibility, but in our product analysis we found no ester aminolysis product. The leaving group in the present case is EtO 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. Ialani *et al.*[6] have reported on the kinetic studies of the BA additions to ECC in acetonitrile using various BAs. Their data disagree with our corresponding results. One reason may be that they plotted log [ECC] *vs.* time instead of ln [ECC] *vs.* time, and they have not reported how well the reaction temperature was controlled. Otherwise, we are not sure why there are such disagreements.

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 acetonitrile (eq. 1), effects of the activating (electron-withdrawing) groups (Z,Z′) on the rate are found to be different: In water the stabilization of the imbalanced transition state (delocalization of which into the activating groups (Z,Z′) lags behind the C_α-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 acetonitrile, 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)[2b,7] and the sum of the normal substituent constants ($\Sigma\sigma_p$). For ECC the data in aqueous solution are not available, but we can predict that the log k_0 values will fall in between benzylidenemalononitrile (BMN) and benzylidene-1,3-indandione (BID). In acetonitrile, however, only the through conjugative electron shift, $\Sigma\sigma_p^-$ or ΣR^-, *i.e.*, the electron shift through π-

Table 2. Comparisons of reactivity parameter for the amine addition reaction, YC_6H_4CH=CZZ'+$XC_6H_4CH_2NH_2$, in acetonitrile

Entry	Z, Z′	$k_2{}^a$/$M^{-1}s^{-1}$	log $k_0{}^c$	$\rho_X{}^e$	$\rho_Y{}^e$	$\rho_{XY}{}^f$	$\Sigma\sigma^g$	$\Sigma\sigma^{-h}$	ΣR^{-i}	Ref.
1 (BMN)	CN, CN	1.48^b	4.94 (≈7.0)^d	-1.62	-0.55	-0.31	1.32	2.00	0.98	1b
2 (BID)	(CO)$_2$C$_6$H$_4$	1.48	– (3.13)	-1.10	0.41	-0.33	0.83	2.08	1.30	1c
3 (NS)	NO$_2$, H	2.63 × 10^{-2}	2.55 (0.73)	-1.22	1.73	-0.40	0.78	1.27	0.62	1a
4 (ECC)	CN, COOEt	1.62 × 10^{-2} (30 °C)	–	-1.15	0.38	-0.22	1.11	1.00^j+0.75^k	0.49^j+0.41^k	This work

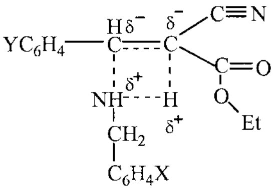
[a] For X=Y=H at 25 °C unless otherwise noted. [b] Extrapolated to 25.0 °C. [c] Intrinsic rate constants, k_0, for carbanion forming reactions (k_a in eq. 2) in 50% Me_2SO-50% H_2O at 20.0 °C with amines.[2b,7] [d] The same as *b* but for CH_2ZZ'+R_2NH. [e] For Y=H or X=H. [f] Correlation coefficients are better than 0.997 in all cases. [g] Normal Hammett substituent constants (σ_p). [h] Exalted substituent constant (σ_p^-). [i] Swain-Lupton resonance constant. [j] For CN. [k] For COOEt.

orbital, is important. Table 2 shows that the rate for ECC is slower than that for NS (nitrostyrene) which indicates that the through conjugative electron withdrawing power of the COOEt group ($\sigma_p^- = 0.75$ and $R^- = 0.41$) is not fully operative.

