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Brønsted Acid Catalyzed Morita–Baylis–Hillman Reaction: A New Mechanistic View for Thioureas Revealed by ESI-MS(/MS) Monitoring and DFT Calculations

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Abstract: A Morita–Baylis–Hillman (MBH) reaction catalyzed by thiourea was monitored by ESI-MS(/MS) and key intermediates were intercepted and characterized. These intermediates suggest that thiourea acts as an organocatalyst in all steps of the MBH reaction cycle, including the rate-limiting proton-transfer step. DFT calculations, performed for a model MBH reaction between formaldehyde and acrolein with trimethylamine as base and in the presence or the absence of thiourea, suggest that thiourea accelerates MBH reactions by decreasing the transition-state (TS) energies through bidentate hydrogen bonding throughout the whole catalytic cycle. In the rate-limiting proton-transfer step, the thiourea acts not as a proton shuttle, but as a Brønsted acid stabilizing the basic oxygen center that is formed in the TS.

Keywords: Density functional calculations · ESI mass spectrometry · Morita–Baylis–Hillman reaction · reaction mechanisms · thiourea

Introduction

Nature is rich in ingenious designs that have been used by chemists as a source of inspiration in the development of new synthetic strategies. The pivotal role of enzymes in biological systems has, for instance, inspired the use of organic molecules as catalysts for organic reactions. The role of enzymes has therefore established the theoretical basis of the metal-based bifunctional Lewis base–Lewis acid catalysis in asymmetric synthesis.[1] More recently, a new concept has emerged in which metal-free organic molecules are used as efficient catalyst of organic reactions.[2] Generally known as (bifunctional) organocatalysis, these new catalysts combine, within a single molecule, hydrogen-bonding donors and Lewis base functionalities[2] that accelerate organic reactions with substoichiometric amounts of metal-free organic molecules.[2c] Pioneered by Hajos and Parrish,[3] who used proline as the catalyst for an asymmetric Robinson annulation, interest in this field has increased owing to the high efficiency and selectivity of many organocatalysts in key organic reactions.[2c] These efforts have led to the development of asymmetric versions[4] of the Mannich,[5] Diels–Alder,[6] Michael,[7] Biginelli,[8] Aldol,[9] and epoxidation reactions.[4c,10]

The Morita–Baylis–Hillman (MBH) reaction has occupied a prominent position in organic synthesis because it provides

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a straightforward route to new C–C σ bonds under mild conditions.[11] MBH reactions are also "green" and highly atom efficient; they provide multifunctionalized derivatives have been used as for starting materials in the total syntheses of natural products,[12] heterocycles,[13] and drugs.[14]

Despite the synthetic versatility, MBH reactions suffer from a serious drawback: for some substrates the reaction is very slow. Several methods have been employed to accelerate these reactions, such as ultrasound,[15] microwave,[16] salts,[17] ionic liquids,[18] and organocatalysis. Connon and Mather[19] recently described that thioureas function as efficient organocatalysts for MBH reactions with significant increases in rates and yields, even for deactivated aromatic aldehydes. Initial efforts in this area were concentrated on increasing the reaction rates, however, asymmetric approaches using chiral ureas as the catalyst have now became the main focus.[20] The catalytic role of thioureas on the mechanism of the MBH reaction, which leads to the impressive improvements in yield, rate, and enantioselectivity is, however, still unclear.[19]

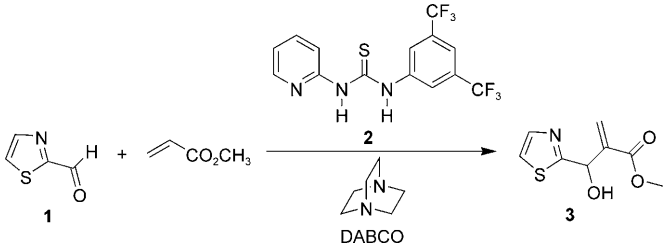
Recently, we used ESI-MS(/MS) monitoring to probe the mechanism of a MBH reaction[21] and we were able to intercept and characterize the key intermediates proposed by Isaacs and Hill.[22] In related studies, we proposed (from ESI-MS(/MS) studies) a new mechanism for the preparation of *N*-oxide hydroxyquinolines[23] and we probed the catalytic role of ionic liquids in MBH reactions.[18c] ESI-MS(/MS) monitoring permits rapid and efficient "fishing" of reactants, intermediates, and/or products either in their intact ionic forms or in their protonated or deprotonated forms directly from the reaction solution into the diluted gas-phase environment of mass spectrometers. The measurement of their masses and online characterization by collision-induced dissociation (CID) can then be achieved.[24] ESI-MS(/MS) monitoring therefore provides continuous and comprehensive snapshots of the ionic composition of reaction solutions.[25]

