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# Water Catalysis in the Morita–Baylis–Hillman Reaction: A Mechanistic Perspective

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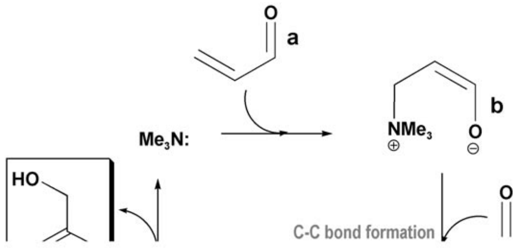
The Morita–Baylis–Hillman (MBH) reaction is a tertiary amine catalyzed reaction between an activated olefin and an electrophile, leading to densely functionalized product.[1,2] Despite the plethora of reports on its applications, the general sluggishness of MBH reaction continues to be a prime concern. Over the years, a large variety of empirical improvements based on modified reaction conditions have been suggested towards improving the speed of MBH reaction.[3] Amongst all the modifications attempted to date, rate enhancement in the presence of polar protic co-solvents and additives deserves special attention.

The first ab initio and density functional study on the mechanism of MBH reaction under polar aprotic medium (DMSO as the dielectric continuum) was very recently reported from our laboratory.[4] It has been demonstrated that under polar aprotic conditions, an intramolecular proton transfer is the rate-limiting step (Scheme 1). This is contrary to the commonly employed qualitative mechanistic schemes, in which the C−C bond formation is proposed to be the rate-limiting step. The mechanistic recourse could be quite different in polar protic medium. For instance, our preliminary calculations showed that protic solvents, such as water, could help reduce the barrier for intramolecular proton transfer.[4] Another recent report on how methanol can affect the reaction energetics of MBH reaction further endorses this view.[5] However, mechanistic insights on the role of water on the kinetics of MBH reaction is conspicuously absent in literature.



Scheme 1. Proposed mechanism of the MBH reaction.

Interesting examples are available wherein reduction in reaction barrier through explicit participation of solvents is noticed.[6] More importantly in the present context are the examples of water catalysis involving a proton relay mechanism.[7] Polar protic solvents in MBH reaction could participate in an analogous manner.[8] The rate acceleration in MBH reaction in the presence of polar protic co-solvents such as water and methanol are well known.[9] These examples allude to an explicit participation of co-solvents besides providing a polar dielectric continuum. It was initially suggested that polar protic solvents influence the reaction by offering additional stabilization to the zwitterionic intermediate(s) generated in the MBH reaction through hydrogen bonding.[3b,10] Such stabilization of transition states and intermediates through hydrogen bonding network is a common feature proposed in various enzyme catalyzed reactions[11] as well as in hydrogen-bonding organocatalysis.[12] Reports are also available on the deterioration of stereoselectivity in MBH reaction in presence of water.[8b,13] While such qualitative propositions are valuable, a more direct involvement of polar solvents, such as water, can be envisaged owing to their ability to act as general acid–base catalyst. We have therefore decided to undertake a detailed examination with an objective of gaining a molecular-level understanding of the role of polar protic co-solvents/additives in

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the MBH reaction. The results summarized herein could have wider implications in a variety of other reactions as well.

We have studied the $NMe_3$-catalyzed MBH reaction between acrolein and formaldehyde, both in the presence and the absence of water as the co-solvent by using ab initio and DFT methods. The choice of these substrates is guided by the reported rate acceleration in the MBH reaction between methyl acrylate and paraformaldehyde under aqueous $NMe_3$ conditions.[14]

In this communication, we report some interesting observations on the role of water in the MBH reaction. The approach consists of computations in 1) the gas phase with and without explicit water molecule(s), and 2) the condensed phase with water-bound substrates. A qualitative understanding of the primary solvation is desirable to establish the number, preferred site, and nature of the solute–solvent interactions. In an effort to identify what would be the minimal number of intimately bound solvent molecules, we first placed water molecules around the substrate on the basis of its polarity. Such intuitively driven initial guess geometries for water-bound substrates were subsequently compared with the position and orientation of water molecules in the near vicinity of the reaction site obtained through ab initio molecular dynamics simulations.[15]

