

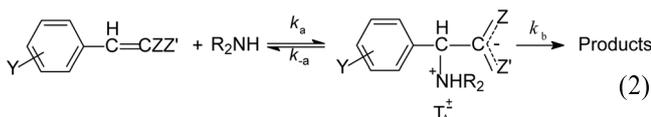
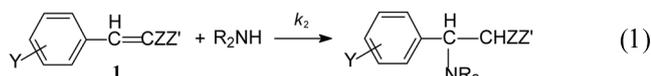
Kinetics and Mechanism of the Addition of Benzylamines to Benzylidenedimethylmalonates in Acetonitrile

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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 intermediate² (eq. 2).



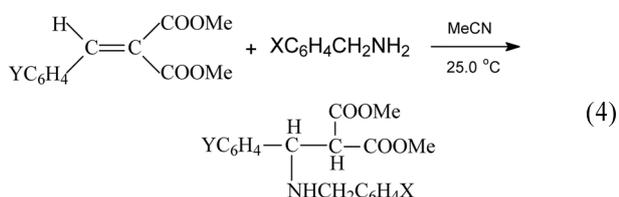
In most cases in aqueous solution the acid-base equilibria, $\text{T}_A^{\pm} \rightleftharpoons \text{T}_A^-$, is rapidly established subsequently and hence nucleophilic addition, k_a , is rate limiting.² In this mechanism, the development of resonance into the activating (electron-acceptor) group (Z,Z') 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_{α} 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 $\Sigma\sigma_{p,2}^-$ since the addition step, k_2 , involves π -orbitals through an sp^2 carbon center, C_{α} .

Another point of interest is the sign and magnitude of the cross-interaction constant, ρ_{XY} in eq. (3)³ where X and Y are substituents in the nucleophile, benzylamine (BA), and

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

$$\rho_{XY} = \partial\rho_Z/\partial\sigma_Y = \partial\rho_Y/\partial\sigma_Z \quad (3b)$$

in the substrate, benzylidenedimethylmalonate (BMM),



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

Results and Discussion

The simple second-order rate law obeyed by all the reactions studied in this work is given by eqs. (5) and (6) where [BMM] and [BA] are concentration of substrate (1 with Z = Z = COOMe) and benzylamine, respectively.

$$\text{Rate} = k_{\text{obsd}} [\text{BDM}] \quad (5)$$

$$k_{\text{obsd}} = k_2 [\text{BA}] \quad (6)$$

The second order rate constants, k_2 , were obtained from the slopes of the linear plots of k_{obsd} vs [BA] and are summarized in Table 1. The Hammett ρ_X and ρ_Y values and the Brönsted β_X values are also shown in Table 1 together with the cross-interaction constant ρ_{XY} (eqs 3). The β_X values are based on

Table 1. The Second Order Rate Constants, $k_2 \times 10^3 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for the Addition Reactions of Benzylidenedimethylmalonates with X-Benzylamines in Acetonitrile at 25.0 °C

X	Y					ρ_Y^d
	<i>p</i> -OMe	<i>p</i> -Me	H	<i>p</i> -Cl	<i>p</i> -Br	
<i>p</i> -OMe	4.58 3.30 ^b 2.34 ^c	5.90	8.96	14.0	16.3 11.9 8.57	1.04 ± 0.06
<i>p</i> -Me	3.78 2.56	4.62 3.10	6.84 4.58	10.4 6.56	12.2 7.49	0.96 ± 0.06 0.88 ± 0.05
<i>p</i> -Cl	1.53 1.12 0.795	1.81	2.52	3.64	4.01 2.97 2.17	0.80 ± 0.04
ρ_X^d	-0.97 (± 0.02)	-1.03 (± 0.01)	-1.10 (± 0.04)	-1.17 (± 0.02)	-1.23 (± 0.01)	$\rho_{XY}^e = -0.45$ (± 0.12)
β_X^f	0.92 (± 0.05)	0.98 (± 0.03)	1.09 (± 0.03)	1.11 (± 0.03)	1.17 (± 0.04)	

