Morita-Baylis-Hillman Reaction. A Caveat

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Abstract: It is an oversight to consider that a Lewis base such as a trialkylamine adds to an activated alkene in conjugate fashion to generate an enolate as a 1,5-zwitterion, which next reacts in aldol fashion with an electrophile such as an aldehyde to move on further through other events to the Morita-Baylis-Hillman product. It is demonstrated from computational investigations that the union of trialkylamine and activated alkene leads possibly to a very low level charge-transfer entity, wherein the π -electron density of the alkene has little perturbed to call it an enolate in the conventional sense. It is suggested to consider the aldol reaction as the first step of the Morita-Baylis-Hillman reaction and arrive at the corresponding transition state structure directly from the three entities.

KEYWORDS: Morita-Baylis-Hillman reaction, trialkylamine, conjugate addition, enolate, aldol reaction

Introduction

Morita-Baylis-Hillman (MBH) reaction is an atom-economic green reaction that allows coupling of an activated alkene with an electrophile to result in a multi-functional product for exploitation by synthetic organic chemists.¹⁻³ Reaction is generally carried out simply by mixing the activated alkene and electrophile in the presence of a trialkylamine as catalyst, with or without a solvent, at low temperatures. The ease of conducting the reaction and also the great utility of the resultant product has prompted extensive exploration over the past four decades to expand the substrate and catalyst scope.⁴⁻¹² The asymmetric version of the reaction has been developed by using either specifically designed catalysts or chiral electrophiles for the aldol process.¹³⁻¹⁵ Efforts have also been expended to understand the mechanism of the reaction to aid the design of asymmetric versions for greater synthetic exploitation.¹⁶⁻²²

It has been argued that the MBH reaction is initiated by the conjugate addition of a nucleophilic amine to an activated alkene and an enolate is formed. This enolate then enters aldol reaction with an electrophile such as an aldehyde to generate an alcoholate, which undergoes proton-transfer and E1cB reactions, in that order, to yield the product along with

release of the amine. The proton-transfer has lately been demonstrated to take place via a lower energy seven-membered transition state structure as shown in [Scheme 1](#) by taking 2-cyclopentenone **1** as the activated alkene, acetaldehyde **4** as the electrophilic aldol partner and trimethylamine **2** as the nucleophilic amine catalyst.^{21, 22} The ammonium ylide **6** formed from proton-transfer undergoes Hofmann elimination to form the product **7** and the catalyst is released to re-enter the reaction cycle.

Scheme 1. MBH reaction involving proton-transfer via a seven-membered transition state structure. **TS1** = TS structure for conjugate addition of Me₃N to 2-cyclopentenone, **TS2** = TS structure for aldol reaction, **TS3** = TS structure for proton transfer, **TS4** = TS structure for Hofmann elimination

Computational methods: All the geometry optimizations and TS structure searches were carried out using the global hybrid meta-GGA M06-2X density functional and 6-311++G(d,p) basis set at 298.15 K under 1.0 atm pressure.²³ The optimized structures were verified as minima or first order saddle points on their potential energy surfaces by harmonic vibrational frequency analysis. The solvent effects on the reaction profile were estimated using the Conductor Polarized Continuum Model (CPCM).^{24, 25} All the energies reported herein are Gibbs free energies (sum of electronic and thermal free energies) expressed in kcal/mol. Calculations were carried out using the Gaussian 16 suite of programs.²⁶

Results and Discussion

During the course of our investigations of the mechanism of MBH reaction, we noticed that the new carbon-nitrogen bond in the projected enolate was excessively long and there was hardly any perturbation in the electron density of the enone function, whether the reaction

was studied in the gas phase or under solvent effects for the subtle change in $\pi_{C=C}$ bond length. The lengths of $\pi_{C=C}$ bonds in 2-cyclopentenone, the corresponding $\pi_{C=C}$ bonds and also the new σ_{C-N} bonds in the apparent enolates generated from the reactions of 2-cyclopentenone with Me_3N , DABCO and Me_2NOH in the gas phase and under different solvent effects are collected in Table 1. We have recently reported Me_2NOH as a superior catalyst for MBH reaction and implicated the α -effect of oxygen on the nitrogen as the cause for its improved nucleophilicity.²⁷

Table 1. The σ_{C-N} and $\pi_{C=C}$ distances (Å) in the enolate versus $\pi_{C=C}$ in enone in 2-cyclopentenone in reactions with Me_3N , DABCO and Me_2NOH in the gas phase and also under solvent effects

