Kinetic Studies on the Nucleophilic Addition Reactions of Vinylic β-Diketones

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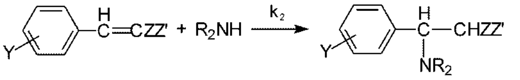
The kinetics of the addition of X-substituted benzylamines (BA) to Y-substituted Benzylideneacetylacetones (BAA) have been investigated in acetonitrile at 25.0 °C. The reaction is studied under pseudo-first-order conditions by keeping a large excess of BA over BAA. The addition of BA to BAA occurs in a single step in which the addition of BA to C_α of BAA and proton transfer from BA to C_β of BAA 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} (= -0.49), is comparatible 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 $\Delta H^{\neq}$ and large negative $\Delta S^{\neq}$ values are also consistent with the mechanism proposed.

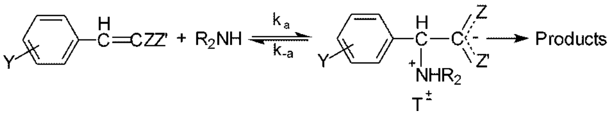
Key Words : Nucleophilic addition reaction, Single-step process, Cross-interaction constant, Kinetic isotope effect, Four-center cyclic transition state

Introduction

Nucleophilic addition of amines ($XRNH_2$) to activated olefins ($YC_6H_4CH{=}CZZ$) is known to proceed in acetonitrile by concerted formation of the C_α-N and C_β-H bonds in a single-step process leading to a neutral product[1] (eq. 1). This is, however, quite in contrast to the mechanism in aqueous solution, which occurs through a zwitterionic intermediate, (eq. 2), with imbalanced transition states (TSs) in which the development of resonance into the activating group (Z, Z') lags behind charge transfer or bond formation.[2] The rates of amine additions in acetonitrile are in general much slower than in aqueous solution. The mechanistic difference found between amine additions to the activated olefins in aqueous and acetonitrile solutions has been attributed to weak solvation by MeCN to stabilize the carbanion in the putative intermediate ($T^{\pm}$), and hydrogen bonding to negative charge localized on C_β in the TS due partly to the well known "imbalance", which causes a lag in charge delocalization into the activating groups (Z, Z') behind C-N bond formation.[2]



(1)

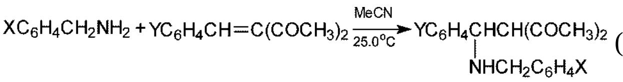


(2)

Another point of interest is the sign and magnitude of the cross-interaction constant, ρ_{XY} in eq. 3[3] where X an Y are substituents in the nucleophile, benzylamine (BA), and in the substrate, benzylideneacetylacetone (BAA), respectively, in eq. 4. The ρ_{XY} has been shown to have a negative sign in addition processes, *e.g.*, bond formation in the S_N2 reactions and in the addition of amines to an olefin with *ca.* -0.6 to -0.8.[3]

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \tag{3a}$$

$$\rho_{XY} = \partial\rho_Z/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_Z \tag{3b}$$



$$XC_6H_4CH_2NH_2 + YC_6H_4CH{=}C(COCH_3)_2 \xrightarrow[25.0^{\circ}C]{MeCN} YC_6H_4\underset{\substack{|\\ NHCH_2C_6H_4X}}{C}HCH(COCH_3)_2 \tag{4}$$

Results and Discussion

The reactions investigated in the present work obeyed a simple kinetic law given by eqs. (5) and (6) wehere k_2 is the second-order rate constant for the benzylamine (BA) addition to substrate (BAA).

$$-d[BAA]/dt = k_{obs}[BAA] \tag{5}$$

$$k_{obs} = k_2[BA] \tag{6}$$

No catalysis by a second benzylamine molecule was detected, which is similar to the benzylamine additions to benzylidenemalononitrile (BMN)[1b] but in contrast with the benzylamine catalysis found in additions to β-nitrostyrene (NS).[1a] Plot of k_{obs} against [BA] were linear with a *ca.* 10-fold increase in [BA]. The k_2 values obtained from the slopes of these plots are summarized in Table 1. The Hammett ρ_X and ρ_Y and the Brönsted β_X values are also shown in the table together with the cross-interaction constant, ρ_{XY}[eq. (3)]. Comparison of the rates with those in aqueous solution[4] shows that the rate constant in acetonitrile are lower by more than 10^2-fold as we found for other substrates, *e.g.*, BMN[1b] and 2-benzylidene-1,3-dione(BID)[1c]; for BAA, the rate constant for addition step is 0.82 with piperidine in 50% Me_2SO-50% water at 20°C[4a] and 4.61×10^{-2} with BA in acetonitrile at 25 °C. We have collected reactivity parameters

