

A Mechanistic Study on the Nucleophilic Addition Reactions of Benzylamines to the Activated Olefins

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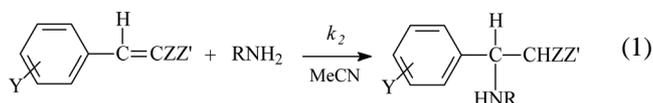
Received April 1, 2008

Kinetic studies of the additions of benzylamines to a noncyclic dicarbonyl group activated olefin, methyl α -acetyl- β -phenylacrylates (MAP), in acetonitrile at 30.0 °C are reported. The rates are lower than those for the cyclic dicarbonyl group activated olefins. The addition occurs in a single step with concurrent formation of the C α -N and C β -H bonds through a four-center hydrogen bonded transition state. The kinetic isotope effects ($k_H/k_D > 1.0$) measured with deuterated benzylamines (XC₆H₄CH₂ND₂) increase with a stronger electron acceptor substituent ($\delta\sigma_X > 0$) which is the same trend as those found for other dicarbonyl group activated series (1-4). 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 relatively low ΔH^\ddagger and large negative ΔS^\ddagger values are also consistent with the mechanism proposed.

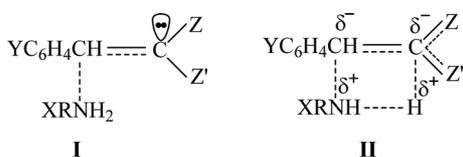
Key Words : Nucleophilic addition reaction, Single-step process, Cross-interaction constant, Kinetic isotope effects, Four-center cyclic transition state

Introduction

Nucleophilic addition of amines (XRNH₂) to olefins (YC₆H₄CH=CZZ') activated by electron-withdrawing groups (Z, Z') is known to proceed in acetonitrile by concerted formation of the C α -N and C β -H bonds in a single-step process to a neutral product,¹ eq. (1).

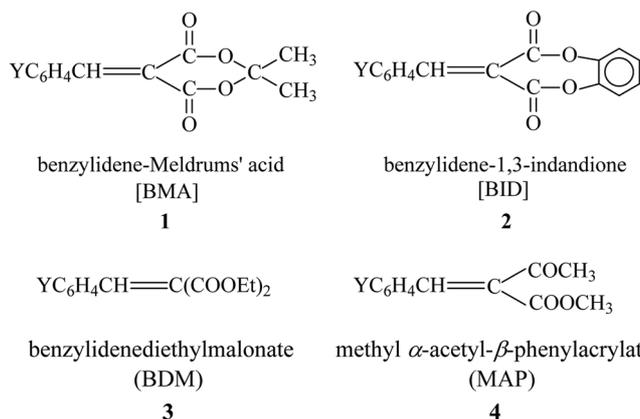


In contrast, the reactions in aqueous solution are reported to occur through a zwitterionic intermediate, T[±], with an imbalanced transition state (TS) in which the development of resonance into the activating groups (Z, Z') lags behind C α -N bond formation.² The imbalance in the TS is mainly caused by the poorly developed resonance into Z, Z' and solvation with the negative charge largely localized on carbon (C β), an exaggerated form of which can be given as I. The imbalance phenomenon is pronounced in the amine additions in aqueous solution, which was expressed semi-quantitatively by using structure-reactivity coefficients such as Brønsted α and β values.² In contrast, the imbalance was hardly observable in the amine addition reactions in acetonitrile, mainly due to the concerted formations of C α -N and C β -H bonds.¹