Phase	Catalyst	$\pi_{C=C}$ (enone)	$\pi_{C=C}$ (enolate)	σ_{C-N} (enolate)
Gas	Me_3N	1.3339	1.3357	3.0611
CH_3CN	Me_3N	1.3369	1.3386	3.0452
DMSO	Me_3N	1.3370	1.3387	3.0448
THF	Me_3N	1.3365	1.3382	3.0509
DCM	Me_3N	1.3366	1.3383	3.0494
gas	DABCO	1.3339	1.3358	3.0350
DMSO	DABCO	1.3370	1.3388	3.0333
gas	Me_2NOH	1.3339	1.3356	3.0694
DMSO	Me_2NOH	1.3370	1.3382	3.1165
DCM	Me_2NOH	1.3366	1.3378	3.1318

Figure 1. The computed enolate formed from the conjugate addition of Me_3N to 2-cyclopentenone in the gas phase (the $\pi_{C=C}$ bond length in 2-cyclopentenone alone is 1.3339 Å)

It can be seen from the data in the table that the σ_{C-N} bond distances are always too long and the $\pi_{C=C}$ bond in the enolate differs little from the corresponding $\pi_{C=C}$ bond in 2-cyclopentenone. Due to this little change in $\pi_{C=C}$ bond length before and after the reaction with amine, the perturbation in enone electron density is little to qualify for what we typically consider enolate. The bond distances in the computed enolate for the reaction of Me_3N with 2-cyclopentenone are given in [Figure 1](#) to illustrate the point.

The situation with acyclic activated alkenes is similar to that of the cyclic activated alkene above. The relevant data from the reactions of methyl acrylate and acrylonitrile with catalysts such as DABCO and Me_3N are collected in [Table 2](#). The σ_{C-N} distances are too long and $\pi_{C=C}$ distances in the enolates are hardly any different from those in the activated alkenes. The change in delocalization of the enone electron density in the proposed enolate being little, its formation could be arguably doubted.

Table 2. The σ_{C-N} and $\pi_{C=C}$ distances (Å) in the enolate versus $\pi_{C=C}$ in select activated acyclic alkenes in reactions with DABCO and Me_3N in the gas phase and also under solvent effects

Alkene	Phase	Catalyst	$\pi_{C=C}$ (alkene)	$\pi_{C=C}$ (enolate)	σ_{C-N} (enolate)
methyl acrylate	Gas	DABCO	1.3279	1.3295	2.9874
methyl acrylate	DMSO	DABCO	1.3289	1.3300	3.0942
methyl acrylate	CH₃CN	DABCO	1.3289	1.3300	3.0930
methyl acrylate	DCM	DABCO	1.3288	1.3299	3.0574
methyl acrylate	THF	DABCO	1.3288	1.3299	3.0525
acrylonitrile	Gas	Me_3N	1.3299	1.3316	2.9519
acrylonitrile	DMSO	Me_3N	1.3308	1.3325	2.9625

Consequently, we consider it appropriate to involve the amine catalyst, activated alkene and electrophile for the crucial aldol reaction in one go rather than the customary step-wise enolate formation and then aldol reaction. To test this hypothesis, we computed this transition state structure from Me_3N , 2-cyclopentenone and acetaldehyde in the gas phase and discovered it to be 47.5 kcal/mol higher than the sum of the ground state energies of the three reacting entities. This activation energy is 5.6 kcal/mol higher than the one computed from the typical enolate. The other features of the reaction mechanism being the same as discussed elsewhere,²¹ the noted raise in activation energy of the aldol reaction truly makes

it the rate-controlling step under the normal catalytic conditions. The computed transition state structure is shown in [Figure 2](#).

Figure 2. The transition state structure for aldol reaction constructed from Me₃N, 2-cyclopentenone and CH₃CHO in the gas phase. Me₃N was placed 1.60 Å away from the olefinic carbon in order to allow sufficient perturbation of the π -electron density in the enone.

Conclusion

The long-held notion of enolate formation from the conjugate addition of a nucleophilic catalyst (usually a trialkylamine) to an activated alkene as the first step of the MBH reaction is untenable because computations in the gas phase and also under solvent effects reveal little perturbation in the π -electron density of the alkene for little change in the length of its $\pi_{C=C}$ bond. It is advisable to directly approach the transition state structure for aldol reaction by engaging the catalyst, activated alkene and electrophile in one go.

The resultant raise in the activation energy over the follow up reactions in the gas phase as well as under solvent effects truly makes the aldol reaction rate-controlling.²⁸

ASSOCIATED CONTENT

Supporting Information

Supporting Information (SI) available: Cartesian coordinates of the optimized ground state structures, TS structures and Gibbs free energies

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