Hydroxylamine as a superior organocatalyst for Morita-Baylis-Hillman reaction

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Abstract. Computational investigations indicate that the use of *N,N*-dimethylhydroxylamine as organocatalyst enhances the rate of Morita-Baylis-Hillman reaction by lowering the activation energy of the rate-controlling aldol step. The rate enhancement is understood to originate from the α -effect of oxygen on nitrogen in hydroxylamine, which enhances the nucleophilicity of the nitrogen and results in its more effective conjugate addition to the enone to form an advanced and, thus, reactive enolate to participate in the aldol process. The activation energy of the aldol reaction is therefore reduced.

Keywords. Morita-Baylis-Hilman reaction, *N,N*-dimethylhydroxylamine, α -effect, 2-cyclopentenone, acetaldehyde, rate-acceleration, solvent effects

Introduction

Morita-Baylis-Hillman (MBH) reaction is one of the finest examples of versatile atom-economic carbon-carbon bond-forming reactions in which an activated olefin reacts with a carbonyl species under catalysis by generally a nucleophilic tertiary amine to form an α -hydroxyalkyl activated olefin, which serves as a very useful multifunctional building block in organic synthesis.¹ The synthetic application of this reaction due to the multi-functional nature of the product is so very significant that several reports on expanding the substrate scope, catalysis by different nucleophiles in efforts to obtain high yields in less time, and development of the asymmetric version have prominently appeared in the literature.²

The reaction mechanism was long understood to involve proton transfer from the α -carbon of the activated olefin to the alcoholate formed from aldol reaction through a four-membered transition state (TS) followed by E1cB event to generate the product as shown in [Scheme 1](#).³ This mechanism has lately been revised and computationally shown to follow the lower energy pathway sketched in [Scheme 2](#).⁴ In this pathway, proton is transferred from an alkyl group of the ammonium ion to the

alcoholate through a seven-membered TS structure and the resultant undergoes syn elimination in Hofmann manner to form the MBH product.

Scheme 1. The previously accepted pathway for the Me₃N-catalysed MBH reaction of 2-cyclopentenone with CH₃CHO involving proton transfer through a four-membered TS structure (5 → 6a)

Scheme 2. The new pathway for the Me₃N-catalysed MBH reaction of 2-cyclopentenone with CH₃CHO involving proton transfer through a seven-membered TS structure. **TS1** = TS for conjugate addition of Me₃N to cyclopentenone, **TS2** = TS for aldol reaction, **TS3** = TS for proton transfer through seven-membered ring, **TS4** = TS for Hofmann elimination

We reasoned that the use of hydroxylamine in place of trialkylamine was likely to enhance the reaction rate for the enhanced nucleophilicity of nitrogen due to the α -effect⁵ of oxygen. Thus, the more effective conjugate addition of hydroxylamine to the activated alkene will result in a relatively more advanced and, hence, more reactive enolate to subsequently enter the rate-controlling^{3, 6, 7} aldol step. The activation energy of the aldol reaction may, therefore, diminish to result in a faster reaction. A careful search of the literature revealed that hydroxylamine has neither been used nor suggested before this report. Herein, we present the results of our study by taking 2-cyclopentenone as the

activated alkene and CH_3CHO as electrophile for the aldol reaction under catalysis by *N,N*-dimethylhydroxylamine (Me_2NOH) in following the route given in [Scheme 3](#).

Scheme 3. Me_2NOH -catalysed MBH reaction of 2-cyclopentenone with CH_3CHO . **2'** = Me_2NOH , **3'** = enolate formed from conjugate addition of Me_2NOH to 2-cyclopentenone, **5'** = aldol product, **TS1'** = TS structure for conjugate addition of Me_2NOH to 2-cyclopentenone, **TS2'** = TS structure for aldol reaction, **TS3'** = TS structure for proton transfer, **TS4'** = TS structure for *N*-oxide 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.⁸ 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 of CH_2Cl_2 and DMSO on the reaction profile were estimated using the Conductor Polarized Continuum Model (CPCM).⁹ 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.¹⁰

Results and Discussion

The profile of the MBH reaction of 2-cyclopentenone with CH_3CHO under Me_3N -catalysis is shown in [Figure 1](#) and that of Me_2NOH -catalysis in [Figure 2](#) for comparison. It could be easily inferred that the activation energy of the rate-controlling aldol step is lowered from 41.9 kcal/mol under Me_3N -catalysis to 32.6 kcal/mol under Me_2NOH -catalysis. This reduction in activation energy, 9.3 kcal/mol, is substantial to significantly facilitate the reaction. The activation energy of the conjugate addition step is also lowered by 5.1 kcal/mol, which must be due to the enhanced nucleophilicity of the nitrogen under the α -effect of oxygen in Me_2NOH , the cornerstone for the present investigation.

