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Ab Initio and Density Functional Theory Evidence on the Rate-Limiting Step in the Morita–Baylis–Hillman Reaction

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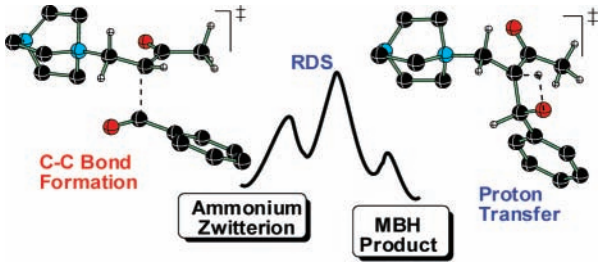
ABSTRACT



The first ab initio and DFT studies on the mechanism of the MBH reaction show that the rate-limiting step involves an intramolecular proton transfer in the zwitterionic intermediate generated by the addition of enolate to electrophile. The activation barrier for the C–C bond-formation is found to be 20.2 kcal/mol lower than the proton-transfer step for the MBH reaction between methyl vinyl ketone and benzaldehyde catalyzed by DABCO.

The Morita−Baylis−Hillman (MBH) reaction has received enormous attention from the organic chemistry community. The carbon−carbon bond-formation between activated vinyl groups and a range of electrophiles has been achieved through the effective use of the MBH reaction.[1] Typically, a tertiary amine coupled with an activated alkene (vinyls bearing electron-withdrawing groups) is reacted with a suitably chosen electrophile leading to a densely functionalized product.[2] The MBH adduct serves as an important skeletal motif for further synthetic manipulations toward biological and medicinally important compounds.[3]

One of the noticeable issues with the MBH reaction is the relatively sluggish reaction rate. In fact, a variety of empirical improvements based on the changes in the reaction conditions are now available toward improving the speed of the MBH reaction. These approaches include the use of metal salts and/or other additives, pressure, microwave irradiation, and so on.[4] While the overall speed could depend on various factors, knowledge about the mechanism and the critical kinetic parameters is very valuable. A logical approach in improving the reaction efficiency therefore demands detailed understanding of the mechanism as well as kinetic features.

In the most commonly accepted mechanism, the MBH reaction is triggered by the reversible conjugate addition of a tertiary amine (nucleophilic catalysis) to an activated olefin (e.g., α,β-unsaturated carbonyl) to generate an enolate. In the second step, long thought of as the rate-determining step,

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(2) (a) Basaviah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049. (c) Deb, I.; Dadwal, M.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2006**, *8*, 1201.

(3) Atkinson, R. S.; Fawcett, J.; Russell, D. R.; Williams, P. J. *Chem. Commun.* **1994**, 2031.

(4) (a) Rafel, S.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 1521. (b) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183. (c) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 102. (d) Luo, S.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 555.

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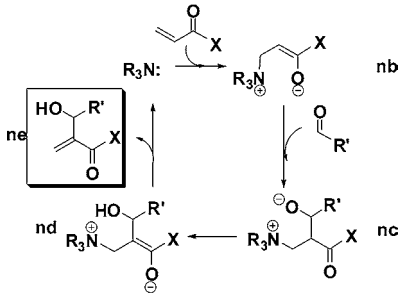
an aldol-type reaction between the enolate and the electrophile takes place to yield another zwitterionic intermediate. The aldol intermediate thus generated undergoes an intramolecular protrotopic shift and subsequent expulsion of the tertiary amine to produce the MBH product.[5] According to the widely employed Hill and Isaacs's mechanism, the addition of the enolate to the electrophile is the rate-limiting step (Scheme 1). The proposed empirical rate equation for

Scheme 1. Key Steps Leading to the MBH Product



the MBH reaction between acrylonitrile and acetaldehyde catalyzed by diazabicyclo[2.2.2]octane (DABCO) exhibits a linear dependence on the concentrations of each of the three reactants.[6] The overall third-order kinetics for the MBH reaction received further support through NMR experiments by Bode et al.[7] There are two interesting recent reports on the isolation and characterization of the key intermediates in the MBH reactions.[8,9]

