Kinetics and Mechanism of the Addition of Benzylamines to Benzylidene Meldrum's Acids in Acetonitrile

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Nucleophilic addition reactions of benzylamines (XC₆H₄CH₂NH₂) to benzylidene Meldrum's acids (BMA; YC₆H₄CH=C(COO)₂C(CH₃)₂) have been investigated in acetonitrile at 20.0 °C. The rates of addition are greatly enhanced due to the abnormally high acidity of Meldrum's acid. The magnitudes of the Hammett (ρₓ and ρᵧ) and Brönsted (βₓ) coefficients are rather small suggesting an early transition state. The sign and magnitude of the cross-interaction constant, ρₓᵧ (=−0.33), and kinetic isotope effects (k_H/k_D 1.5-1.7) involving deuterated benzylamine nucleophiles (XC₆H₄CH₂ND₂) are indicative of hydrogen-bonded cyclic transition state. The activation parameters, ΔH‡ 4 kcal mol⁻¹ and ΔS‡ −37 e.u., are also in line with the proposed mechanism.

Key Words: Benzylidene Meldrum's acid, Nucleophilic addition reaction, Cross-interaction constant

Introduction

The nucleophilic attack to carbon-carbon double bonds has been the subject of numerous investigations.¹ Nucleophilic vinylic substitution reactions activated by electron-withdrawing groups (Z,Z') are known to proceed by the two-step mechanism, eq. (1), where LG = leaving group and Nu = nucleophile.¹ The primary addition step, 𝑘ₐ, leads to an association complex or intermediate which for amine base is a zwitterion, T⁺.

\[
\text{L}^+ + \text{Nu} \xrightarrow{\text{amine base}} [\text{T}⁺] \rightarrow \text{Nu}^+ \text{Nu} \xrightarrow{\text{amine base}} [\text{T}⁺]^{−1} \quad (1)
\]

In the simple nucleophilic vinylic additions, however, when the amines are primary or secondary, intramolecular proton transfer may immediately follow or even simultaneously upon formation of T⁺, i.e., eq. (2). Previous works have shown that in aqueous solution²⁻³ the mechanism of nucleophilic addition to activated olefins is complex involving group separated products formation following the rate-limiting addition step, 𝑘ₐ, with imbalanced transition states in which the development of resonance to the activating groups (Z,Z') lags behind charge transfer or N-C bond formation. In contrast, the amine addition in acetonitrile³ has attracted considerable attention due to its high acidity,⁴ higher (pKₐ = 7.3) than its acyclic analogues such as dimethyl malonate (2; pKₐ = 15.9) or even the diketone analogue (3; pKₐ = 11.2).⁴b The nucleophilic addition reactions to BMA in aqueous solution have been investigated extensively by Bernasconi et al.⁵ They reported some unusual kinetic behaviors in the addition reaction of BMA.

\[
\text{Y} \text{C}₆\text{H}₄\text{CH} = \text{C} \text{NHCH}₂\text{COO}₂\text{C} \text{CH₃} (3)
\]

The primary purpose of this study is to elucidate the mechanism of primary amine addition to BMA in acetonitrile. Since the Meldrum's acid in BMA is known to have unusually strong power of stabilizing the anion formed in the primary attack,²⁻³ we are interested especially in the rates of addition (𝑘₂ step in eq. (3)) and in the degree of bond formation in the TS by determining the Hammett (ρₓ) and Brönsted coefficients (βₓ), and cross-interaction constant, ρₓᵧ in eqs. (4), where X and Y are the substituents in the nucleophile (benzylamine) and substrate (BMA), respectively.

\[
\log (𝑘ₓᵧ/𝑘_{HH}) = ρₓσₓ + ρᵧσᵧ + ρₓᵧσₓσᵧ \quad (4a)
\]
\[ \rho_{NY} = \frac{\partial \rho_N}{\partial \sigma_N} = \frac{\partial \rho_Y}{\partial \sigma_Y} \] (4b)

In aqueous solution, the magnitude of \( \beta_N(\beta_{\text{BnA}}) \) determined with piperidine and morpholine pair has been shown to be exceptionally small (\( \beta_N = 0.07^{3a} \)) but that with primary amines is somewhat larger with \( \beta_N = 0.22^{5c} \). It is of interest to find out whether such unusual behaviors in aqueous solution persist in acetonitrile or not.

