DFT Study of the Asymmetric Nitroaldol (Henry) Reaction Catalyzed by a Dinuclear Zn Complex

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Abstract: We report the mechanism of asymmetric nitroaldol (Henry) reaction catalyzed by a dinuclear Zn complex using density functional theory. The experimentally proposed catalytic cycle is validated, in which the first step is the deprotonation of nitromethane by the ethyl anion of the catalyst, subsequently a C—C bond formation step, and then the protonation of the resulting alkoxide. Three mechanistic scenarios (differing in binding modes) have been considered for the C—C bond formation step. The origin of the enantioselectivity is discussed. Our calculations supported that the S configurations are the major products, which is in agreement with the experimental observations.


Key words: nitroaldol (Henry) reaction; density functional theory; enantioselectivity; dinuclear Zn catalyst

Introduction

The Henry or nitroaldol reaction, between carbonyl compounds and nitroalkanes, constitutes a very important synthetic method for the construction of carbon–carbon bonds in organic chemistry. The resulting β-nitroaldols, especially in an optically active form, are useful precursors to a variety of valuable functionalized structural motifs, such as β-amino alcohols, z-hydroxy carboxylic acids, etc. These derivatives are common building blocks presented in biologically active nature products and pharmaceuticals. Consequently, considerable efforts have been made toward the development of efficient asymmetric catalysts for this kind of reactions with impressive breakthrough achieved over the last two decades.

With the presence of a number of environmentally friendly organocatalysts for the nitroaldol reaction, many bifunctional metal/chiral ligand complexes have also been described with high efficiency, including lanthanoid, Zn, Cu, and Co complexes. Apparent, zinc-based catalysts are especially interesting because they parallel class II aldolase enzymes in the light of relying on zinc. Several efficient mononuclear zinc catalysts with different chiral ligands have been developed for this reaction, such as chiral amino alcohol, bisoxazolidine, and ferrocenyl-substituted aziridinylmethanol. In addition, some other mononuclear Zn-based catalysts have also been reported, however, with lower enantiomeric excesses. Beside these mononuclear zinc catalysts, Trost and Yeh reported the first asymmetric dinuclear zinc complexes with a chiral semi-aza crown ligands (see Scheme 1), which were found to be efficient catalysts for inducing unparalleled enantioselectivity.

The dinuclear zinc catalyst designed by Trost also led to a number of other efficient, catalytic, enantioselective transformations, including aldol reactions, Mannich reactions, Michael addition, alknylations of aldehydes, desymmetrizations of meso 1,3-diols, and Friedel-Crafts alkylations. The catalyst has also been successfully applied in natural product synthesis and other important chemical reactions. For nitroaldol reactions, Trost proposed a possible catalytic cycle, as depicted in Scheme 2. The initial step of the reaction is deprotonation of nitromethane by the ethyl anion attached to one of the zinc ions in the catalyst, resulting in the formation of a zinc nitronate intermediate and 1 equiv of ethane. Coordinations of the aldehyde to the other zinc ion undergo the C—C bond formation step. Finally, the association of nitromethane followed by a proton transfer to the oxygen anion produced in the previous step gives the product and restart the catalytic cycle.

A number of zinc-catalyzed reactions have been investigated by means of quantum chemical methods. However, accord-

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ing to our knowledge, little theoretical attention has been paid for this dinuclear zinc catalyst. Despite the great achievements in the experimental area on the study of the reaction, insight into the energetic, the detailed mechanism and the origin of the enantioselectivity of this catalytic reaction are still lacking. These have prompted our theoretical investigation for the mechanism of the reaction catalyzed by this binuclear Zn catalyst. In our present study, we performed the density functional calculations with the well-established B3LYP functional, and chose the benzaldehyde and nitromethane as substrates, yielding 2-nitro-1-phenylethanol (see Scheme 3). Our calculations are relevant to further understanding of many other reactions catalyzed by this dinuclear Zn catalyst.