The role of thioureas as organocatalysts in the MBH reaction has not been previously studied from a theoretical point of view, but studies have been performed on both the MBH reaction[26–28] and the organocatalytic properties of thiourea.[19,29,30] Nowadays, computational techniques are increasingly used to understand and predict the roles of catalysts in organic and organometallic chemistry.[31] Robiette et al.[28] systematically studied MBH reactions between methyl acrylate and benzaldehyde with trimethylamine as a base by using B3LYP optimization in THF and calibration with calculations up to a G3MP2 level.[21b] For MBH reactions performed in the absence of protic solvents, they confirmed the proposal of McQuade et al.[32] that the rate-determining step (RDS) is the deprotonation of the α-position by a hemiacetal alkoxide.[21b] For the role of thiourea as organocatalyst, Connon and Mather[19] performed computational studies on the stability of hydrogen-bonded complexes between the thiourea and different electrophiles to evaluate the best catalyst in relation to a given electrophile. Pápai et al.[29] studied Michael addition reactions between acetylacetone and a nitroolefin catalyzed by thiourea. They reported that multiple hydrogen bonds stabilize the transition state leading to the Michael adduct.

Herein, we report new mechanistic findings obtained by using ESI-MS(/MS) monitoring of the role of thiourea as a organocatalyst in MBH reactions. The important mechanistic implications of the MS data were also investigated and corroborated by DFT calculations.

Results and Discussion

ESI-MS: Owing to its high efficiency and rate, we studied the MBH reaction between 2-thiazolecarboxaldehyde (**1**) and methyl acrylate in the presence of 1,4-diazabicyclo-[2,2,2]octane (DABCO) with thiourea **2** as a model organocatalyst. The presence of the basic pyridine substituent was to facilitate ESI(+)-MS detection of intermediates in their protonated forms (Scheme 1).



Scheme 1. MBH reaction monitored by ESI-MS and catalyzed by thiourea **2**.

Relying on the high speed and sensitivity of ESI(+)-MS monitoring, we hoped to "fish out" the key players of this MBH reaction, even the most transient intermediates. The reaction of aldehyde **1** (0.23 mmol) with an excess of methyl acrylate (1.16 mmol) in methanol (100%) and in the presence of DABCO (0.23 mmol) and thiourea (50% mol) was then continuously monitored by ESI(+)-MS. After 10 min, a fairly clean and mechanistically enlightening ESI(+) mass spectrum was recorded (Figure 1). The three intermediates intercepted previously[21] are detected as **7** (*m*/*z* 312), **8** (*m*/*z* 200), and **9** (*m*/*z* 199), but now three new reaction intermediates anchored with the thiourea **2** were also detected: **4** (*m*/*z* 677), **5** (*m*/*z* 564), and **6** (*m*/*z* 452).

Intermediate **6** corresponds to a complex of thiourea **2** with methyl acrylate, which indicates that **2** facilitates the Michael addition of DABCO during the first step of the MBH process. This complexation should have direct consequences on the LUMO coefficient of the double bond of methyl acrylate. Intermediate **5** corresponds to the complex of **2** and the zwitterionic ammonium enolate intermediate and indicates that **2** also acts in this crucial MBH reaction step by stabilizing its intermediate and thus facilitating the next step of aldol condensation. Intermediate **4** corresponds to the complex of **2** with the zwitterionic ammonium enolate intermediate **7**. Interception of **4** is important because it in-