In the present study, two key possibilities are explored in greater detail: 1) one water, and 2) two water molecule(s) coordinated to the reactants (Figure 1). In the single-water-molecule-assisted pathway, three possibilities are considered in which the water molecule is bound to the Michael acceptor (**1Wa**), the electrophile (**1Wb**), or participates in a relay proton-transfer (**1Wc**) mechanism.[16] Similarly with two water molecules, four key possibilities are identified. The first mode involves monofunctional coordination of one water molecule each with formaldehyde and the Michael acceptor, depicted as pathway **2Wa**. This situation is reminiscent of commonly proposed enolate stabilization by polar protic solvents. In mode **2Wb**, one of the water molecules coordinated to the formaldehyde moiety participates in a relay proton-transfer process. Another situation in which both water molecules are bound to formaldehyde gives rise to two more pathways, in which either one or both water molecules facilitate a relay proton-transfer mechanism, designated as **2Wc** and **2Wd**, respectively. An illustration of these possibilities is provided in Figures 1 and 2 with the help of the optimized geometries of transition states for the C–C bond formation and proton-transfer steps, respectively.

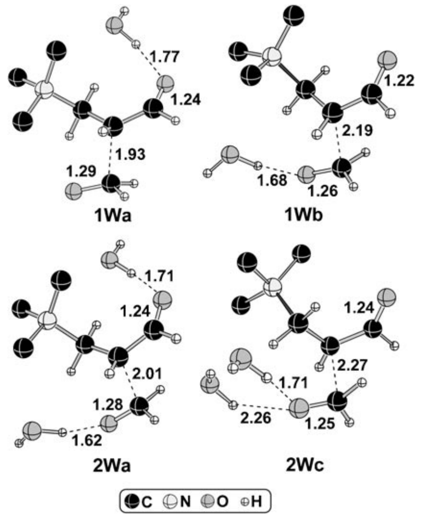

Figure 1. The CBS-4M geometries (in Å) for the optimized transition states for the C–C bond-formation step [TS(**b**–**c**)] in the MBH reaction between acrolein and formaldehyde catalyzed by $NMe_3$. Only selected hydrogen atoms are shown for improved clarity.

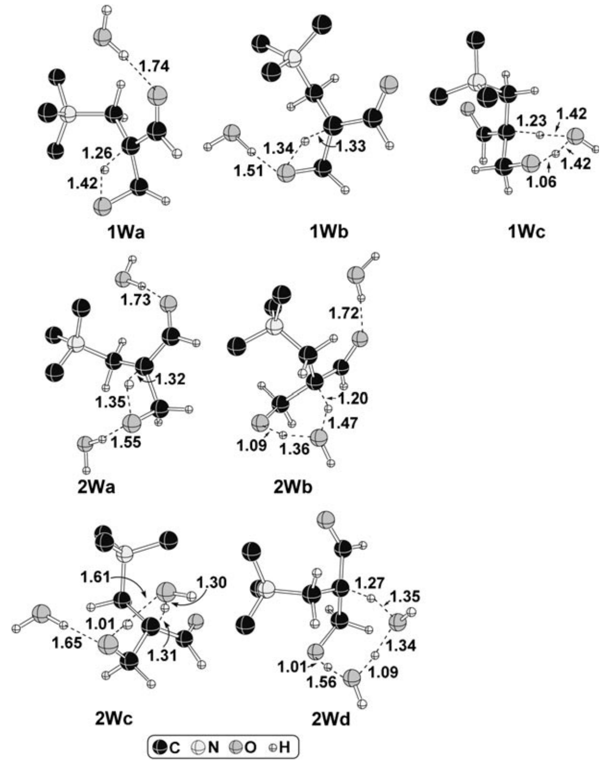

Figure 2. The CBS-4M geometries (in Å) for the optimized transition states for the proton transfer step [TS(**c**–**d**)] in the MBH reaction between acrolein and formaldehyde catalyzed by $NMe_3$. Only selected hydrogen atoms are shown for improved clarity.