**Computational Details**

All calculations were performed at the density functional theory (DFT) level with the B3LYP functional as implemented in the Gaussian 03 package. For the geometry optimizations, the 6-31G(d,p) basis sets were used for the C, N, O, and H elements and the SDD pseudopotential for Zn. Based on the optimized geometries, more accurate energies were obtained by performing single-point calculations with the 6-311++G(2d,2p) basis sets for all elements. All geometries were optimized in vacuo. To estimate the energetic effects of the THF (ε = 7.58) environment, solvation effects were calculated at the same theory level as the optimizations by performing single-point calculations on the optimized structures using the conductor-like polarizable continuum model (CPCM) method. Frequency calculations were performed at the same theory level as the optimizations to obtain zero-point energies (ZPE) and to confirm the nature of all stationary points. The latter implied no negative eigenvalues for minima and only one negative eigenvalue for transition states. The energies reported herein were corrected for both solvation and zero-point vibrational effects.

To compare the results obtained with the B3LYP method, we also used a new hybrid density functional BB1K that has recently been shown to produce results for accurate potential energy surface (PES) calculation of reactions. Based on the optimized geometries with B3LYP for some important configurations, we carried out single-point calculations by BB1K, and the 6-31G(d,p) basis sets were used for the C, N, O, and H elements and the SDD pseudopotential for Zn. Additionally, single-point calculations with the 6-311++G(2d,2p) basis sets for all elements were also carried out to get more accurate energies. All results have been corrected for both solvation in THF and zero-point vibrational effects.

**Results and Discussion**

Based on our calculations, it was found that the catalytic reaction involves three chemical steps: (1) deprotonation of nitrome-
The overall reaction between nitromethide and benzaldehyde yielding nitroalkoxide (Re, TS, and Pr in SI) was calculated to

Scheme 3. The Henry reaction between benzaldehyde and nitromethane discussed in this paper.

thane, (2) C–C bond formation, and (3) proton transfer and regeneration of the reactive species.

**Step 1: Deprotonation**

The first step is the deprotonation of nitromethane by the ethyl anion coordinated to Zn1 in Com1 (Com1A and Com1B, see Supporting Information) with the formation of Int1 and ethane. Because of the coordination of nitromethane to Zn2, the energy of Com1A is 9.7 kcal/mol lower than that of isolated reactants in the gas phase and 5.7 kcal/mol in the THF. Two plausible mechanistic pathways have been considered, one is with the retention of the carbon configuration, marked as 1A, whereas the second is with the inversion of the carbon configuration, marked as 1B. The corresponding transition states are labeled as TS1A and TS1B (Fig. 1) with the barriers to be 20.6 (22.6) kcal/mol (energetic pathways have been considered, one is with the retention of the carbon configuration, marked as 1A, whereas the second is with the inversion of the carbon configuration, marked as 1B. The corresponding transition states are labeled as TS1A and TS1B). The C–H distances in TS1A are 1.967 Å and 2.011 Å, respectively. In addition, the corresponding dihedral angles of O31-C30-C29-N27 in both transition states (Fig. 4) are 27.2° and −9.3°, respectively. Downhill from the transition states, the nitroalkoxide catalyst complex (Int3, see SI) is formed, and the energies of Int3SA and Int3A are 5.4 and 4.3 kcal/mol relative to Int2SA and Int2A, respectively. During the step of C–C bond formation, the negative charge is transferred from the nitronate oxygen to benzaldehyde oxygen. In Int3A, the newly formed oxyanion is stabilized by Zn1 with the corresponding distance of 1.910 Å. But the oxyanion is coordinated to both Zn ions in Int3RA, with the Zn1-O31 and Zn2-O31 distances of 1.968 and 2.052 Å, respectively. Both Zn ions provide electrostatic stabilization on both the transition states and intermediates, thereby lowering the barrier for the C–C bond formation.