Recently, however, we found that a stronger localized anionic charge on C β due to the lag in the development of

resonance induces a larger kinetic isotope effect involving deuterated amines (XRND₂), $k_H/k_D > 2.3$, which is caused by a larger N-H bond stretching (II) in the concerted single step addition in acetonitrile.^{1a-d} In the absence of, or insignificantly small, imbalance, the isotope effects were smaller ($k_H/k_D < 2.0$)^{1e-g} and the trends of change in k_H/k_D with substituents X in the nucleophile and Y in the ring were exactly opposite to those for the reactions with substantial imbalances (*vide infra*). Since we noted that the dicarbonyl activated olefins,^{1e-g} Z, Z' = (CO)₂-R₁R₂, especially with the cyclic structure, 1^{1e} and 2^{1f}, belong to such a class with smaller k_H/k_D values and insignificant imbalances, it is of much interest to verify that the cyclic dicarbonyl structure of the activating group is a prerequisite to the negligible imbalance in the amine additions in acetonitrile. Although we found the same behavior with a noncyclic dicarbonyl activated olefin, 3^{1g}, we test further in this work with another acyclic dicarbonyl activated group, 4, methyl α -acetyl- β -phenylacrylates. The purpose of this work is to examine (i) whether such a negligible imbalance is limited to the cyclic dicarbonyl activated



olefins (**1** and **2**) or not, and (ii) why do dicarbonyl, or cyclic dicarbonyl, activated olefins^{1e-g} behave differently from other activated olefins?^{1a-d} In this work, the rate constants for the reactions of MAP with benzylamines (BA) were determined in acetonitrile and derived a reasonable reaction mechanism.

Results and Discussion

The reactions studied in the present work followed a simple second-order rate are the concentrations of substrate, **4**, and

$$-d[\text{MAP}] / dt = k_{\text{obs}} [\text{MPA}] \quad (2)$$

$$k_{\text{obs}} = k_2 [\text{BA}] \quad (3)$$

benzylamine, respectively. No catalysis by a second amine molecule was detected. The second-order rate constants, k_2 , were obtained from the slopes of the linear plots of k_{obs} vs [BA], eq. 3, and are summarized in Table 1. The Hammett ρ_X and ρ_Y values and Brønsted β_X values are also shown in Table 1 together with the cross-interaction constant ρ_{XY} , which is defined as eqs. 4.³ The β_X values were determined by the plots of $\log k_2$ (MeCN) against

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

Table 1. The second order rate constants, $k_2 \times 10^2 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for the addition reactions of methyl α -acetyl- β -phenylacrylates with X-benzylamines in acetonitrile at 30.0 °C

X	Y					ρ_X^a
	<i>p</i> -OMe	<i>p</i> -Me	H	<i>p</i> -Cl	<i>p</i> -Br	
<i>p</i> -OMe	6.70 4.82 ^b 3.37 ^c	8.28	11.9	18.8	20.7	0.94 ± 0.02
<i>p</i> -Me	5.79	7.11	10.1	14.8	17.0	0.88 ± 0.02
H	4.43	5.38	7.48	10.8	12.3	0.83 ± 0.02
<i>p</i> -Cl	3.16 2.26 1.56	3.69	5.03	7.24	7.95	0.77 ± 0.02
					5.49 3.73	
ρ_X^d	-0.66 (±0.01)	-0.71 (±0.01)	-0.75 (±0.01)	-0.83 (±0.04)	-0.83 (±0.01)	$\rho_{XY}^e = -0.35$ (±0.01)
β_X^f	0.63 (±0.03)	0.67 (±0.03)	0.72 (±0.03)	0.78 (±0.02)	0.80 (±0.02)	

^aThe s values were taken from ref. 10a. Correlation coefficients were better than 0.998 in all cases. ^bAt 20.0 °C. ^cAt 10.0 °C. ^dThe source of s is the same as for footnote a. Correlation coefficients were better than 0.998 in all cases. ^eCorrelation coefficients was 0.998. ^fThe pK_a values were taken from ref. 10b. Correlation coefficients were better than 0.998 in all cases. $pK_a = 9.67$ was used for X=*p*-CH₃O. (ref. 1c.).