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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 Y-Benzylideneacetylacetones in Acetonitrile at 25.0 °C

X	Y				ñY[a]
	p-Me	H	*p*-Cl	*p*-Br	
p-OMe	4.09	6.24	11.9	13.1	1.23 ± 0.07
	2.91[b]			9.11	
	2.06[c]			6.26	
p-Me	3.72	5.60	10.2	11.6	1.18 ± 0.08
H	3.09	4.61	8.23	8.71	1.10 ± 0.04
p-Cl	2.63	3.79	6.17	6.61	0.97 ± 0.04
m-Cl	2.28	3.13	5.13	5.38	0.92 ± 0.04
	1.56			3.77	
	1.05			2.63	
ρ_X [a,d]	-0.39 ± 0.02	-0.46 ± 0.02	-0.56 ± 0.01	-0.60 ± 0.02	ρ_{XY}[e]
β_X[f]	0.38 ± 0.02	0.44 ± 0.02	0.55 ± 0.01	0.59 ± 0.03	= -0.49 ± 0.09

[a]The values were taken from reference 6. Correlation coefficients were better than 0.995 in all cases. [b]At 15.0 °C. [c]At 5.0 °C. [d]Correlation coefficients were better than 0.997 in all cases. [e]Correlation coefficient was 0.998. [f]The pK_a values were taken from Fischer, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588. pK_a = 9.67 was used for X = *p*-CH_3O (reference 10). Correlation coefficients were better than 0.996 in all cases.

Table 2. Comparisons of Reactivity Parameter for the Addition Reaction, $YC_6H_4CH=CZZ'+XC_6H_4CH_2NH_2$, in Acetonitrile at 25.0 °C

Entry	Z,Z′	k_2 [a] /$M^{-1}s^{-1}$	log k_0[b]	ρ_X [c]	ρ_Y [c]	ρ_{XY} [d]	Σσ[e]	Σσ⁻ [f]
1 (BMN)[g]	CN, CN	1.48	4.94*	-1.62	-0.55	-0.31	1.32	2.00
2 (BID)[h]	$(CO)_2C_6H_4$	1.48	4.20	-1.10	0.41	-0.33	0.83	2.08
3 (BAA)[I]	$COCH_3$, $COCH_3$	4.61×10^{-2}	0.30	-0.46	1.10	-0.49	1.00	1.68
4 (NS)[j]	NO_2, H	2.63×10^{-2}	2.55	-1.22	1.73	-0.40	0.78	1.27
5 (NSB)[k]	NO_2, C_6H_5	2.69×10^{-2}	1.42	-0.82	1.27	-0.52	0.77	1.27[l]
6 (CNS)[k]	CN, *p*-$NO_2C_6H_4$	1.26×10^{-3} (30 °C)	≈3.35	-1.15	1.10	-0.67	0.92	1.00[m]

[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_2O 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]This work. [j]β-Nitrostyrene.[1a] [k]β-Nitrostilbene and β-cyano-β-4-nitrostilbene.[1d] [l]The value of Ph group is excepted.[1d] [m]The value of *p*-NO_2Ph group is excepted.[1d]

for various activating groups, Z, Z', in Table 2. An essential difference between the reactivity in aqueous solution (log k_0)[5] and that acetonitrile solution is that the former increases with the (polar) electron-withdrawing power (normal substitutent constant σ) of the activating groups. Z, Z' (8th column in Table 2), whereas the latter depends on the through conjugative electron-withdrawing strength (σ^-)[6] of the Z, Z' groups.