In a more recent study, McQuade and co-workers have established that the C−C bond-formation is not the rate-limiting step in the MBH reaction under aprotic conditions.[10] Careful rate measurements in conjunction with kinetic isotope experiments on the reaction between methyl acrylate and *p*-nitrobenzaldehyde have revealed that the proton transfer in the zwitterionic intermediate, generated by the addition of enolate to the electrophile, is the rate-limiting step. Despite the widely recognized potential of the MBH reaction, the available evidence on the mechanistic details does not seem to have concurrence on the rate-limiting step as well as on the order of reaction with respect to reagents.

Systematic effort directed toward an atomistic understanding of the mechanism of the MBH reaction is conspicuously absent in the literature.[11] In this letter, we intend to report the first DFT as well as ab initio investigations on the mechanism of the MBH reaction between (i) acrolein and formaldehyde catalyzed by trimethylamine (model system) and (ii) methyl vinyl ketone and benzaldehyde catalyzed by DABCO (real system).

The gas-phase calculations on the reaction between acrolein and formaldehyde catalyzed by NMe_3 are first used as models to establish the reaction profile at the CBS-4M,[12] MP2/6-31+G*, and mPW1K/6-31+G* levels of theories.[13] The computed activation barrier for the Michael addition **TS(1a−1b)**, addition of enolate to the aldehyde **TS(1b−1c)**, intramolecular proton transfer **TS(1c−1d),** and the elimination of Lewis base **TS(1d−1e)** are summarized in Table 1. These transition state geometries are depicted in Figure 1. Several interesting aspects emerge by comparing the energies of various transition states along the reaction profile. The barrier for the initial addition of the Lewis base is relatively low. The resulting enolate intermediate is found to be only marginally more stable than the pre-reacting complex, implying a reversible Michael addition step.[14]

Table 1. The Gas-Phase Activation Parameters (in kcal/mol) for the Model Reaction Obtained at Different Levels of Theory[a]

	CBS-4M		MP2[b]	
TS	$\Delta H^{\dagger}$	$\Delta G^{\dagger}$	$\Delta H^{\dagger}$	$\Delta G^{\dagger}$
TS(1a−1b)	8.57	22.11	5.58	19.07
TS(1b−1c)	13.06	39.27	10.73	36.75
TS(1c−1d)	38.70	65.56	36.35	62.52
TS(1d−1e)	−9.11	16.14	−9.62	14.95

[a] Activation parameters are reported with respect to infinitely separated reactants. [b] The 6-31+G* basis set is employed.

The most important point at this juncture pertains to the rate-limiting step of the reaction. It is quite evident from the data given in Table 1 that an intramolecular proton transfer (**TS(1c−1d)**) in the zwitterionic intermediate is the

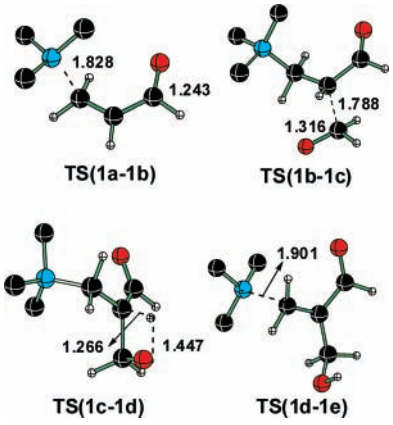


Figure 1. The CBS-4M geometries for the optimized transition states (in Å) for the MBH reaction between acrolein and formaldehyde catalyzed by NMe_3. Only selected hydrogens are shown for improved clarity.

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(11) Except for a rare report on the PMe_3-catalyzed MBH reaction between acrylonitrile and acetaldehyde. Xu, J. *THEOCHEM* **2006**, *767*, 61.

rate-limiting step. In general, the density functional theory (mPW1K) predicted barriers are found to be in good agreement with those of other theoretical models with inherently higher degrees of electron correlation, such as the CBS-4M. On the basis of this observation, we have decided to use the mPW1K functional for further studies on the real system.