The calculated barriers for various steps in the single-water-molecule-assisted modes are found to be in general lower than in the unassisted mode (Table 1). As anticipated, the effect of explicit water on the first step (i.e., the C–N bond formation) is found to be modest. The computed barriers for the C–C bond formation and proton transfer in the unassisted pathway ($\mathbf{W_0}$) are found to be 39.3 and 65.6 kcal mol$^{-1}$, respectively, at the CBS-4M level of theory. The lowering of C–C bond-formation barrier (**b**–**c**) is 3.3 kcal mol$^{-1}$ in **1Wb** with respect to $\mathbf{W_0}$.[17] This can readily be attributed to the LUMO stabilization of formaldehyde as well as the

Table 1. The gas-phase Gibbs free energies of activation [in kcal mol$^{-1}$] for the MBH reaction in absence and presence of water molecule(s) at the CBS-4M level.[a,b,c]

| | $\mathbf{W_0}$ | **1Wa** | **1Wb** | **1Wc** |
|---|---|---|---|---|
| **a–b** | 22.1 (22.3) | 24.8 (21.6) | –[d] | –[d] |
| **b–c** | 39.3 (38.7) | 40.9 (37.0) | 36.0 (32.1) | 36.0 (32.1) |
| **c–d** | 65.6 (62.1) | 57.6 (53.5) | 54.4 (49.5) | 43.9 (38.6) |
| **d–e** | 16.1 (13.2) | 17.3 (12.1) | 18.6 (14.9) | 23.1 (17.2) |
| | **2Wa** | **2Wb** | **2Wc** | **2Wd** |
| **a–b** | 24.8 (21.6) | 24.8 (21.6) | –[d] | –[d] |
| **b–c** | 36.3 (30.4) | 36.3 (30.4) | 38.6 (41.3) | 38.6 (41.3) |
| **c–d** | 56.4 (48.7) | 45.5 (37.9) | 34.5 (27.1) | 42.5 (34.8) |
| **d–e** | 22.9 (12.5) | 22.4 (15.8) | 23.1 (17.2) | 26.4 (18.4) |

[a] The notations $\mathbf{W_0}$, **1W** and **2W**refer to 0, 1 and 2 bound water molecules, respectively, in the TS. [b] Free energies of activation are reported with respect to the infinitely separated reactants. [c] Free energies of activation obtained at the mPW1K/6-31+G** level are given in parenthesis. [d] Identical to $\mathbf{W_0}$ mode.

hydrogen-bonding stabilization of the developing alkoxide offered by the water molecule.[18] The same effect gets further modulated in **2Wc**, in which two water molecules interact with formaldehyde.

The most important observation pertains to the proton-transfer step, involving the transition state TS(**c**–**d**), for which a large reduction in activation barrier in the water-assisted modes is noted. The pathway **1Wc** is found to be the most favored mode amongst the single-water-molecule-assisted pathways as compared with the unassisted pathway. Further, the barrier for **1Wc** involving a relay proton transfer is more than 10 kcal mol$^{-1}$ lower than in **1Wb**. This prediction can be taken as a manifestation of the efficiency of relay proton-transfer process facilitated by catalytic water. The large decrease in the free energy of activation in this mode can be ascribed to the alleviation of ring strain in TS-(**c**–**d**) upon changing from a four- to a six-membered chair-like transition state.[19] In the final step, in which the catalyst is expelled from the zwitterionic intermediate (**c**), the energetics between the assisted and the unassisted pathways do not show as significant differences as in the proton-transfer step. In all the three single-water-molcule-assisted pathways, the proton-transfer step is evidently the rate-limiting step.

In the case of assisted pathways involving two water molecules, the relay proton transfer is found to be a more prominent feature. Most importantly, the proton transfer continues to be the rate-limiting step in **2W** models in which the water molecule(s) stabilizes the enolate through hydrogen bonding. The comparison of **2Wa** with **2Wb** evidently brings out the importance of relay proton transfer towards reducing the activation barrier associated with TS(**c**–**d**). The free energy of activation for all key steps is summarized in Table 1. While the water molecules in **2Wa** help stabilize the zwitterionic intermediate through effective hydrogen bonding, it fails to facilitate the proton-transfer process. In other words, the modes of interactions with protic solvents that do not perturb the reaction coordinate and are farther from the reaction site are less effective in modulating the reaction rate. For instance, the computed barriers for the relay proton transfer are in general more than 10 kcal mol$^{-1}$ lower than that for **2Wa**. This prediction is of potential relevance with regard to the possible rate acceleration of MBH reaction in polar protic solvents. However, to our surprise the barrier for the C–C bond formation in mode **2Wc**, in which the proton relay and hydrogen-bonding interaction co-exist (Figure 2), is found to ~4 kcal mol$^{-1}$ higher than the corresponding proton-transfer step. This observation indicates that the C–C bond formation step is the rate-limiting step in this mode. Another long-range proton transfer through **2Wd** is identified to be effective as well. The proton transfer in this case is facilitated by two water molecules through eight-membered transition state. Interestingly, in both **2Wc** and **2Wd** modes, the difference in the activation barrier between the C–C bond formation and the proton transfer is found to be around 4 kcal mol$^{-1}$. In both these modes, the water molecules are present near the formaldehyde fragment. Central to the present discussion is a likely competition between the proton transfer and the C–C bond formation steps as the rate-determining step under polar protic conditions.