In pathway B, the nitrate is coordinated to Zn2 with both oxygen atoms (Fig. 3). The calculated Zn–O distances are 2.194 and 2.098 Å in Int2SB and 2.195 and 2.094 Å in Int2RB, respectively. The barriers for the C–C bond formation starting from these structures are 6.3 (5.1) kcal/mol for the S-product (Int3SB) and 9.0 (6.6) kcal/mol for the R-product (Int3RB). The key C–C distances are 2.132 Å and 2.053 Å in TS2SB and TS2RA (Fig. 4), respectively. Additionally, the dihedral angles of O31-C30-C29-N27 in TS2SB and TS2RA are 40.5° and 34.7°, respectively. The energy of the Int3SB lies at −4.2 kcal/mol relative to Int2SB, whereas that of Int3RB is 8.6 kcal/mol higher than Int2RB. It can be seen from Figure 5 that the formation of R-product through pathway B is not favorable since the barrier for the reverse step is just 0.4 kcal/mol. The transfer of Int2SB to Int3RB or Int3RB should require at least several kcal/mol, indicating that the formation of R-product through pathway B is not competitive with pathway A, although TS2RB is only 0.2 kcal/mol lower than TS2RA.

Based on our calculations, in pathway B, an oxygen atom of the nitrate is coordinated to both Zn ions (Fig. 3), with the Zn1-O and Zn2-O distances of 2.163 and 1.990 Å in Int2SB, 2.132 and 1.987 Å in Int2RB. The transition states of C–C bond formation from Int2SB and Int2RB (TS2SB and TS2RB, see Fig. 4) are located with the C–C bond distance of 2.255 and 2.258 Å, with the energetic barriers of 7.3 (7.2) and 4.5 (5.2) kcal/mol, respectively. Furthermore, the dihedral angle of O31-C30-C29-N27 in the TS structures was calculated as 69.1° and 63.3°. The reaction of this pathway for the formation of S and R products (Int3SC and Int3RC) is exothermic by 7.2 and 7.7 kcal/mol, respectively. In both Int3SC and Int3RC, the nitroalkoxide oxygen anion is bridging the two Zn ions (see SI).

In the three pathways discussed above, according to their relative reaction barriers, the pathway A is energetically the most favorable (see Fig. 5), whereas the pathway B is next. There could be a couple of reasons. One reason for the order could be that the Int2SA and Int2RA adopt an energetically more feasible conformation, evidenced by the relative energies of six reactants in this step (see Fig. 5). Another reason might be the stronger interactions between Zn1 and n electrons of O31. At TS2, O31 changes from sp2 hybridization in Int2 to partially sp2 hybridization. The angle of C30-O31-Zn1 (labeled as z in Fig. 4) is 123.0° in TS2RA. However, the angles are 129.4° in TS2SB and 135.7° in TS2SC.

The overall reaction between nitromethide and benzaldehyde.
be endothermic by 7.3 (7.7) kcal/mol, indicating that the dinuclear zinc center provides more stabilization on the unprotonated product by as much as 8.3 kcal/mol in THF. However, the barrier for the catalytic C–C bond formation does not change much compared with uncatalyzed one [8.6 (8.4) kcal/mol]. Our results are different from previous calculations on reaction between nitromethide and formaldehyde. The recent results show that the barrier and the reaction energy are 3.2 and −1.4 kcal/mol at the CCSD(T)/aug-cc-pVDZ//MP2/6-31+G(d) level in gas phase. The main reason is due to the stronger hydrogen

**Figure 1.** Optimized structures of the transition states for the proton transfer from nitromethane to the ethyl anion in two pathways (distances in Å).

**Figure 2.** Calculated relative energetic (kcal/mol) profile (including solvation) for the deprotonation step.

**Figure 3.** The six segments of the intermediates corresponding to three reaction pathways (distances in Å).
bond between nitromethide and benzaldehyde comparing with that between nitromethide and formaldehyde, which stabilizes the reactant too much.