In general, the rates in aqueous solution are dependent on the polar electron-withdrawing effect (σ) of Z, Z', while those in acetonitrile are determined by the direct resonance electron-withdrawing strength of the activating groups (σ^-), Z, Z'. This difference is of course originated by the difference in the amine addition mechanism in the two different media. It has been well established that the amine addition reactions of activated olefins in aqueous solution proceed by the initial rate-limiting addition of the amine to form a zwitterionic intermediate, $T^\pm$, which is deprotonated to an anionic intermediate (T^-) in a later fast step and then on a longer time scale T^- eventually decomposes.[2] In the rate-limiting addition step, k_a, the positive charge on C_α is important, which is determined by the electron-withdrawing polar effect of Z, Z'. The development of negative charge on Z, Z' lags behind bond making of the N---C_α bond in water to some extent depending on the Z, Z' groups.[2] Thus the ease of the initial attack by amine on C_α and hence the polar electron-withdrawing effect of Z, Z' is the rate determing factor for the reaction in aqueous solution as evidenced by the rate sequence of the intrinsic rate constant with Σσ in Table 2. In contrast, however, the same reactions in a dipolar aprotic solvent, acetonitrile, proceed in a single step by concurrent formation of N---C_α and H---C_β bonds to a saturated product.[1] In this concerted addition in acetonitrile there is no transition state (TS) imbalance due to the lag in the negative charge delocalization within the Z, Z' groups, and the direct resonance, or toward the Z, Z' groups is the most important TS stabilization which determined the reactivity. Thus for the reactions in acetonitrile the reactivity depends primarily on the resonance electron withdrawing effect of the Z, Z' groups. Table 2 shows that the rate for BAA is slower than that for NS, NCB and BID which indicate that the polar electron-withdrawing effect of $COCH_3$ group (σ_p = 0.50) is not fully operative. The magnitudes of ρ_X (= -0.39 ~ -0.60) and β_X (= 0.38-0.59) are somewhat smaller than those corresponding values of the other series (BMN, BID, NS, NSB and CNS). This is an indication of a smaller degree of bond formation in the TS. The ρ_Y values are relatively large so that charge transfer

Table 3. Kinetic Isotope Effects on the Second-Order Rate Constants for the Addition of Deuterated X-Benzylamines ($XC_6H_4CH_2ND_2$) to Y-Benzylideneacetyl-acetones in Acetonitrile at 25.0 °C

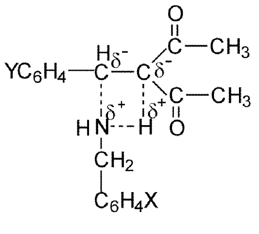
X	Y	$k_H \times 10^2/M^{-1}s^{-1}$	$k_D \times 10^2/M^{-1}s^{-1}$	k_H/k_D
p-OMe	*p*-Me	4.09(± 0.05)	2.09(± 0.02)	1.95 ± 0.03[a]
p-OMe	H	6.24(± 0.07)	3.58(± 0.05)	1.74 ± 0.03
p-OMe	*p*-Cl	11.9(± 0.10)	7.82(± 0.09)	1.52 ± 0.02
p-OMe	*p*-Br	13.1(± 0.15)	9.77(± 0.10)	1.34 ± 0.02
p-Cl	*p*-Me	2.63(± 0.03)	1.31(± 0.01)	2.01 ± 0.03
p-Cl	H	3.79(± 0.03)	2.04(± 0.01)	1.85 ± 0.02
p-Cl	*p*-Cl	6.17(± 0.08)	3.83(± 0.04)	1.61 ± 0.03
p-Cl	*p*-Br	6.61(± 0.09)	4.55(± 0.06)	1.45 ± 0.03

[a] Standard deviations.

from the benzylamine nucleophile to the vinylic carbon in the TS may be large.

The cross-interaction constants, ρ_{XY} in eq. 3, are all negative for the these series (Table 3). This shows that the cross-interaction constant, ρ_{XY}, in the bond formation process is always negative[3] irrespective of whether the reaction center, C_α, becomes more negative or positive in the TS, in agreement with the negative ρ_{XY} values observed in the associative ($\rho_Y > 0$) as well as in the dissociative ($\rho_Y < 0$) S_N2 processes.[7] The size of ρ_{XY} for BAA has again an intermediate value, but is well within the range of the ρ_{XY} values found for S_N2 processes (ρ_{XY} = -0.6 ~ -0.8) provided the fall-off factor of *ca.* 0.47[8] for an intervening CH_2 group in the benzylamine is accounted for $\rho_{XY} \cong 0.42$.

The kinetic isotope effects, k_H/k_D (Table 3), involving deuterated benzylamine nucleophiles[9] ($XC_6H_4CH_2ND_2$) are greater than unity, k_H/k_D = 1.3-2.0, suggesting a possibility of forming hydrogen-bonded four-center type TS, **I**, as has often been proposed for similar reactions.[8b] The Hydrogen bonding of N-H proton toward a carbonyl oxygen (**II**) may



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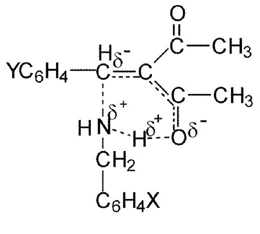