After having recognized the importance of water-bound transition structures towards influencing the kinetically significant steps, a detailed sampling of different binding modes in two-water-molecule-assisted pathways was undertaken.[20] For instance, additional transition states TS(**b**–**c**) and TS(**c**–**d**) were located in which the catalytic water molecules are hydrogen bonded to each other, besides interacting with the developing charges.[20] Interestingly, these transition states for the C–C bond formation as well as the subsequent proton transfer are in general predicted to be higher in energy than mode **2Wc**.[21]

The identification of water catalysis in the critical steps of MBH reaction prompted us to evaluate the origin of the catalytic power of water.[22] In both one- and two-water-molecule-assisted modes, the highest catalytic power is noted in the relay proton-transfer step. In the preceding C–C bond-formation step, the estimated catalytic power of water is found to be much lower.[23] On the basis of the reduction in free energies of activation as well as the estimated catalytic power, it is rational to propose that the rate acceleration under polar protic conditions is most likely to be due to the relay proton transfer promoted by water molecule(s), while hydrogen-bonding stabilization offers a supporting role.

An evident consideration at this point relates to the inclusion of more than two explicit water molecules around the reaction site. Notwithstanding the impending entropic disadvantages, some useful evidence gathered through ab initio MD calculations suggests that for large part of the simulation, only two water molecules are intimately associated with the transition state.[24] Further, these water molecules tend to maintain interactions primarily with the formaldehyde fragment.[25] We have therefore considered only two water molecules in the present study.

The discussions thus far have focused on the results obtained by using gas-phase calculations. To compare how systems with explicitly bound water molecule(s) respond to the polarity of the bulk solvent, we have calculated the activation barriers, in the most commonly employed solvents for MBH reaction, such as water, DMSO, and THF. It is interesting to note that the predicted barriers as well as the trends at the mPW1K/6-31+G** level (Table 1) are in very good agreement with those obtained by using higher level composite methods such as CBS-4M.[26] The mPW1K/6-31+G** level of theory was therefore used for single-point energy calculations in solvent continuum by using the gas-phase geometries at the same level.

The activation barriers in the condensed phase, as summarized in Table 2, are generally found to be lower than the corresponding values in the gas-phase. The most significant reductions in barriers are noticed for the C−C bond-formation (TS(**b**–**c**)) as well as the proton-transfer (TS(**c**–**d**)) steps in water. This is due to the electrostatic stabilization of the charge-separated (zwitterionic) transition states in the dielectric continuum.[27] More interestingly in the present context are the mode-dependent changes in the rate-limiting step. For example, in **2 Wc** the proton-transfer step exhibits a lower barrier than the C−C bond formation. These predictions allude to a likely change over, or existence of competing rate-limiting steps, under polar protic conditions. Further, it is evident that the inclusion of explicit protic solvent molecule(s) is essential along with implicit continuum solvation treatments for an improved description of specific solute–solvent and other long-range interactions. High volume ratio of protic co-solvents in experiments additionally justifies the use of the cluster-continuum method, as employed in this study.