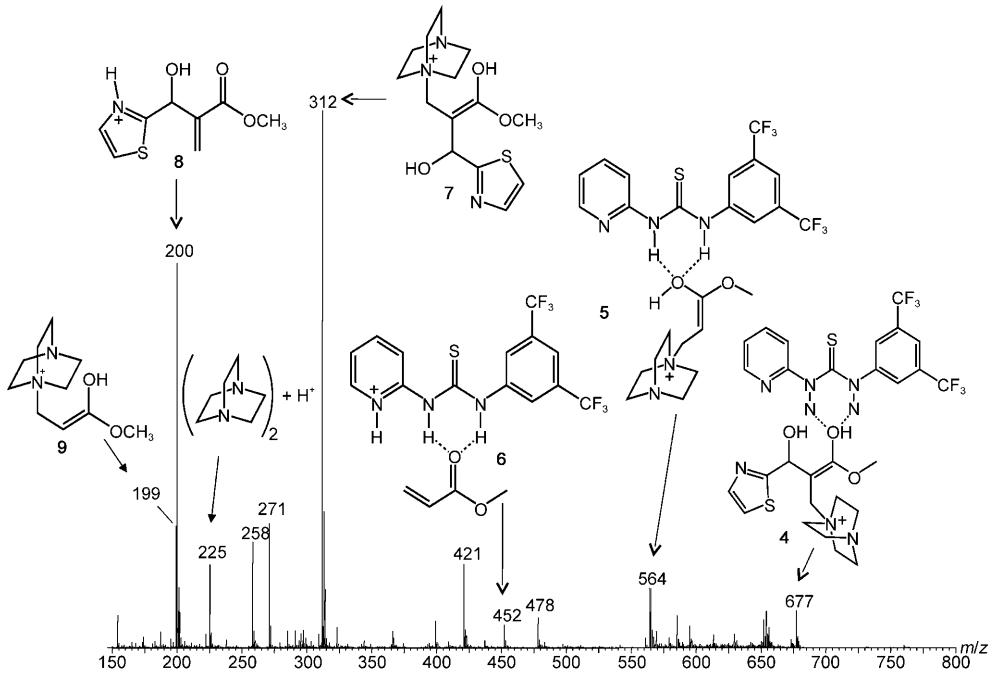
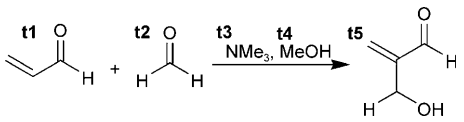


Figure 1. ESI-MS of the reaction solution after 10 min.

dicates that **2** also has a role in the crucial, rate-limiting proton-transfer step.

ESI-MS/MS: The MBH intermediates, gently transferred from the reaction solution directly to the gas phase in their intact protonated forms, were then individually selected for characterization with ESI-MS/MS. Intermediate **7** (*m*/*z* 312), as previously observed,[21] dissociates into the protonated MBH adduct (*m*/*z* 200) on loss of neutral DABCO or upon loss of the neutral MBH adduct to form protonated DABCO (*m*/*z* 113) (Figure 2a). The new intermediate **6** (*m*/*z* 452) dissociates to form mainly the ion of *m*/*z* 332 on loss of H_2S and methyl acrylate (120 Da), whereas protonated methyl acrylate (*m*/*z* 87) is also formed as an important fragment (Figure 2b). Intermediate **5** (*m*/*z* 564) (Figure 2c) mainly dissociates, as easily rationalized from its proposed structure, into the ion of *m*/*z* 452 on loss of DABCO (112 Da). Other minor fragments are protonated DABCO (*m*/*z* 113), as well as the ion of *m*/*z* 199, which is formed by the nucleophilic addition of DABCO to methyl acrylate. Intermediate **4** (*m*/*z* 677) dissociates to a great extent to form protonated DABCO (Figure 2d). Another major fragment ion is that of *m*/*z* 565 from the loss of DABCO (112 Da), whereas the protonated MBH adduct (*m*/*z* 200) is also observed as a major dissociation product. The ESI-MS/MS data therefore support the findings that compound **2** participates in all the important steps of the catalytic cycle, including the elimination step in which the MBH adduct is formed.[33]

Computational results—overall mechanism on a model system: The catalytic role of thiourea **2** must consist in reducing the barrier for the rate-limiting step of the MBH process. The first step for understanding the catalytic role is therefore to identify the transition state (TS). A computational study was performed on a model system (Scheme 2),



Scheme 2. Model MBH reaction investigated computationally.

that is, theoretical (**t**) models were evaluated for the MBH reaction between acrolein (**t1**) and formaldehyde (**t2**) in the presence of trimethylamine (**t3**) as Lewis base and methanol (**t4**) as solvent leading to allylic alcohol **t5** as the MBH adduct.

The computed profile for the MBH reaction in methanol is shown in Figure 3. All values are reported with respect to reactants. A methanol molecule is explicitly included and the effect of the rest of the solvent is introduced as a dielectric continuum. The overall shape of the energy profile reproduces previous studies.[26–28] The energy profile is quite smooth and the proton-transfer step via **mTSA3** is clearly the RDS. The highest-energy point is that of **mTSA3**, lying 1.4 kcal mol^{-1} above the separate reactants; the barrier with respect to the preceding intermediate **mIA3** is also the highest (6.8 kcal mol^{-1}). The role of methanol is critical as proton shuttle between the carbon and oxygen centers, as previously proposed by Robiette et al.[28] In nonprotic solvents, they found the reaction to follow a different path that