**Results and Discussion**

A clean second-order kinetics according to eqs. (5) and (6) was obtained throughout this work, where \( k_2 \) is the second-order rate constant for the benzylamine (BnA) addition to

\[ \text{Rate} = k_{\text{obsd}} [\text{BMA}] \] (5)

\[ k_{\text{obsd}} = k_2 [\text{BnA}] \] (6)

the benzylidene Meldrum's acid (BMA) under pseudo-first-order condition (\( k_{\text{obsd}} \)) with large excess of amine nucleophiles. Plots of \( k_{\text{obsd}} \) against [BnA] were linear for all cases. The correlation coefficients were better than 0.993 in all cases.

\( \beta_2(\beta_{\text{BmN}}) \) was obtained throughout this work, where \( \beta_2 \) is the second-order rate constant for the benzylamine (BnA) addition to BMA to the lowest place but the logarithm of \( k_2 \) value is the second after that of BMN for which \( \rho_{NY} = 1.32 \). Again the \( \rho_{NY} = 1.38 \) should give the reactivity of BMA in acetonitrile less than that of BID (\( \Sigma \sigma^2 = 2.08 \)) but the reactivity of BMA in acetonitrile is the largest. The enhanced reactivity of the amine addition to BMA no doubt reflects the unusually strong acidity of the Meldrum's acid due to strong stabilizing power of the Meldrum's acid anion,\(^{2,4,5} \) in which the anionic charge is delocalized, 1A.

The anomalously high acidity of 1 has been a subject of extensive theoretical as well as experimental investigations.

**Table 1.** The second-order rate constants, \( k_2 \) (M\(^{-1}\)s\(^{-1}\)), and selectivity parameters\(^a\) for the addition of X-benzylamines to Y-benzylidene Meldrum's acids in acetonitrile at 20.0 °C

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>p-OMe</th>
<th>p-Me</th>
<th>H</th>
<th>p-Cl</th>
<th>( \rho_{NY} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-OMe</td>
<td></td>
<td>74.4</td>
<td>86.4</td>
<td>101</td>
<td>132</td>
<td>0.49 ± 0.02</td>
</tr>
<tr>
<td>p-Me</td>
<td>48.7(^{e})</td>
<td>67.2</td>
<td>79.3</td>
<td>93.5</td>
<td>117</td>
<td>0.42 ± 0.01</td>
</tr>
<tr>
<td>H</td>
<td>42.1</td>
<td>59.3</td>
<td>70.4</td>
<td>78.9</td>
<td>0.26 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>p-Cl</td>
<td>28.4</td>
<td>20.1</td>
<td>0.15</td>
<td>0.21</td>
<td>0.02</td>
<td>-0.33 ± 0.03</td>
</tr>
<tr>
<td>m-Cl</td>
<td>0.15</td>
<td>0.21</td>
<td>0.23</td>
<td>0.32</td>
<td>0.02</td>
<td>-0.33 ± 0.03</td>
</tr>
</tbody>
</table>

\( \rho_{NY} \) values were taken from ref. 7. The \( \rho_{NY} \) values were taken from ref. 8. The \( \rho_{XY} = 9.67 \) was used for X=p-CH\(_3\)O (ref. 9). \(^a\)Correlation coefficients were better than 0.996 in all cases. \(^b\)At 10.0 °C. \(^c\)At 0.0 °C. \(^d\)Correlation coefficients were better than 0.994 in all cases. \(^e\)Correlation coefficients were better than 0.993 in all cases. \(^f\)Correlation coefficient was 0.998.