Table 2. Comparison of rates (k_2) and other parameters for the benzylamine additions to **1-4** in acetonitrile

	k_2 (°C) ^a	$\Delta H^{\ddagger b}$	$-\Delta S^{\ddagger c}$	$k_{\text{H}}/k_{\text{D}}^d$	β_X^e	ρ_{XY}	Ref.
BMA (1)	86.6(20)	~ 4.0	~ -37	1.45-1.74	0.23	-0.33	1e
BID (2)	1.48(25)	~ 6.2	~ -37	1.25-1.81	1.09	-0.33	1f
BDM (3)	2.48×10^{-2} (20)	~ 6.4	~ -48	1.52-2.07	0.88	-0.45	1g
MAP (4)	7.48×10^{-2} (30)	~ 5.3	~ -43	1.71-2.01	0.72	-0.35	This work

^aFor X = Y = H : M⁻¹ s⁻¹. ^bkcal mol⁻¹. ^ccal mol⁻¹ K⁻¹. ^dWith deuterated benzylamine (XC₆H₄CH₂ND₂). ^eFor Y = H.

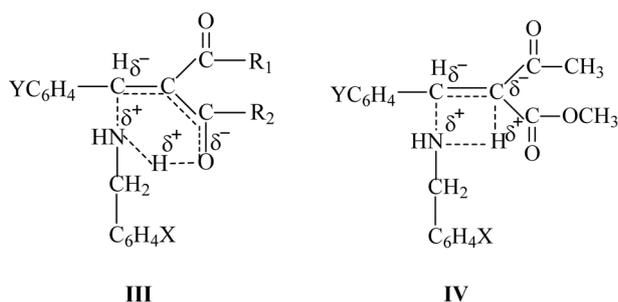
$$\rho_{XY} = \partial \rho_X / \partial s_Y = \partial r_Y / \partial s_X \quad (4b)$$

pK_a (H₂O) of benzylamines. This procedure was found to be reliable, since the pK_a (MeCN) varies in parallel with the pK_a (H₂O) with a reasonably constant difference of $\Delta pK_a (= pK_a$ (MeCN) - pK_a (H₂O)) $\cong 7.5$.⁴ The rates and other relevant parameters for the benzylamine additions to the dicarbonyl activated benzylidene series of substrate (**1-4**) in acetonitrile are compared in Table 2. We note that the rates are significantly faster for the cyclic dicarbonyl activated substrates (**1** and **2**) than the noncyclic dicarbonyl activated ones (**3** and **4**). This is caused by the π -overlap effect of the ring structure which alleviate the rate lowering due to the lag in the resonance stabilization.⁵ In noncyclic systems the resonance develops late along the reaction coordinate but in the ring system the π -overlap is already maximally built into the olefin so that the structural reorganization that may be needed to achieve this overlap in noncyclic system is not required and hence the activation barrier is lowered. The sign of ρ_{XY} is negative in all cases, which is consistent with those reported for nucleophilic bond formation processes.³ The magnitudes of ρ_{XY} for the cyclic series (-0.33) are somewhat smaller than those for the noncyclic series (-0.45 and -0.35), which could be an indication of an earlier TS for the cyclic compounds. This is supported by smaller $k_{\text{H}}/k_{\text{D}}$ values for **1** and **2** than for **3** and **4**. The kinetic isotope effect, $k_{\text{H}}/k_{\text{D}}$, involving deuterated nucleophiles (XC₆H₄CH₂ND₂) reflects bond stretching of the N-H (N-D) bond of the amine in the TS due to the hydrogen bonding of the amine proton toward the anionic center developing on C _{β} forming a four-membered type (**II**), or alternatively hydrogen bonding to a carbonyl oxygen forming a six-membered type, (**III**), structure, albeit the latter possibility has been shown to be less likely^{1g} (*vide infra*). The $k_{\text{H}}/k_{\text{D}}$ values

Table 3. Kinetic isotope effects on the second-order rate constants (k_2) for the reactions of methyl α -acetyl- β -phenylacrylates with deuterated X-benzylamines in acetonitrile at 30.0 °C