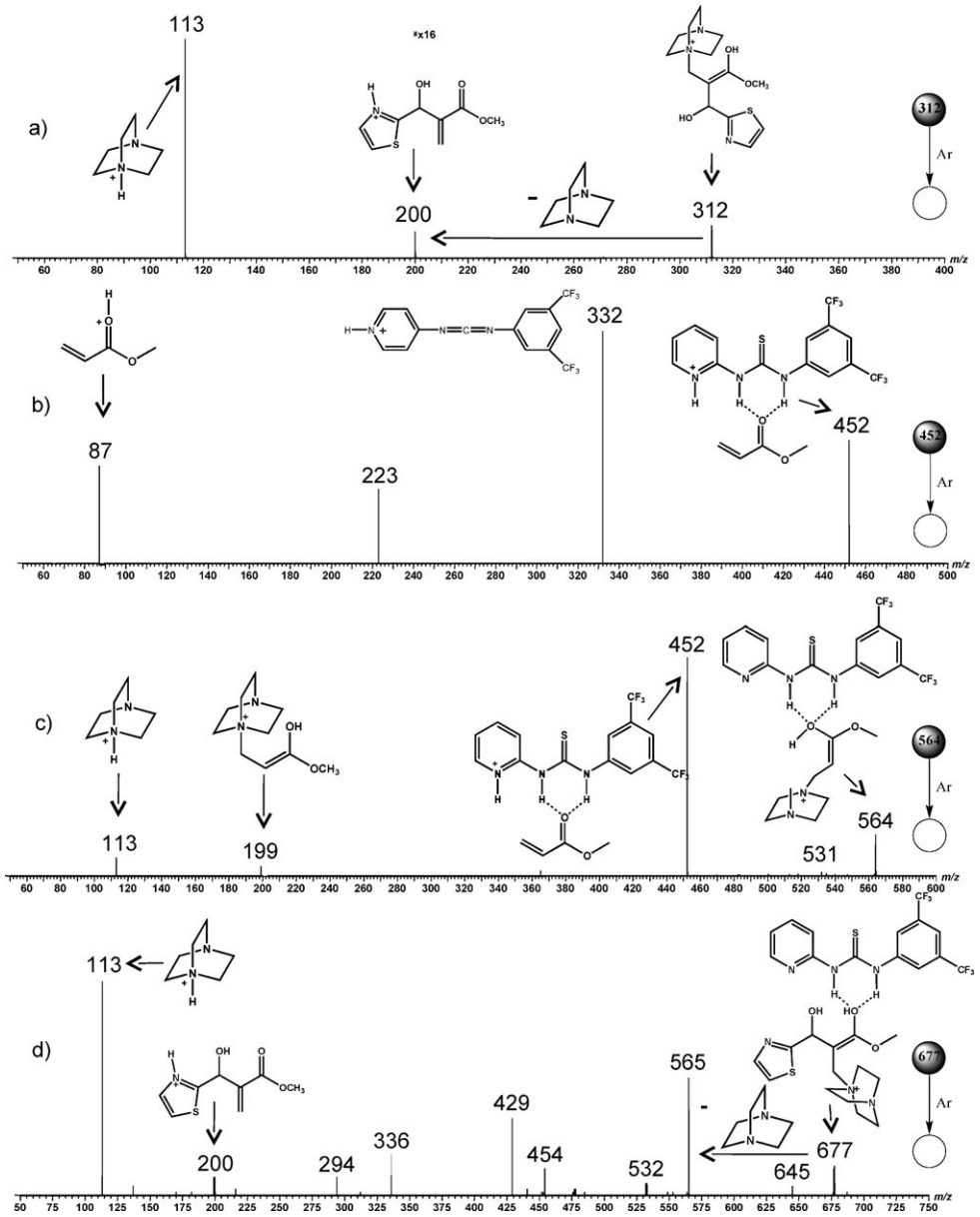


Figure 2. ESI-MS/MS of MBH intermediates detected in their protonated forms: a) **7** (*m*/*z* 312), b) **6** (*m*/*z* 452), c) **5** of (564), and d) **4** (*m*/*z* 677).

involved a hemiacetal species, as proposed by McQuade et al.[32] It seems clear that the proton transfer is the RDS of the whole process, hence we will concentrate the calculations that follow on this step.

Methanol shuttle versus thiourea shuttle: The simplest possible role of thiourea as the catalyst in the MBH reaction would be to replace the methanol as the proton shuttle. We investigated this possibility by computing the barrier corresponding to the key TS by using various thioureas (**t6**, **t9**, **t10**) and hydrogen donors (Table 1). Trimethylamine was used as the base because replacing it with DABCO would be very computationally demanding and is unlikely to affect the mechanism.