Table 2. The computed activation energies[a] [in kcal mol$^{-1}$] for the MBH reaction in different solvent continuum.

| | $\mathbf{W_0}$ | **1 Wa** | **1 Wb** | **1 Wc** | **2 Wa** | **2 Wb** | **2 Wc** | **2 Wd** |
|---|---|---|---|---|---|---|---|---|
| THF | | | | | | | | |
| **a–b** | 4.2 | −0.9 | –[b] | –[b] | –[c] | –[c] | –[b] | –[b] |
| **b–c** | −5.6 | −10.7 | −7.6 | −7.6 | −16.1 | −16.1 | −4.4 | −4.4 |
| **c–d** | 21.3 | 10.9 | 7.6 | −11.6 | 1.2 | −14.2 | −22.4 | −16.0 |
| **d–e** | −18.0 | −24.1 | −22.0 | −20.2 | −26.8 | −26.6 | −26.7 | −26.2 |
| DMSO | | | | | | | | |
| **a–b** | 3.5 | −0.8 | –[b] | –[b] | –[c] | –[c] | –[b] | –[b] |
| **b–c** | −8.5 | −12.2 | −7.5 | −7.5 | −15.2 | −15.2 | −3.6 | −3.6 |
| **c–d** | 19.0 | 10.6 | 7.5 | −13.1 | 2.0 | −13.7 | −21.3 | −15.3 |
| **d–e** | −18.4 | −23.5 | −21.4 | −19.8 | −25.3 | −25.2 | −25.3 | −25.1 |
| water | | | | | | | | |
| **a–b** | 1.6 | −0.2 | –[b] | –[b] | –[c] | –[c] | –[b] | –[b] |
| **b–c** | −16.0 | −15.8 | −7.7 | −7.7 | −12.3 | −12.3 | −0.9 | −0.9 |
| **c–d** | 13.3 | 10.5 | 7.5 | −20.1 | 4.7 | −11.2 | −17.3 | −12.0 |
| **d–e** | −21.7 | −22.8 | −21.0 | −19.8 | −22.7 | −21.5 | −21.6 | −22.9 |

[a] Activation energy in THF ($\varepsilon$=7.58), DMSO ($\varepsilon$=46.7), and water ($\varepsilon$=78.39) refers to IEF-PCM single-point energies on the mPW1K/6-31+G** gas-phase geometries. The values are reported with respect to the separated reactants. [b] Identical to $\mathbf{W_0}$ mode. [c] Identical to **1 Wa** mode.

In conclusion, we have demonstrated that the inclusion of explicit water molecule(s) in transition-state models results in reduction of activation barrier in the rate-limiting step of the MBH reaction between acrolein and fomaldehyde catalyzed by trimethylamine. The predicted lowering of the activation barrier concurs with the experimental observation on the rate enhancements of MBH reaction in the presence of polar protic co-solvents. On the basis of the overall reduction in activation barrier predicted using a cluster-continuum model, we propose that MBH reaction could enjoy water catalysis, a point of potential mechanistic relevance. In the presence of loosely bound co-solvent(s), several near-degenerate transition states are possible and therefore a careful sampling of the water-bound transition states are desirable towards identifying the rate-limiting step in MBH reaction.

## Computational Methods

All the stationary points were optimized at the CBS-4M and mPW1K/6-31+G** levels of theory by using Gaussian 03 suite of programs.[28] Transition states were first characterized by their imaginary frequencies pertaining to the desired reaction coordinate and subsequently by using the intrinsic reaction coordinate (IRC) calculations. Single-point energies in the condensed phase were computed by using the IEF-PCM formalism at the mPW1K/6-31+G** level of theory by employing UAKS radii.[29] This approach is termed as "cluster-continuum" model, in which the cluster consists of water-bound transition states.

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**Keywords:** ab initio calculations · relay proton transfer · transition states · water chemistry

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[15] See Supporting Information for more details on ab initio MD simulation.

[16] Different coordination possibilities are summarized in Figures S1 and S2 in the Supporting Information.

[17] An alternative higher energy transition state is also identified. (See Figure S12 in Supporting Information, **1Wb(1)**).

[18] The LUMOs of the one- and two-water-molcule-bound formaldehyde were found to be 0.21 and 0.33 kcal mol$^{-1}$, respectively, lower than the free formaldehyde. (See Table S6, Supporting Information).

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[20] See Figure S12 in Supporting Information for these additional transition states.

[21] See Table S7 in the Supporting Information for the activation parameters.

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[23] See Supporting Information for details of calculation and estimated catalytic power (Table S1).

[24] Only C–C bond formation step is considered for the ab initio MD simulations.

[25] Severe geometric convergence issues were encountered in electronic structure calculations when systems with three water molecules were attempted.

[26] A full list of activation parameters at the mPW1K/6-31+G** level is provided in Table S5 in the Supporting Information.

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