^aThe σ values were taken from ref. 5. Correlation coefficients were better than 0.994 in all cases. ^bAt 15.5 °C. ^cAt 5.0 °C. ^dThe source of σ is the same as for footnote a. Correlation coefficients were better than 0.999 in all cases. ^eCorrelation coefficients was 0.998. ^fThe pKa values were taken from ref. 6. Correlation coefficients were better than 0.999 in all cases. pKa = 9.67 was used for X = *p*-CH₃O. (ref. 7).

the plots of $\log k_2(\text{MeCN})$ against $\text{p}K_{\text{a}}(\text{H}_2\text{O})$ of benzylamines. This procedure was found to be reliable, since the $\text{p}K_{\text{a}}(\text{MeCN})$ varies in parallel with the $\text{p}K_{\text{a}}(\text{H}_2\text{O})$ with a reasonably constant difference of $\Delta\text{p}K_{\text{a}} (= \text{p}K_{\text{a}}(\text{MeCN}) - \text{p}K_{\text{a}}(\text{H}_2\text{O})) \cong 7.5$.⁴ In acetonitrile the rate, k_2 , was found to increase with the sum of electron-accepting power of Z,Z' through π -orbitals,^{1c,d} i.e., the sum of through-conjugative electron-accepting power, $\Sigma\sigma_{\text{p}}^-$ or ΣR^- . These values for BMM ($\Sigma\sigma_{\text{p}}^- = 1.50$ and $\Sigma R^- = 0.82$)⁵ are smaller than those for benzylidenemalononitrile (BMN; Z = Z' = CN in **1**, with 2.00 and 0.98, respectively)^{1b} and benzylidene-1,3-indandione (BID; Z,Z' = (CO)₂C₆H₄, with 2.08 and 1.30, respectively)^{1c} but are larger than those for β -cyano-4'-nitrostilbene (CNS).^{1c} The rate estimated for BMM at 25.0 °C ($4.58 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$) fits roughly in the order expected from the order of the direct resonance effect,^{1c,d} $\Sigma\sigma^-$ or ΣR^- . We have collected reactivity parameters for various activating groups, Z,Z', in Table 2. An essential difference between the reactivity in aqueous solution ($\log k_0$)⁸ and that in acetonitrile solution is that the former increases with the (polar) electron-withdrawing power (normal substituent 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^-)⁵ 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[±], 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 determining factor for the reaction in aqueous solution as evidenced by

the rate sequence of the intrinsic rate constant with $\Sigma\sigma$ 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. The magnitudes of ρ_{X} ($= -0.97 \sim -1.23$) and β_{X} ($= 0.92 \sim 1.17$) are somewhat smaller than those corresponding values of the other series (BMN, BID, 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 from the benzylamine nucleophile to the vinylic carbon in the TS may be large.

The cross-interaction constants, ρ_{XY} in eqs. (3), are all negative for the four series in Table 2. This shows that the cross-interaction constants, ρ_{XY} , in the bond formation process is negative.^{1c,3} The size of ρ_{XY} for BMM has again an intermediate value, but is well within the range of the ρ_{XY} values found for S_N2 processes ($\rho_{\text{XY}} = -0.6 \sim -0.8$) provided the fall-off factor of ca. 0.47⁹ for an intervening CH₂ group in the benzylamine is accounted for $\rho_{\text{XY}} \cong 0.42$. It is also notable that the magnitude of ρ_{XY} (-0.45) as well as ρ_{Y} (+0.88) value for BMM is larger than those for BMN ($\rho_{\text{XY}} = -0.31$) and BID ($\rho_{\text{XY}} = -0.33$).^{1d} These are consistent with somewhat higher degree of N-C_α bond formation in the TS than for the BA addition to other activated olefins listed in Table 2.

The kinetic isotope effects, $k_{\text{H}}/k_{\text{D}}$ (Table 3), involving deuterated benzylamine nucleophiles¹⁰ (XC₆H₄CH₂ND₂) are greater than one, $k_{\text{H}}/k_{\text{D}} = 1.6 \sim 2.2$, suggesting a possibility of hydrogen-bond formation (**2** and/or **3**) 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 COOMe group, **3**, (mostly toward the ester oxygen, since the trans 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_α=C_β π -bond almost vertically from above (or below) the molecular plane of BMM.