Since the reaction involves zwitterionic intermediates with a fair degree of charge separation, the role of solvation is incorporated by using the continuum dielectric method with the integral equation formalism included in the polarizable continuum model (IEF-PCM).[15] The computed activation parameters in the gas phase as well as polar aprotic and protic solvents are provided in Table 2. A pre-reacting complex,

Table 2. The Activation Parameters[a] (in kcal/mol) for the MBH Reaction for the Model as Well as the Real Systems Obtained at the mPW1K/6-31+G* Level of Theory[b]

TS	$\Delta H^{\dagger}$	$\Delta G^{\dagger}$	$\Delta G^{\dagger}_{(\mathrm{DMSO})}$	$\Delta G^{\dagger}_{(\mathrm{water})}$
TS(1a−1b)	9.25	22.46	3.36	1.43
TS(1b−1c)	12.81	38.64	−3.82	−9.71
TS(1c−1d)	37.90	63.89	21.40	15.68
TS(1d−1e)	−8.78	15.95	−15.97	−19.24
TS(2a−2b)	10.22	22.98	6.50	4.96
TS(2b−2c)	16.44	44.56	13.29	11.89
TS(2b−2c′)	20.72	49.31	17.52	14.23
TS(2c−2d)	45.76	73.42	39.65	34.81
TS(2c′−2d)	41.63	69.99	37.73	34.13
TS(2d−2e)	8.10	34.67	7.25	4.33

[a] Activation parameters are reported with respect to infinitely separated reactants. [b] $\Delta G^{\dagger}$ for DMSO and water refers to single-point energies on the mPW1K/6-31+G* geometries obtained by using the IEF-PCM method.

where the Lewis base NMe_3 is bound with the Michael acceptor through hydrogen bonding, is identified. The zwitterionic ammonium salt (**1b**) is generated by Michael addition through transition state **TS(1a−1b)**. The activation barrier for this step is found to be 3.36 kcal/mol in DMSO. In the next step, the zwitterionic ammonium enolate (**1b**) undergoes a facile aldol-type addition to formaldehyde via transition state **TS(1b−1c)** to give **1c** (Scheme 1). The rate-limiting intramolecular proton transfer through **TS(1c−1d)** then yields intermediate **1d**. This step proceeds with an activation barrier of 21.4 kcal/mol in DMSO. This prediction indicates a substantial reduction in the gas-phase barrier for the intramolecular proton transfer is taking place upon inclusion of a polar aprotic solvent continuum. Interestingly, McQuade and co-workers have proposed that the proton transfer is the rate-limiting step under aprotic conditions in the MBH reaction between methyl acrylate and *p*-nitrobenzaldehyde catalyzed by DABCO.[10] The last step involving the elimination of NMe_3 is found to possess only a low barrier **TS(1d−1e)** leading to the MBH product (**1e**).

After establishing the key features on the MBH reaction pathway using the model substrates, we turned our attention to the reaction between methyl vinyl ketone and benzaldehyde catalyzed by DABCO. The optimized transition state geometries are provided in Figure 2. The overall reaction

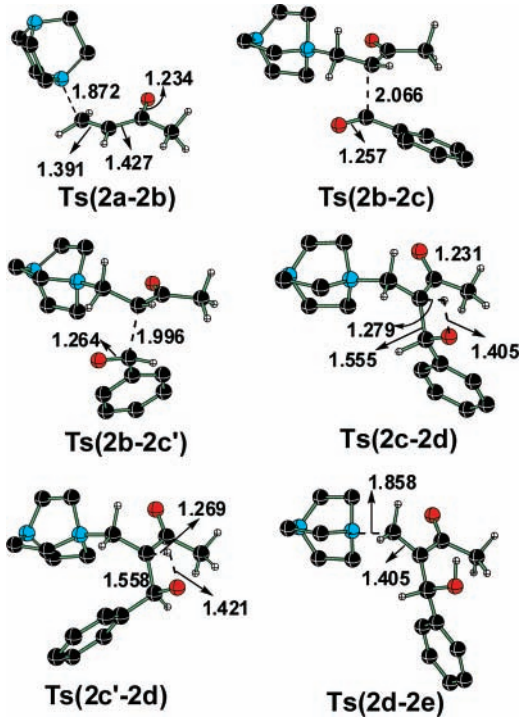

Figure 2. The mPW1K/6-31+G* optimized transition state geometries (in Å) for the MBH reaction between MVK and benzaldehyde catalyzed by DABCO. Only selected hydrogens are shown for improved clarity.