**Table 2.** Comparisons of reactivity parameter for the addition reaction, YC\(_2\)H\(_4\)CH=CH(ZZ')+X(C\(_6\)H\(_5\)CH\(_2\)NH\(_2\))\(_2\), in acetonitrile

<table>
<thead>
<tr>
<th>Entry</th>
<th>Z(_{ZZ'})</th>
<th>( k_2 ) (M(^{-1})s(^{-1}))</th>
<th>( \log k_{\text{obsd}} )</th>
<th>( \rho_{XY} )</th>
<th>( \rho_{X'Y} )</th>
<th>( \rho_{YX} )</th>
<th>( \rho_{XY} )</th>
<th>( \Sigma \sigma^2 )</th>
<th>( \Sigma \sigma^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (BMA)(^f)</td>
<td>(COO)(_2)CMe(_2)</td>
<td>86.6 (20 °C)</td>
<td>( \approx ) 4.10</td>
<td>-0.24</td>
<td>0.40</td>
<td>-0.33</td>
<td>0.75</td>
<td>1.38</td>
<td></td>
</tr>
<tr>
<td>2 (BMN)(^f)</td>
<td>CN, CN</td>
<td>1.48</td>
<td>4.94</td>
<td>-1.62</td>
<td>-0.55</td>
<td>-0.31</td>
<td>1.32</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>3 (BD)(^f)</td>
<td>(COO)(_2)C(_6)H(_4)</td>
<td>1.48</td>
<td>-1.10</td>
<td>0.41</td>
<td>-0.33</td>
<td>0.83</td>
<td>2.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (NS)(^f)</td>
<td>NO(_2), H</td>
<td>2.63 \times 10(^{-2})</td>
<td>2.55</td>
<td>-1.22</td>
<td>1.43</td>
<td>-0.40</td>
<td>0.78</td>
<td>1.27</td>
<td></td>
</tr>
<tr>
<td>5 (NSB)(^f)</td>
<td>NO(_3), C(_6)H(_5)</td>
<td>2.69 \times 10(^{-2})</td>
<td>1.42</td>
<td>-0.82</td>
<td>1.27</td>
<td>-0.52</td>
<td>0.77</td>
<td>1.27(^a)</td>
<td></td>
</tr>
<tr>
<td>6 (CNS)(^f)</td>
<td>CN, p-pNO(_2)C(_6)H(_4)</td>
<td>1.26 \times 10(^{-2}) (30 °C)</td>
<td>3.35</td>
<td>-1.15</td>
<td>1.10</td>
<td>-0.67</td>
<td>0.92</td>
<td>1.00(^a)</td>
<td></td>
</tr>
</tbody>
</table>

\( \rho_{NY} \) values were taken from ref. 7. The \( \rho_{XY} \) values were taken from ref. 8. The \( \rho_{XY} = 9.67 \) was used for X=p-CH\(_3\)O (ref. 9). \(^a\)Correlation coefficients were better than 0.996 in all cases. \(^b\)At 10.0 °C. \(^c\)At 0.0 °C. \(^d\)Correlation coefficients were better than 0.994 in all cases. \(^e\)Correlation coefficients were better than 0.993 in all cases. \(^f\)Correlation coefficient was 0.998.
Arnett et al. measured acidity constants of esters and lactones that are relevant to the Meldrum’s acid and attributed the strong acidity of 1 to restricted rotation which faces the ester groups to adopt unfavorable anti conformation in Meldrum’s acid. Wiberg et al. studied the acidity difference between syn and anti rotamers of methyl acetate theoretically at the MP3/6-31G**//HF/6-31G* level and concluded that the change in charge distribution that accompanies the more facile loss of proton from the anti rotamer (by 4.7 kcal mol⁻¹) leads to the unusual acidity of Meldrum’s acid, having a bis (anti) conformation. Wang and Houk also reported ab initio calculations on the acidity of methyl acetate in syn and anti conformations at the HF/6-31+G**//HF/3-21G level. They attributed the strong acidity of the anti form (Meldrum’s acid has a bis (anti) form) to greater dipole-dipole electrostatic repulsion interaction between the ether and carbonyl oxygen atoms in the anti conformation, which is significantly relieved in the corresponding enolate anion.