Table 2. Comparisons of Reactivity Parameter for the Addition Reaction, YC₆H₄CH=CZZ' + XC₆H₄CH₂NH₂, in Acetonitrile at 25.0 °C

Entry	Z,Z'	$k_2^a / \text{M}^{-1}\text{s}^{-1}$	$\log k_0^b$	ρ_{X}^c	ρ_{Y}^c	ρ_{XY}^d	$\Sigma\sigma^e$	$\Sigma\sigma'^f$	$\Sigma R'^g$
1 (BMN) ^h	CN, CN	1.48	4.94	-1.62	-0.55	-0.31	1.32	2.00	0.98
2 (BID) ⁱ	(CO) ₂ C ₆ H ₄	1.48	4.20	-1.10	0.41	-0.33	0.83	2.08	1.30
3 (BMM) ^j	COOMe, COOMe	4.58×10^{-3}	-	-1.10	0.88	-0.45	0.90	1.50	0.82
4 (CNS) ^k	CN, <i>p</i> -NO ₂ C ₆ H ₄	1.26×10^{-3} (30 °C)	≈ 3.35	-1.15	1.10	-0.67	0.92	1.00 ^l	0.49 ^l

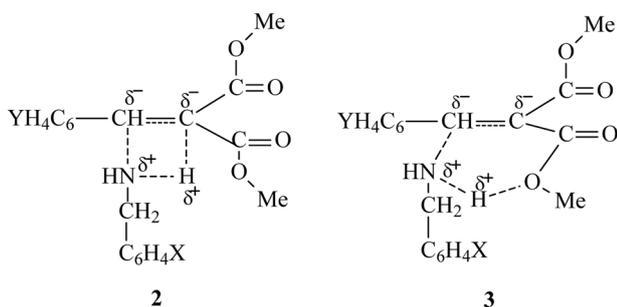
^aFor X=Y=H at 25.0 °C unless otherwise noted in parentheses. ^bExtrapolated value. ^cIntrinsic rate constants, k_0 , for carbanion forming reactions (k_{a} in eq. 2) in 50% DMSO-50% H₂O at 20.0 °C with amines.^{2b} ^dFor Y=H and X=H, respectively. ^eCorrelation coefficients are better than 0.997 in all cases. ^fNormal Hammett substituent constant (σ_{p}). ^gExalted substituent constant (σ_{p}^-) for direct conjugation with anionic functional center.⁵ ^hSwain-Lupton resonance constant. ⁱBenzylidenemalononitrile. ^jBenzylidene-1,3-indandione. ^kThis work. ^l β -cyano- β -4-nitrostilbene. ^lThe value of *p*-NO₂Ph group is excepted.^{1d}

Table 3. Kinetic Isotope Effects on the Second-Order rate constants (k_2) for the Reactions of Benzylidenedimethylmalonates with Deuterated X-Benzylamines in Acetonitrile at 25.0 °C

X	Y	$k_H \times 10^3$ ($M^{-1}s^{-1}$)	$k_D \times 10^3$ ($M^{-1}s^{-1}$)	k_H/k_D
<i>p</i> -OMe	<i>p</i> -OMe	4.58(±0.08)	2.27(±0.03)	2.01 ± 0.04 ^a
<i>p</i> -OMe	<i>p</i> -Me	5.90(±0.10)	3.02(±0.04)	1.95 ± 0.04
<i>p</i> -OMe	H	8.96(±0.12)	4.81(±0.05)	1.86 ± 0.03
<i>p</i> -OMe	<i>p</i> -Cl	14.0(±0.15)	8.00(±0.10)	1.75 ± 0.03
<i>p</i> -OMe	<i>p</i> -Br	16.3(±0.25)	10.0(±0.15)	1.63 ± 0.04
<i>p</i> -Cl	<i>p</i> -OMe	1.53(±0.02)	0.711(±0.002)	2.15 ± 0.03
<i>p</i> -Cl	<i>p</i> -Me	1.81(±0.03)	0.891(±0.003)	2.03 ± 0.03
<i>p</i> -Cl	H	2.52(±0.03)	1.30(±0.01)	1.93 ± 0.03
<i>p</i> -Cl	<i>p</i> -Cl	3.64(±0.05)	1.96(±0.03)	1.85 ± 0.04
<i>p</i> -Cl	<i>p</i> -Br	4.61(±0.07)	2.68(±0.04)	1.72 ± 0.04

^aStandard deviations.