X	Y	$k_{\text{H}} \times 10^2$ (M ⁻¹ s ⁻¹)	$k_{\text{D}} \times 10^2$ (M ⁻¹ s ⁻¹)	$k_{\text{H}}/k_{\text{D}}$
<i>p</i> -OMe	<i>p</i> -OMe	6.70 (± 0.06)	3.40 (± 0.02)	1.97 ± 0.02 ^a
<i>p</i> -OMe	<i>p</i> -Me	8.28 (± 0.1)	4.40 (± 0.06)	1.88 ± 0.03
<i>p</i> -OMe	H	11.9 (± 0.1)	6.65 (± 0.06)	1.79 ± 0.02
<i>p</i> -OMe	<i>p</i> -Cl	18.8 (± 0.2)	10.6 (± 0.09)	1.71 ± 0.02
<i>p</i> -Cl	<i>p</i> -OMe	3.16 (± 0.03)	1.57 (± 0.02)	2.01 ± 0.03
<i>p</i> -Cl	<i>p</i> -Me	3.69 (± 0.04)	1.92 (± 0.02)	1.92 ± 0.03
<i>p</i> -Cl	H	5.03 (± 0.06)	2.78 (± 0.02)	1.81 ± 0.02
<i>p</i> -Cl	<i>p</i> -Cl	7.24 (± 0.07)	4.18 (± 0.04)	1.73 ± 0.02

^aStandard deviations.



determined in this work are collected in Table 3. We note that the k_H/k_D values are smaller (1.78-2.24) for a stronger nucleophile ($\delta\sigma_X < 0$) than for a weaker nucleophile (1.82-2.38) *i.e.*, $\delta\sigma_X < 0 \rightarrow \delta(k_H/k_D) < 0$. Admittedly the differences are marginal but *the trend is clear*. Exactly the same trend was found for the benzylamine additions to other dicarbonyl activated series in acetonitrile, irrespective of whether the dicarbonyl group has a ring structure (BMA (1) and BID (2))^{1e,f} or not (BDM (3))^{1g} and MAP (4)).

In nucleophilic substitution reactions, the two product stabilizing factors are (i) a stronger nucleophile ($\delta\sigma_X < 0$) and (ii) a better leaving group ($\delta\sigma_Z > 0$), for which the TS shift is predicted based on thermodynamic models,⁶ such as Hammond postulate,^{6a} Bell-Evans-Polanyi^{6b} (BEP) principle etc. According to these models, a stronger nucleophile ($\delta\sigma_X < 0$) leads to an earlier TS with a lower degree of bond formation (and bond cleavage of the leaving group), which in the present case should give a lower degree of C α -N bond formation with a low degree of progress in the hydrogen bonding by the N-H (D) proton *i.e.*, a smaller k_H/k_D value for a stronger nucleophile ($\delta\sigma_X < 0 \rightarrow \delta(k_H/k_D) < 0$) as it was observed with all the dicarbonyl activated compounds, 1-4. This means that the TS structure, or the TS position along the reaction coordinate, are largely determined by the product stability, and a greater reactivity is accompanied by a lower selectivity, *i.e.*, the reactivity-selectivity (RSP)⁷ holds for the dicarbonyl activated olefins.^{1a,e}

The activation parameters, ΔH^\ddagger and ΔS^\ddagger , are shown in Table 4. Since the reaction proceeds by a concurrent bond formation of N-C α and H-C β bonds, the ΔH^\ddagger values are rather low, but the $-\Delta S^\ddagger$ values are large due to a constrained hydrogen bonded TS structure, IV. In this structure the amine hydrogen is bonded to C β not to a carbonyl oxygen as in the six-membered TS structure, III.⁸ The charge on C β in the TS should be stronger due to the lag (although it may be small, it is not absent entirely) in the resonance delocalization

Table 4. Activation parameters^a for the reactions of methyl α -acetyl- β -phenylacrylates with X-benzylamines in acetonitrile