Our MO theoretical calculations (B3LYP/6-31+G* optimized geometries[8]) for $H_2C{=}C(CN)COOEt$ show that the COOEt group is coplanar with the vinylic π-orbital and the *trans* C=C/C=O form is more stable than the *cis* C=C/C=O form with a substantial rotational barrier (*ca*. 7 kcal mol^{-1}) between the two conformers. If we compare the natural bond orbital (NBO)[9] $\pi^*_{c=c}$ MO levels (at the HF/6-31+G*//B3LYP/6-31+G*level[8]) in the mono CN (0.183 a.u.) and COOEt substituted (0.209 a.u.) with that in the CN+COOEt disubstituted (0.175 a.u.) ethylene, the $\pi^*_{c=c}$ level in the latter disubstituted ethylene is quite closer to that of the mono CN substituted one, albeit the $\pi^*_{c=c}$ level of the mono CN ethene is depressed somewhat by an additional COOEt substituent. It is well established that the π^* LUMO level is important in determining the rate of the initial π-attack of the nucleophile to the olefins; the lower the π^* level the faster is the rate of the addition.[10] This means that although the R^- value of COOEt (0.41)[11] is only smaller by 0.08 than that for CN ($R^- = 0.49$),[11] the effect on $\pi^*_{c=c}$ lowering by COOEt is relatively small, *i.e*., the R^- (and/or σ_p^-) is not fully additive. This could be the reason why the rate for ECC is slower than that for NS.

The cross-interaction constants, ρ_{XY} in eqs. 4, are all negative for the four series in Table 2. This shows that the cross-interaction constants, $\rho_{XY,}$ in the bond formation process is negative.[1c,3] It is also notable that the magnitude of ρ_{XY} (-0.22) as well as ρ_Y (+0.38) value for ECC is smaller than those for BMN (ρ_{XY}= -0.31)[1b], BID (ρ_{XY}= -0.33)[1c] and NS (ρ_{XY}= -0.40).[1a] This is consistent with somewhat lower degree of N-C$_\alpha$ bond formation in the TS for ECC than those for the BA addition to other activated olefins listed in Table 2.[3]

The kinetic isotope effects, k_H/k_D (Table 3), involving deuterated benzylamine nucleophiles[12] ($XC_6H_4CH_2ND_2$) are greater than one, $k_H/k_D = 2.5\text{-}2.8$, suggesting a possibility of hydrogen-bond formation (**1** and/or **2**) 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 COOEt group, **2**, (mostly toward the ester oxygen, since the *trans* C=C/C=O form is more stable) 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$_\alpha$=C$_\beta$ π-bond almost vertically from above (or below) the molecular plane of ECC.



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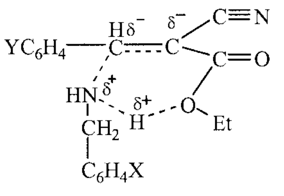

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The k_H/k_D (>1.0) values increase with an electron acceptor Y and an electron donor X, which is in line with the C$_\alpha$-N bond formation in the TS with a greater degree of bond making by a stronger electron-donor X, $\delta\sigma_X < 0$ (with a larger positive Y, $\delta\rho_Y > 0$) and by a stronger electron-accepter Y, $\delta\sigma_Y > 0$ (with a larger negative X, $\delta\rho_X < 0$) leading to a negative cross-interaction constant ρ_{XY}, eq. 4b. The activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (Table 4), are quite similar to those for the corresponding reaction of other activated olefins in Table 2 in acetonitrile with low $\Delta H^{\neq}$ and large negative $\Delta S^{\neq}$ values. These are consistent with the concurrent N-C$_\alpha$ and H-C$_\beta$ bond formation in the TS, **1**. Since exclusion repulsion energy in the N-C$_\alpha$ bond making is partially offset by the bond energy of the partial bond formed, and also by the H-C$_\beta$ bond formation, barrier to bond formation in the rate determining step should be low with little variation depending on X and/or Y. This is because the higher barrier for a weaker nucleophile ($\delta\sigma_X > 0$) is partially offset by a stronger acidity of the N-H proton in the H-bond formation. The large negative entropy of activation is in line with fourcentered constrained TS structure, **1**.