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_{α} -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-acceptor 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).



The activation parameters, ΔH^\ddagger and ΔS^\ddagger (Table 4), are quite similar to those for the corresponding reaction of other activated olefins in Table 2 in acetonitrile with low ΔH^\ddagger and large negative ΔS^\ddagger values. These are consistent with the concurrent N- C_{α} and H- C_{β} bond formation in the TS, **2**. Since exclusion repulsion energy in the N- C_{α} bond making is partially offset by the bond energy of the partial bond formed, and also by the H- C_{β} bond formation, barrier to bond formation in the rate determining step should be low

Table 4. Activation Parameters^a for the Reactions of Benzylidenedimethylmalonates with X-Benzylamines in Acetonitrile

X	Y	$\Delta H^\ddagger/kcal\ mol^{-1}$	$-\Delta S^\ddagger/cal\ mol^{-1}\ K^{-1}$
<i>p</i> -OMe	<i>p</i> -OMe	5.1	52
<i>p</i> -OMe	<i>p</i> -Br	4.7	51
<i>p</i> -Cl	<i>p</i> -OMe	4.9	55
<i>p</i> -Cl	<i>p</i> -Br	4.6	55

^aCalculated by the Eyring equation. The maximum errors calculated (by the method of K. B. Wiberg,¹¹) are ± 0.5 kcal mol⁻¹ and ± 2 e.u. for ΔH^\ddagger and ΔS^\ddagger , respectively.

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 four-centered constrained TS structure, **2**.¹²

In summary, the addition of benzylamine (BA) to benzylidenedimethylmalonate (BMM) take place in a single step in which the C_{α} -N bond formation and proton transfer to C_{β} of BMM occur concurrently with a four-membered cyclic TS structure, **2**. 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 stronger than that for the reactions of BID. 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 (XC₆H₄CH₂ND₂), are somewhat smaller than those corresponding values for the reaction of CNS due to the smaller extent of bond formation in the TS. The relatively low ΔH^\ddagger and large negative ΔS^\ddagger values are also consistent with the mechanism proposed.

Experimental Section

Materials. Merck GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used after recrystallization. Demethylmalonate and benzaldehydes were Aldrich reagent.

Preparations of benzylidenedimethylmalonates. The benzylidenedimethylmalonates were prepared by the literature method of Horning, E. C. *et al.*^{12b,13}

Kinetic measurement. The reaction was followed spectrophotometrically by monitoring the decrease in the concentration of benzylidenedimethylmalonate, [BMM], at λ_{max} of the substrate to over 80% completion. The reaction was studied under pseudo-first-order condition, [BMM] = 8.0×10^{-5} M and [BA] = 0.30-0.45 M at 25.0 ± 0.1 °C. The pseudo first-order rate constant, k_{obsd} , was determined from the slope of the plot ($r > 0.995$) $\ln[BMM]$ (2.303 log [BMM]) vs time. Second-order rate constants, k_N , were obtained from the slope of a plot ($r > 0.993$) of k_{obsd} vs. benzylamine with more than four 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 20.0 °C. Initially we found a peak for CH in the reactant, *p*-CH₃OC₆H₄CH=C(CO₂CH₃)₂, at 7.66 ppm, which was gradually reduced, and a new two peaks for CH-CH in the product, *p*-CH₃OC₆H₄(*p*-MeOC₆H₄CH₂NH)CH-CH(CO₂CH₃)₂, grew at 3.53 and 4.84 ppm as the reaction proceed. No other peaks or complications were found during the reaction except the 3

peak height changes indicating that the reaction proceeds with no other side reactions.

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