System A (Table 1) is analogous to the model system used above for the full catalytic cycle, but operates on the real system (methyl acrylate instead of acrolein and acetaldehyde instead of formaldehyde). Figure 4 displays the geometries of the rate-determining TS **TSA3**. Changes in the key parameters with respect to **mTSA3** (see the Supporting Information) are minimal. The relative energy with respect to the separate reactants does change, however, with values of 16.7 kcal mol^{-1} for **TSA3** and 1.4 kcal mol^{-1} for **mTSA3**. This result, probably explained by the superior stabilization of the electron-rich methyl acrylate and acetaldehyde reactants, is unlikely to change the identity of the rate-determining step. The relative energy of **TSA3** can be compared with that obtained by Robiette et al.,[28] with more sophisticated computational methods (including geometry optimization in

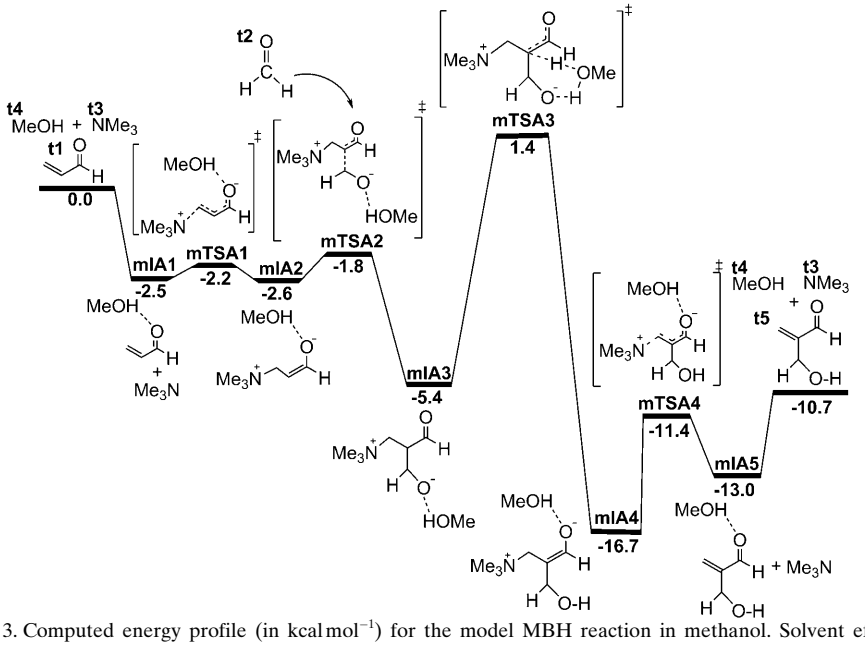
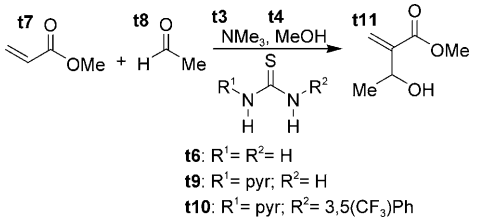
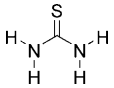
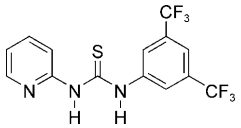
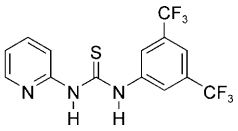


Figure 3. Computed energy profile (in kcal mol^{-1}) for the model MBH reaction in methanol. Solvent effects were considered by polarizable continuum model (PCM) single-point calculations in methanol. The prefix **m** stands for model system.



Scheme 3. Larger MBH reaction models investigated computationally.

Table 1. Different mechanisms and hydrogen donors for the model MBH reaction depicted in Scheme 3.

Mechanism	Hydrogen donors
A	MeOH
B	
C	
D	MeOH + 
E	MeOH + MeOH
F	MeOH + 2 MeOH

solution and corrections up to the G3MP2 level) on the related system with benzaldehyde instead of acetaldehyde. Their reported value was 24.6 kcal mol^{-1}, but with a different definition of the origin of the reactant energies. Once this aspect was corrected, the difference with our more affordable calculations on a similar, but not identical system, was only 2.6 kcal mol^{-1}, which confirms the overall validity of our computational approach.[34]

In system B, simple replacement of methanol by a small model thiourea **t6** does not lower the barrier. The resulting **TSB3** (Figure 4) has an energy of 21.3 kcal mol^{-1} above the separate reactants. The barrier is therefore more than 5 kcal mol^{-1} higher than that for **TSA3**. If this were the mechanism, thioureas would not catalyze the reaction, which is at odds with our experimental results and those by Connon and Maher.[19] The high barrier can be explained by the much longer N···H distances involved in the proton-transfer step in **TSB3** (1.309, 2.522 Å) than the corresponding O···H distances in **TSA3** (1.305, 1.899 Å).