The reaction profile under Me_2NOH -catalysis is distinct from the one under Me_3N -catalysis in yet another significant aspect. The product **6b'** formed from proton transfer is 21.2 kcal/mol more stable than the aldol product **5'**. This is unlike the Me_3N -catalysis, wherein the product **6b** is higher on the energy scale than the corresponding aldol product **5**. Such a steep drop in energy from **5'** to **6b'** under

Me₂NOH-catalysis must thermodynamically push the reaction forward to allow early completion. From **TS2'** onward, every reaction is a low energy event. The *N*-oxide elimination is rapid under the reaction conditions for the low energy requirement in comparison to the aldol event.

Figure 1. Profile of the Me₃N-catalysed MBH reaction of 2-cyclopentenone with CH₃CHO in the gas phase

Figure 2. Profile of the Me₂NOH-catalysed MBH reaction of 2-cyclopentenone with CH₃CHO in the gas phase

The drop in energy over the transformation **5'** → **6b'** is likely due to the greater stability of the resultant *N*-oxide in comparison to the carbon-nitrogen ylide **6** formed under Me₃N-catalysis.

An often used organocatalyst for the MBH reaction is 1,8-diazabicyclo[2.2.2]octane (DABCO),¹¹ which has been recognised as more effective than many other tertiary amines. How does Me₂NOH fare against DABCO? This question arises naturally and must be addressed. The profile of the reaction under DABCO-catalysis is shown in Figure 3. Comparison of the energies of activation of the rate-controlling aldol reaction reveals that the reaction under Me₂NOH-catalysis is 7.2 kcal/mol more facile than the reaction under DABCO-catalysis. The conjugate addition of Me₂NOH to cyclopentenone is also more facile than the addition of DABCO by 3.2 kcal/mol. These observations, taken with the steep drop in energy after proton transfer, Me₂NOH appears to have the potential of being a more effective catalyst than DABCO also.

Figure 3. Profile of the DABCO-catalysed MBH reaction of 2-cyclopentenone with CH₃CHO in the gas phase. **D** = DABCO, **TS1''** = TS structure for conjugate addition of DABCO to 2-cyclopentenone, **3''** = enolate formed from conjugate addition, **TS2''** = TS structure for aldol reaction, **5''** = product of aldol reaction, **TS3''** = TS structure for proton transfer, **6b''** = ylide formed after proton transfer, **TS4''** = TS structure for Hofmann elimination

The above discussion is applicable to gas phase reactions or reactions under solvent-less conditions, which, at times, have been found to be faster and better yielding than those in solvents.¹² Since the MBH reactions are conducted in solvents as well, we chose to study the Me₂NOH-catalysed reaction of 2-cyclopentenone with CH₃CHO under the solvents effects of dimethyl sulfoxide (DMSO) and CH₂Cl₂ to assess whether there was any noticeable change in the reaction profile other than the generally observed facilitation of the aldol reaction.⁷ The reaction profile under the influence of DMSO, Figure 4, is largely similar to that under CH₂Cl₂, Figure 5. The *N*-oxide formed on proton transfer is sufficiently stable to thermodynamically assist the reaction go forward. As expected, the activation energy of the

aldol reaction in both instances is lower than in the gas phase, and this may be due to the positive effect of the solvent.

Figure 4. Profile of the Me₂NOH-catalysed MBH reaction of 2-cyclopentenone with CH₃CHO under the solvent effects of DMSO.

Figure 5. Profile of the Me₂NOH-catalysed MBH reaction of 2-cyclopentenone with CH₃CHO under the solvent effects of CH₂Cl₂

The energy level of the TS for proton transfer is shown to be the same as the energy level of the aldol product in Figures 1–5. Our attempts at searching this TS structure failed as it always collapsed to the aldol product with vibration in other region of the molecule. We believe that the proton transfer is barrier-less and concurrent with the aldol reaction.

Conclusion

We have shown from computational investigations in the gas phase and also under the solvent effects of DMSO and CH₂Cl₂ that *N,N*-dialkylhydroxylamines, such as Me₂NOH, have potential to act as better catalysts than the often used simple tertiary amines, including DABCO, to promote the Morita-Baylis-Hillman reaction. The α -effect of oxygen raises the nucleophilicity of nitrogen, which brings about its relatively more facile conjugate addition to the activated alkene and result in an advanced and, hence,

more reactive enolate species for the subsequent rate-controlling aldol reaction. The high stability of the *N*-oxide, formed on proton transfer, provides additional thermodynamic fillip to the reaction for early completion.

ASSOCIATED CONTENT

Supporting Information

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

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Computational investigation reveals that the enhanced nucleophilicity of nitrogen due to the α -effect of oxygen in Me_2NOH may significantly raise the facility of Morita-Baylis-Hillman reaction.