profile is found to be qualitatively similar to that of the model reaction. The Michael addition step is predicted to possess a relatively low barrier, as revealed by the **TS(2a−2b)** energies. Further, this step appears to be quite reversible as per the calculated energetics. The ammonium enolate thus produced can add to both faces of benzaldehyde, through either **TS(2b−2c)** or **TS(2b−2c′)**. The computed barrier for the intramolecular proton transfer in **2c′** (or **2c**) is evidently much higher than the addition step. The energy of **TS(2c′−2d)** is found to be about 20.2 kcal/mol higher than the addition step in DMSO (Table 2). Since the proton-transfer

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(14) See Table S1 in the Supporting Information for full details on the energies of various intermediates (**na**, **nb**, **nc**, **nd**, where **n** = **1** or **2**) involved in the reaction.

(15) See the Supporting Information for further details on computational methods.

step involves a strained cyclic four-membered transition state (Figure 2) such high barriers could be anticipated.[16] In the final step, an elimination transition state **TS(2d−2e)**, which has a low barrier, releases DABCO from intermediate **2d** to yield the MBH product (**2e**). The overall reaction is found to be slightly exoergic by about 1.05 kcal/mol. It can be noticed that the initial and final steps of the MBH reaction possess a much lower energy barrier as compared to the C−C bond-formation as well as the proton-transfer steps. The intramolecular proton transfer is found to be the highest point on the reaction profile and therefore is the rate-limiting step in the MBH reaction.

Though the main focus of the this letter is to examine the mechanism of the MBH reaction under aprotic conditions, we did take notice of a number of interesting examples on the rate enhancements in the MBH reaction, when conducted in water and other protic solvents.[17] To examine the role of protic solvents, we have computed the reaction barriers in prototypical water as the solvent. The most striking feature of these calculations is that the intramolecular proton-transfer transition state is further stabilized. These predictions are evidently in line with the experimental observations.[18] It should be reckoned that in polar protic solvents, the proton transfer in the transition state could be facilitated by solvent molecule(s) through a relay-mechanism. Our preliminary calculations with explicitly included water molecules (with the model substrates) indicate that the activation barrier is lowered. More interestingly, the barrier for the proton transfer as well as the C−C bond formation appears to be competitive under polar protic conditions.[19]

Furthermore, additional pathways leading to byproducts such as dioxanone can only be accounted for by considering a higher molecularity for this reaction. Interestingly, earlier experimental reports suggest that dioxanone is formed only in limited quantities (∼5%).[20] The reaction profile might as well show variations with respect to differences in the reaction conditions as well as substrate combinations. These studies, including the pathway leading to dioxanone, are currently being pursued to understand additional mechanistic issues associated with the MBH reaction.

In summary, we have been able to demonstrate that the intramolecular proton transfer in the zwitterionic intermediate generated after the C−C bond-formation between the ammonium enolate and the electrophile is the rate-limiting step in the MBH reaction under polar aprotic conditions.

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Supporting Information Available: Details on computational methods, complete citation for ref 13e, optimized coordinates, energy, and geometry of various intermediates involved in the reaction pathway. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed*. **2005**, *44*, 1706.

(19) See Table S2 and Figure S3 in the Supporting Information.

(20) The Michael acceptor should bear a good leaving group attached to the carbonyl to be able to form a cylic dioxanone. See: (a) Drewes, S. E.; Emslie, N. D.; Field, J. S.; Khan, A. A.; Ramesar, N. S. *Tetrahedron Lett*. **1993**, *34*, 1205. (b) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *Tetrahedron* **1997**, *53*, 16423. (c) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.