Calculations with the thiourea used in experiment C (Table 1) introduces an interesting mechanistic nuance. The pyridyl substituent offers the possibility of protonation at the pyridine N; behavior analogous to the bifunctional role of thiourea derivatives recently studied by computational methods.[31,35,36] The corresponding **TSC3** certainly has the thiourea in the tautomeric form (Figure 5), and the energy of 17.4 kcal mol^{-1} with respect to reactants is lower than that of **TSB3**. The route via **TSC3** is, however, still unable to compete with the rate-limiting energy in the absence of thiourea, which was 16.7 kcal mol^{-1}.

Alternative model—methanol as shuttle, thiourea as an assistant: After failing to substantiate computationally that thiourea is a better proton shuttle than methanol, we investigated an alternative mechanism in which methanol acts as the proton shuttle in the presence of thiourea. We used the methanol plus the thiourea system D (Table 1).

In the corresponding **TSD3** (Figure 6), the presence of the thiourea was indeed able to lower the reaction barrier to 11.5 kcal mol^{-1}. This barrier is significantly lower than that determined in the absence of thiourea (16.7 kcal mol^{-1}, **TSA3**) and proves that the additive plays a catalytic role. Interestingly, thiourea decreases the proton abstraction barrier by forming two hydrogen bonds, a mechanism analogous to that proposed for highly polarized cycloaddition reactions by Houk et al.[37] The thiourea does not act as a proton shuttle, but as a Brønsted acid that stabilizes the basic oxygen center present in the TS. This additional stabilization increases the acidity of the tertiary carbon and facilitates proton transfer.

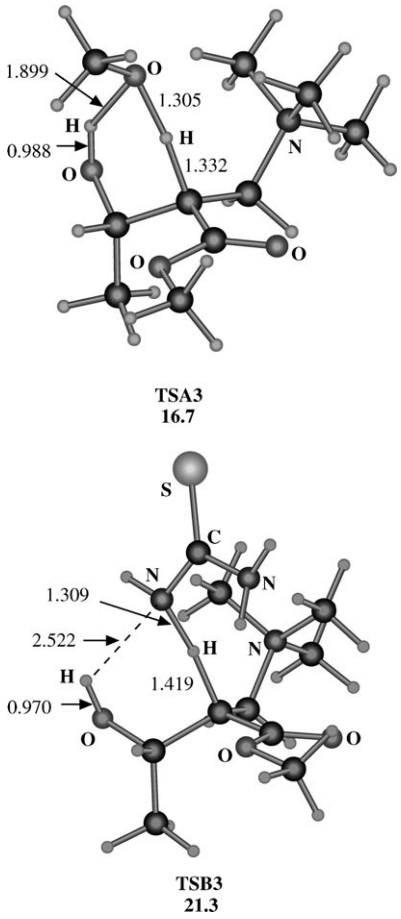


Figure 4. Geometries and relative energies for the proton-transfer transition states on systems A (**TSA3**) and B (**TSB3**). Energies are given in bold in kcal mol^{-1} and distances in Å.

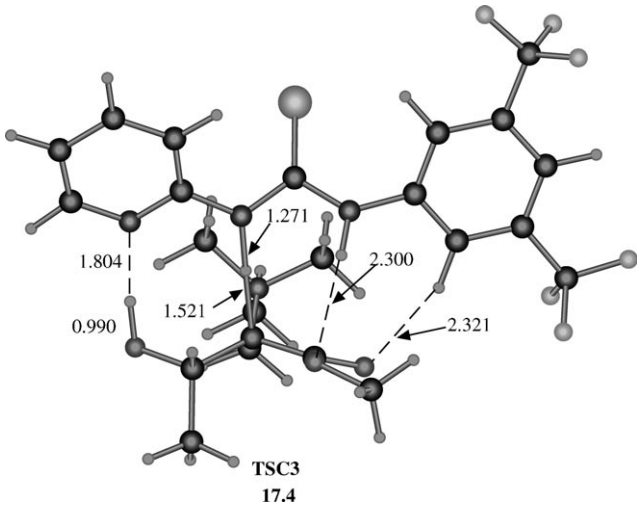


Figure 5. Geometry and relative energy for **TSC3**. Energies are given in bold in kcal mol^{-1} and distances in Å.