II

be a possibility, but involves a too long hydrogen-bond since the lone pair on N of benzylamine approaches almost vertically from above (or below) the molecular plane of BAA to the C_α-C_β π-bond. The relatively smaller values of k_H/k_D (1.34-2.01) than those corresponding values for the reactions of NS ($k_H/k_D \cong$ 2.30-3.08), BMN ($k_H/k_D \cong$ 2.25-2.71), NSB ($k_H/k_D \cong$ 2.42-2.71) and CNS ($k_H/k_D \cong$ 2.15-2.61) could be due to the lower degree of bond formation (smaller magnitude of ρ_X and β_X) in the TS for BAA. Another interesting result is that the k_H/k_D value for BAA increases with an electron-acceptor X ($\partial\sigma_X > 0$) and with an electron-donor Y ($\partial\sigma_Y < 0$), which is exactly opposite to the trends found for NS, BMN, BID and CNS, for which the k_H/k_D value decreases with an electron-acceptor X and an electron-donor Y.[2] This opposite trend may also be due to the looser TS with a lower degree of bond-making. In such a case, the greater negative charge on C_β (with an electron-donor Y) and the greater acidity of NH proton (with an electron-acceptor X) are important for the hydrogen bond bridge formation. This is in contrast to the tightly formed C_α-N bond for the NS, BMN, NSB and CNC for which the k_H/k_D depends on the extent of bond-making, *i.e*., a greater degree of bond-making by an electron-donor X and an electron-acceptor Y leads to a stronger hydrogen bond (larger k_H/k_D) which varies more sensitively with substituents X and Y. The overall size of the k_H/k_D values ranging 1.3-2.0 are smaller than those of the corresponding values for the substrates with weaker electron acceptor Z.Z' exhibiting slower addition rate, *e.g.* for entries 5 and 6 in Table 2 the k_H/k_D values are larger ranging 2.2-3.1.[1a,d] This is in line with the greater degree of bond formation in the TS for those substrates (in NSB and CNS) with large magnitude of the cross-interaction constants, ρ_{XY} = -052 ~ -0.67.

Table 4. Activation Parameters[a] for the Addition of X-Benzylamines to Y-Benzylideneacetylacetones in Acetonitrile

X	Y	$\Delta H^{\neq}$/kcal mol^{-1}	$-\Delta S^{\neq}$/cal mol^{-1}K^{-1}
p-OMe	*p*-Me	5.1	38
p-OMe	*p*-Br	5.5	35
m-Cl	*p*-Me	5.8	37
m-Cl	*p*-Br	5.3	37

[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.

The activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$, for the benzylamine additions to BAA 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_α and H-C_β in the TS, **I**. Since exclusion repulsion energy in the N-C_α bond making is partially offset by the bond energy of the bond formation and also by the proton transfer from N to C_β in the H-C_β 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 (-35 ~ -38 eu) is consistent with a four-centered constrained TS structure, **I**.

In summary, the addition of benzylamine (BA) to benzylideneacetylacetone (BAA) take place in a single step in which the C_α-N bond formation and proton transfer to C_β of BAA occur concurrently with a four-membered cyclic TS structure, **I**. The reaction center carbon, C_α, 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 structure-reactivity behaviors (k_2, ρ_X,

β_X, and ρ_Y) are intermediate between the two series of addition reactions of BA to BMN and BID and to NS, NSB and CNS in acetonitrile. 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 ($XC_6H_4CH_2ND_2$), are somewhat smaller than those corresponding values for the reactions of NSB and CNS 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. Merk GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used after recrystallization. Acetylacetone and benzaldehydes were Aldrich GR grade.

Preparartions of benzylideneacetylacetones. The benzylideneacetylacetones were prepared by the literature method of Horning *et al.*[12] Equimolecular amounts of benzaldehyde (10 mmol) and acetylacetone(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 ^{13}C NMR (JEOL 400 MHz) data were found to agree well with the literture values.[12]

Kinetic measurement. The reaction was followed spectrophotometrically by monitoring the decrease in the concentration of benzylideneacetylacetone, [BAA], at λ_{max} of the sustrate to over 80% completion. The reaction was studied under pseudo-first-order condition, $[BAA] = 6.0 \times 10^{-5}$ 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[BAA] (2.303 log [BAA]) *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 CD_3CN at 25.0 °C. Initially we found a peak for CH in the reactant, p-$ClC_6H_4CH=C(COCH_3)_2$ at 7.65 ppm, which was gradually reduced, and a new two peaks for CH-CH in the product, p-$ClC_6H_4(MeOC_6H_4CH_2NH)CH$-$CH(COCH_3)_2$, grew at 4.67 and 5.58 ppm as the reaction proceed. No other peaks or complecatons were found during the reaction except the 3 peak heights change indicating that the reaction proceeds with no other side reactions.

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