Experimental Section

Materials. Merck GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used after recrystallization. Ethyl cyanoacetate and benz-

Table 3. Kinetic isotope effects on the second-order rate constants (k_2) for the addition reactions of deuterated X-bezylamines ($X\text{-}C_6H_4CH_2ND_2$) to ethyl-α-cyano-Y-cinnamates in acetonitrile at 30.0 °C

X	Y	$k_H\times10^2$/M^{-1}s^{-1}	$k_D\times10^2$/ M^{-1}s^{-1}	k_H/k_D
p-OMe	*p*-Me	2.79(±0.01)	1.04(±0.01)	2.68±0.02[a]
p-OMe	H	3.34(±0.03)	1.23(±0.01)	2.72±0.03
p-OMe	*p*-Cl	4.36(±0.03)	1.59(±0.01)	2.74±0.03
p-OMe	*p*-Br	4.65(±0.04)	1.68(±0.01)	2.77±0.03
p-OMe	*p*-NO$_2$	7.63(±0.08)	2.73(±0.03)	2.79±0.04
p-Cl	*p*-Me	0.828(±0.008)	0.329(±0.003)	2.52±0.03
p-Cl	H	0.929(±0.001)	0.364(±0.003)	2.55±0.03
p-Cl	*p*-Cl	1.11(±0.01)	0.430(±0.004)	2.58±0.03
p-Cl	*p*-Br	1.16(±0.01)	0.446(±0.004)	2.60±0.03
p-Cl	*p*- NO$_2$	1.75(±0.02)	0.663(±0.008)	2.64±0.04

[a]Standard deviations.

Table 4. Activation parameters[a] for the addition reactions of X-benzylamines to ethyl-α-cyano-Y-cinnamates in acetonitrile

X	Y	$\Delta H^{\neq}$/kcal mol^{-1}	$-\Delta S^{\neq}$/cal mol^{-1} K^{-1}
p-OMe	*p*-Me	4.1	52
p-OMe	*p*-NO$_2$	5.4	45
p-Cl	*p*-Me	5.3	51
p-Cl	*p*-NO$_2$	6.1	47

[a]Calculated by the Eyring equation. The maximum errors calculated (by the method of Wiberg, K. B. *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.

aldehydes were Aldrich reagent.

Preparartions of Ethyl-α-Cyanocinnamates. The ethyl-α-cyanocinnamates were prepared by the literature method of Zabicky.[13] A 0.1 M ethanolic solution of both benzaldehyde and ethyl cyanoacetate 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.

Kinetic Measurement. The reaction was followed spectrophotometrically by monitoring the decrease in the concentration of ethyl-α-cyanocinnamates, [ECC], at λ_{max} of the substrate to over 80% completion. The reaction was studied under pseudo first-order condition, $[ECC] = 8.0 \times 10^{-5}$ M and $[BA] = 0.1$-0.4 M at 30.0 ± 0.1 °C. The pseudo first-order rate constant, k_{obs}, was determined from the slope of the plot ($r > 0.994$) of ln [ECC] *vs*. time. Second-order rate constants, k_2, were obtained from the slope of a plot ($r > 0.993$) of k_{obs} *vs*. benzylamine with more than four concentrations of BA and more than three runs at each [BA], and were reproducible to within ± 3%.

Product Analysis. Ethyl-α-cyanocinnamates (0.01 mole) and benzylamine (0.05 mole) were reacted in acetonitrile at 30.0 °C. After more than 15 half lives, solvent was removed under reduced pressure and product was separated by column chromatography (silica gel, 20% ethylacetate/*n*-hexane). Analytical data of the product gave the following results.

***p*-Cl-$C_6H_4CH(NHCH_2C_6H_4$-*p*-$OCH_3)CH(CN)COOEt$**: m.p. 143-45 °C, IR (KBr), 3341 (N-H, stretch), 2919 (C-H, CH_3), 2234 (C≡N), 1718 (C=O), 1589 (C=C, aromatic); ^{1}H NMR (400 MHz, $CDCl_3$), 1.36 (3H, t, $COOCH_2CH_3$), 1.76 (1H, b, NH), 3.73 (3H, s, OCH_3), 3.89 (1H, s, H-C(CN) COOEt), 4.29 (2H, q, $COOCH_2$), 4.75 (1H, s, PhCH), 6.88-7.70 (8H, m, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 190.8, 160.1, 158.7, 153.4, 140.7, 134.7, 134.6, 132.2, 131.9, 114.3, 113.9, 64.4, 55.6, 27.3, 22.8, 14.2.

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