For completeness, we also analyzed cases E and F (Table 1), in which the hydrogen-bonding-donor role of thiourea in D is replaced by additional methanol solvent molecules. When an additional methanol molecule is considered, the energy of the **TSE3** structure lies 13.4 kcal mol^{-1} above the reactants; higher than when thiourea is used. The case in which two additional methanol molecules are considered is subtler. It involves the addition of a new molecule to the system, with entropic implications that question the adequacy of the potential energies that we are using for the comparison of the species. Of course, these same questions also affect the comparison between **TSA3**, **TSB3**, **TSC3** (all with only one proton shuttle) and **TSD3**, **TSE3** (with one proton shuttle plus an assisting thiourea). The difference of 5.2 kcal mol^{-1} in the potential energies between **TSA3** and **TSD3** seems sufficient to offset possible entropic effects. On the contrary, the potential energy for **TSF3** is 11.4 kcal mol^{-1}, just below the 11.5 kcal mol^{-1} of **TSD3**. The gas-phase estimation of the entropic effect associated to the additional molecule in **TSF3** is 5.8 kcal mol^{-1}. The real entropic correction in solution has been estimated to be a fraction of the gas-phase value.[28] Therefore, **TSF3** (one shuttle plus two assistants) is too close (0.1 kcal mol^{-1}) in potential energy to **TSD3** (one shuttle plus one assistant) to be competitive, but **TSD3** is far enough (5.2 kcal mol^{-1}) in potential energy from **TSA3** (only one shuttle) to overcome entropic corrections.

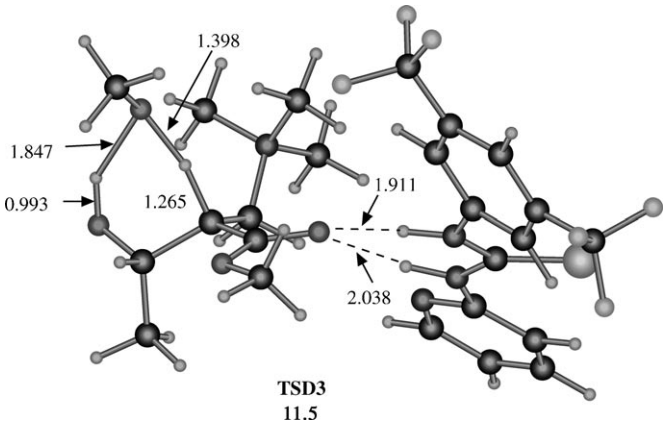


Figure 6. Geometry and relative barrier for **TSD3**. Energies are given in bold in kcal mol^{-1} and distances in Å.

The computational results of this section therefore support a model in which thiourea catalyzes, more efficiently than methanol, MBH reactions in protic conditions mainly due to its ability to perform bidentate hydrogen bonds throughout the whole catalytic cycle. From this mechanistic proposal it follows that a properly constructed diol could also act as catalyst; a hypothesis that should be tested experimentally.

The joint consideration of ESI-MS and DFT results provides a clear mechanistic picture that differs from the expected proton-shuttling role of thiourea. ESI-MS data provide evidence that thiourea remains attached to the reacting system throughout the whole catalytic cycle and indicates the stoichiometry of three different intermediates. The binding arrangement of these three intermediates, **4**, **5**, and **6** (Figures 1 and 2), can be assigned from a revised version of

the computer energy profile for the model system (Figure 3). The introduction of a small model for thiourea yields the three structures shown in Figure 7, in which **mIB1**, **mIB2**, and **mIB3** correspond to the ESI-MS intermediates **6**, **5**, and **4**, respectively.