The Hammett (ρₓ = −0.15 ~ −0.33) and Brønsted coefficients (βₓ = 0.15-0.32) in Table 1 are similar to those obtained in the corresponding reactions with primary amines in aqueous solution (ρₓ = −0.22). The βₓ values are greater than that obtained with secondary amines (βₓ = 0.07⁻¹ by two points correlation using piperidine and morpholine) in aqueous solution, but are rather smaller still than those for other benzylamine addition reactions. Although the βₓ values are not listed in Table 2, they are numerically quite similar to the ρₓ values in Table 2 due to the near unity slope in the correlation between the pKₐ’s of benzylamine and Hammett substituent constants, σ; i.e., δpKₐ/δσ ≈ 1.06 for benzylamines. The larger βₓ value with primary amines than with secondary and tertiary amines seems to represent a common pattern, albeit there are some exceptions.

For example, Skoog and Jencks reported βₓ = 0.19 and 0.17 for the reactions of primary amines and pyridines with phosphorylated 3-methoxy pyridine and βₓ = 0.28 and 0.22 for the corresponding reactions with phosphorylated 4-morpholinopyridine, respectively. The aminolysis of isoquinoline N-phosphonate with primary amines and pyridine-morpholine pair gave βₓ = 0.15 and 0.0, respectively.

For the aminolysis of S-(2,4-dinitrophenyl) O-ethyl carbonate, EtOC(=O)SDNP, βₓ = 0.56⁻¹ and 0.48⁻⁵ are obtained with secondary alicyclic amines and quinuclidines, respectively. The ρₓ values are also small so that charge transfer from the benzylamine nucleophiles to the vinylic carbon in the TS may be small.

On the other hand, the cross-interaction constant, ρₓᵧ, (−0.33), is negative as in other bond forming processes and the magnitude is similar to those for other relatively faster addition reactions with stronger activating groups, entries 2 (BMN; ρₓᵧ = −0.31) and 3 (BID; ρₓᵧ = −0.33) in Table 2. The modest size of the ρₓᵧ value despite the relatively early TS with a lower degree of bond making (lower βₓ values) may point to a possibility of intramolecular hydrogen bonding to an oxygen of the COO⁻ moiety, 6, or to the central carbon atom, 7, since in these types of hydrogen bonded TS structures the interaction between X and Y can be through two routes so that the intensity of interaction, i.e., the magnitude of ρₓᵧ, can have a modest value even though the C=N bond making is small. Normally the amine nucleophiles approach toward an end carbon of the vinylic double bond from almost directly above (or below) the carbon so that distance wise the H····C in 7 may be nearer than H····O in 6.

The kinetic isotope effects involving deuterated benzylamine nucleophiles (XCH₂CH₂ND₂) in Table 3 are all greater than unity (kD/kH = 1.5-1.7) and indeed supports such hydrogen bonded TS structure, 6 and 7. The size of kD/kH increases with a stronger electron acceptor substituent in the substrate (Y) as well as in the nucleophile (X) which is in accord with a greater degree of bond making in the TS with electron acceptor Y (with a greater βₓ value) and the enhanced acidity of the NH proton with an electron-acceptor substituent X in the nucleophile. The overall size of the kD/kH values ranging 1.5-1.7 are, however, smaller than those of the corresponding values for the substrates with weaker electron acceptor Z (with a greater βₓ value) and in the nucleophile (X) which is in accord with a lesser degree of bond making in the TS with electron donor X (with a smaller ρₓ value). The comment is also valid for the kD/kH values ranging 2.2-3.1. This is in line with the greater degree of bond formation in the TS for those substrates (entries 4-6) with larger magnitude of the cross-interaction constants, ρₓᵧ.