X	Y	$\Delta H^\ddagger/\text{kcal mol}^{-1}$	$-\Delta S^\ddagger/\text{cal mol}^{-1} \text{K}^{-1}$
<i>p</i> -OMe	<i>p</i> -OMe	5.3	46
<i>p</i> -OMe	<i>p</i> -Br	5.9	42
<i>p</i> -Cl	<i>p</i> -OMe	5.3	47
<i>p</i> -Cl	<i>p</i> -Br	6.1	43

^aCalculated by the Eyring equation. The maximum errors calculated (by the method of Wiberg¹¹) are $\pm 0.6 \text{ kcal mol}^{-1}$ and $\pm 3 \text{ e.u.}$ for ΔH^\ddagger and ΔS^\ddagger , respectively.

of anionic charge into the activating groups, and hence should lead to a larger k_H/k_D values with a greater degree of N-H (D) bond cleavage than expected from a synchronous resonance delocalization. The hydrogen bonding to a carbonyl oxygen will be very weak since in the TS delocalization will not be complete.

In summary, kinetic studies of the additions of benzylamines to a noncyclic dicarbonyl group activated olefin, methyl α -acetyl- β -phenylacrylates (MAP), in acetonitrile at 30.0 °C are reported. The rates are lower than those for the cyclic dicarbonyl group activated olefins. The addition occurs in a single step with concurrent formation of the C α -N and C β -H bonds through a four-center hydrogen bonded transition state. The kinetic isotope effects ($k_H/k_D > 1.0$) measured with deuterated benzylamines (XC $_6$ H $_4$ CH $_2$ ND $_2$) increase with a stronger electron acceptor substituent ($\delta\sigma_X > 0$) which is the same trend as those found for other dicarbonyl group activated series (1-4). 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 relatively low ΔH^\ddagger and large negative ΔS^\ddagger values are also consistent with the mechanism proposed.

Experimental Section

Materials. Merk GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used after recrystallization.

Preparations of methyl α -acetyl- β -phenylacrylates. The methyl α -Acetyl- β -phenylacrylates were prepared by the literature method of Horning *et al.*⁹ Equimolecular amounts of benzaldehyde (10 mmol) and methyl acetoacetate (10 mmol) were dissolved in the minimal amount of pyridine and refluxed for 1h. Solvent was removed under reduced pressure and product was separated by column chromatography (silica gel, 10% ethylacetate-*n*-hexane) (yield > 85%). IR (Nicolet 5BX FT-IR) and ¹H and ¹³C NMR (JEOL JMM2X 400 MHz) data were found to agree well with the literature value.⁹

Kinetic measurement. The reaction was followed spectrophotometrically by monitoring the decrease in the concentration of methyl α -Acetyl- β -phenylacrylate, [MAP], at λ_{max} of the substrate to over 80% completion. The reaction was studied under pseudo-first-order condition, [MAP] = $8.0 \times 10^{-5} \text{ M}$ and [BA] = 0.02-0.05M at 30.0 \pm 0.1 °C. The pseudo first-order rate constant, k_{obs} , was determined from the slope of the plot ($r > 0.995$) $\ln[\text{MAP}]$ (2.303 $\log [\text{MAP}]$) vs time. Second-order rate constants, k_N , were obtained from the slope of a plot ($r > 0.993$) of k_{obs} vs. benzylamine with more than four concentrations of more than three runs and were reproducible to within $\pm 3\%$.

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 30.0 °C. Initially we found a peak

for CH in the reactant, *p*-ClC₆H₄CH=C(COCH₃)CO₂CH₃, at 7.61 ppm, which was gradually reduced, and a new two peaks for CH-CH in the product, *p*-ClC₆H₄(C₆H₅CH₂NH)-CH-CH(COCH₃)CO₂CH₃, grew at 3.07 and 4.23 ppm as the reaction proceed. No other peaks or complecatons were found during the reaction except the 3 peak height changes indicating that the reacion proceeds with no other side reactions.

Acknowledgements. This paper was supported by research funds of Chonbuk National University in 2007.

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