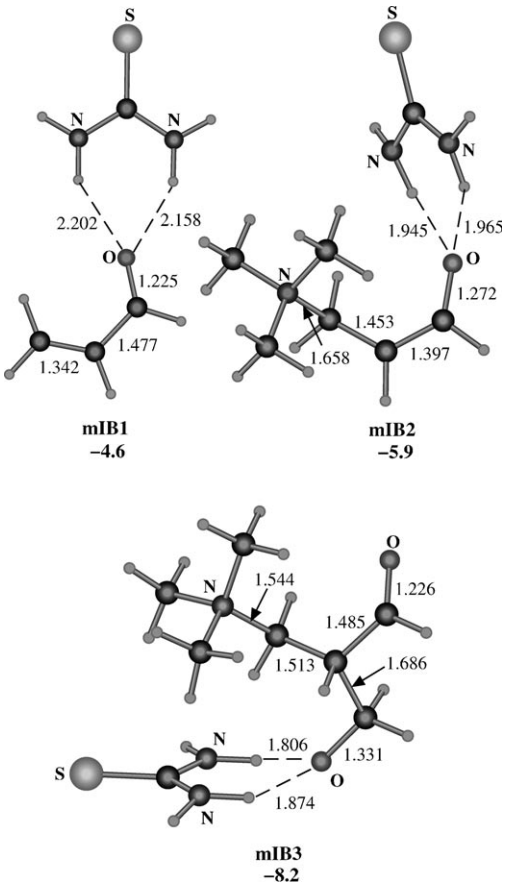
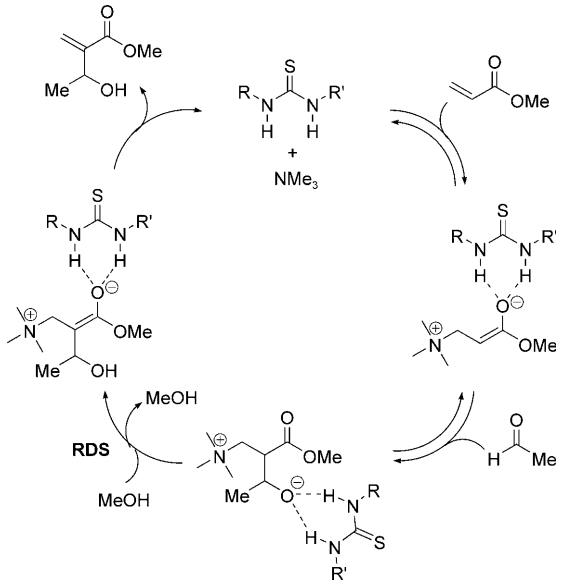


Figure 7. Geometries of selected structures analogous to the intermediates proposed from ESI-MS analysis. Energies are given in bold in kcal mol^{-1} and distances are given in Å.

The theoretical results confirmed the validity of the generally accepted MBH mechanism with four steps (Michael addition, aldol addition, proton transfer, and elimination), also in the presence of thiourea. Furthermore, the proton-transfer step is the RDS, in agreement with recent research in the area. In the mechanism computed as most favorable, however, the thiourea does not act as a proton shuttle; this role is reserved for methanol or some other protic solvent (Scheme 4). The thiourea stays anchored on the MBH adduct acting as a Brønsted acid that stabilizes the concentration of negative charge at the oxygen atom. The ability of thiourea to act as a bidentate ligand and to make two hydrogen bonds contributes critically to the decrease in the barrier of the RDS, thus accelerating the MBH reaction.



Scheme 4. Catalytic cycle for the MBH reaction in presence of thiourea with methanol as solvent.

Conclusion

The joint use of ESI-MS(/MS) and DFT techniques has characterized the role for thiourea as an organocatalyst in the MBH reaction. It forms bidentate hydrogen bonds throughout the whole catalytic cycle and, contrary to what appears to be its mostly likely role, the thiourea does not act as a proton shuttle in the rate-limiting proton-transfer step. Instead, the thiourea acts as a Brønsted acid stabilizing the basic oxygen center being formed in the transition state. The data collected in this paper could probably also be applied for other ureas, commonly used on the catalysis of the Morita–Baylis–Hillman reation

Experimental Section

ESI mass and tandem mass spectra in the positive ion mode were acquired by using a Micromass (Manchester, UK) QTof instrument of ESI-QTof configuration with approximately 5000 mass resolution and less than 50 ppm mass accuracy in the TOF mass analyzer. The following typical operating conditions were used: 4 kV capillary voltage, 40 V cone voltage, and a desolvation gas temperature of 100 °C. ESI-MS(/MS) data were collected after 5 eV CID of selected ions with argon. Selection was performed by Q1 using a unitary m/z window and collisions were performed in the hexapole collision cell followed by m/z measurements of product ions by the TOF analyzer.

Calculations were performed at the DFT level by means of the Becke3-LYP[37,38,39] functional, with a hybrid Becke3 exchange functional and a Lee–Yang–Parr correlation functional[38,39] using the Gaussian suite of programs.[41] The 6-31+G(d) basis set was used for all atoms.[42] The structures of the reactants, intermediates, transition states, and products were fully optimized without any symmetry restriction. Only the favored conformations are presented and these are in good agreement with previous computational studies.[27,28] Transition states were identified by having one negative eigenvalue in the Hessian matrix. Methanol solvation effects (dielectric constant of 32.63) were introduced by single-point

PCM[43] calculations on gas-phase optimized geometries. The problems for the accurate introduction of entropic effects through the statistical thermodynamics approaches commonly used together with DFT calculations are well documented, even in the case of MBH reactions.[28] Most of the results presented are therefore in terms of potential energies unless otherwise stated. When free energy corrections were considered, the conditions were 298.15 K and 1 atm.

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