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>kD/kH</th>
<th>kH/M⁻¹s⁻¹</th>
<th>kD/M⁻¹s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-OMe</td>
<td>p-OMe</td>
<td>74.4 (±0.1)</td>
<td>51.3 (±0.5)</td>
<td>1.45 ± 0.02</td>
</tr>
<tr>
<td>p-OMe</td>
<td>p-Me</td>
<td>86.4 (±0.9)</td>
<td>57.6 (±0.5)</td>
<td>1.50 ± 0.02</td>
</tr>
<tr>
<td>p-OMe</td>
<td>H</td>
<td>101 (±1)</td>
<td>64.7 (±0.8)</td>
<td>1.56 ± 0.03</td>
</tr>
<tr>
<td>p-OMe</td>
<td>p-Cl</td>
<td>132 (±2)</td>
<td>81.5 (±0.9)</td>
<td>1.62 ± 0.03</td>
</tr>
<tr>
<td>p-OMe</td>
<td>p-Me</td>
<td>62.6 (±0.8)</td>
<td>40.9 (±0.4)</td>
<td>1.53 ± 0.03</td>
</tr>
<tr>
<td>p-OMe</td>
<td>p-Cl</td>
<td>68.0 (±0.9)</td>
<td>42.8 (±0.4)</td>
<td>1.59 ± 0.03</td>
</tr>
<tr>
<td>p-OMe</td>
<td>H</td>
<td>76.6 (±0.9)</td>
<td>45.6 (±0.4)</td>
<td>1.68 ± 0.02</td>
</tr>
<tr>
<td>p-Me</td>
<td>p-Cl</td>
<td>91.0 (±0.1)</td>
<td>52.3 (±0.5)</td>
<td>1.74 ± 0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>ΔH°/kcal mol⁻¹</th>
<th>ΔS°/cal mol⁻¹K⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-OMe</td>
<td>p-OMe</td>
<td>3.9</td>
<td>37</td>
</tr>
<tr>
<td>p-OMe</td>
<td>p-Cl</td>
<td>4.1</td>
<td>36</td>
</tr>
<tr>
<td>p-OMe</td>
<td>p-Me</td>
<td>3.8</td>
<td>38</td>
</tr>
<tr>
<td>p-Me</td>
<td>p-Cl</td>
<td>3.8</td>
<td>37</td>
</tr>
</tbody>
</table>

The calculations for the Eyring equation. The maximum errors calculated (by the method of Wiberg, K. B. ref. 17) are ± 0.5 kcal mol⁻¹ and ± 2 e.u. for ΔH° and ΔS°, respectively.
As expected from a hydrogen bonded cyclic TS, the enthalpies of activation are low, \( \Delta H^\ddagger \approx 4 \text{ kcal mol}^{-1} \), and the entropies of activation are large negative \( \Delta S^\ddagger \approx -37 \text{ e.u.} \) (Table 4). The addition step is facilitated by the simultaneous hydrogen bonding (low \( \Delta H^\ddagger \)) but the TS is constrained (large negative \( \Delta S^\ddagger \)) in a cyclic structure.

**Conclusion**

The reactions of benzylidene additions to benzylidene Meldrum's acids (BMA), which can be ascribed to the abnormally high acidity of the Meldrum's acid. The reactions proceed by simultaneous addition of amine and proton to the vinylic double bond with hydrogen bonded cyclic transition state. Relatively low addition of amine and proton to the vinylic double bond with which can be ascribed to the abnormally high acidity of the reactant, \( p\text{-ClC}_6\text{H}_4\text{CH} = (\text{C(OOC}_2\text{H}_4\text{C}(\text{CH}_3)\text{)}_2 \), at 7.62 ppm, which was gradually reduced, and two new peaks for CH-CH in the product, \( p\text{-ClC}_6\text{H}_4(p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{NH})\text{CH} - (\text{C(OOC}_2\text{H}_4\text{C}(\text{CH}_3)\text{)}_2 \), grew at 3.93 and 4.69 ppm as the reaction proceeded. 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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**References**