**Enantioselectivity**

It was found by Trost that this dinuclear Zn catalyst could catalyze many reactions with high efficiency and enantioselectivity. The reaction of benzaldehyde and nitromethane catalyzed by 5 mol% catalyst proceeds with considerable asymmetric induction (91% ee).\(^8\) However, the reason for the high enantioselectivity in the reactions was not well elucidated so far. The phenyl rings of the diphenylcarbinol moiety were suggested to be involved in chiral recognition.\(^22\)

In the present study, we have optimized the transition states leading to both enantiomers for all three pathways. We first note that the TS with the lowest energy (TS\(_{2SA}\)) corresponds to S-product, in agreement with the experimental findings that the major enantiomer of nitroaldol is S-configuration.\(^8\) The energy difference between TS\(_{2SA}\) and TS\(_{2RA}\) is 5.0 (3.8) kcal/mol, which has a gap with the experimentally observed ee of 91%. However, with BB1K functional, the energy difference is 1.8 kcal/mol in THF. So the method may have deviations, but all these results suggested that our results are consistent with the experimental trend.

**Figure 4.** The geometries of optimized transition states for C—C bond formation through pathway A (TS\(_{2SA}\), TS\(_{2SA}\)), pathway B (TS\(_{2SB}\), TS\(_{2SB}\)) and pathway C (TS\(_{2SC}\), TS\(_{2SC}\)). Framed insets define the dihedral angles specified. Relative energies (kcal/mol) for the six transition states including solvation correction are given in the labels (gas phase values in parentheses) (distances in Å).
We noticed that the Mulliken charge of C29 and C30 in Int2SA is 2.0.143 and 2.0.236 e, respectively; whereas it is 2.0.125 and 2.0.223 e in Int2 RA. The stronger electrostatic interaction between C29 and C30 may result in lower barrier for the C-C bond formation. In addition, we noted that the α angles (C30-O31-Zn1) in TS2 with S configurations are all smaller than those with R configurations (see Fig. 4). The reason should be

![Graphical representation of molecular structures](image)

**Figure 5.** Calculated relative energetic (kcal/mol) profile for C-C bond formation (including solvation). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**Figure 6.** The structures of the transition states for S and R products through more favored pathway A with phenyl groups substituted by methyl groups and hydrogen atoms (Distances in Å). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

<table>
<thead>
<tr>
<th></th>
<th>Phenyl–</th>
<th>CH3–</th>
<th>H–</th>
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<tr>
<td>Int2SA</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>TS2SA</td>
<td>9.1 (9.8)</td>
<td>11.0 (8.6)</td>
<td>11.1 (9.7)</td>
</tr>
<tr>
<td>Int3SA</td>
<td>5.4 (6.0)</td>
<td>7.4 (4.7)</td>
<td>7.2 (5.6)</td>
</tr>
<tr>
<td>Int2RA</td>
<td>0.8 (1.4)</td>
<td>2.7 (0.8)</td>
<td>0.4 (–0.3)</td>
</tr>
<tr>
<td>TS2RA</td>
<td>14.1 (13.6)</td>
<td>14.5 (11.4)</td>
<td>13.3 (11.1)</td>
</tr>
<tr>
<td>Int3RA</td>
<td>5.1 (2.2)</td>
<td>6.6 (1.0)</td>
<td>3.3 (–0.6)</td>
</tr>
</tbody>
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We noticed that the Mulliken charge of C29 and C30 in Int2SA is –0.143 and +0.236 e, respectively; whereas it is –0.125 and +0.223 e in Int2RA. The stronger electrostatic interaction between C29 and C30 may result in lower barrier for the C-C bond formation. In addition, we noted that the α angles (C30-O31-Zn1) in TS2 with S configurations are all smaller than those with R configurations (see Fig. 4). The reason should be
the steric repulsions between the phenyl ring of benzaldehyde and the carbinol oxygen coordinated to Zn1.

To clarify the role of the four phenyl rings in the catalyst, we have optimized the structures of the catalyst with phenyl groups replaced by methyl groups and hydrogen atoms. The structures of transition states (M-TS2_SA, M-TS2_RA, and H-TS2_SA, H-TS2_RA) are shown in Fig. 6, whereas the structures of all intermediates are depicted in SI. As expected, the overall geometries are quite similar to the ones with phenyl groups discussed above. However, the energy difference for the two TS leading to S and R products becomes 3.5 (2.8) kcal/mol for CH3-substituted catalyst, and 2.2 (1.4) kcal/mol for H-substituted catalyst (see Table 1). Comparing with the energy difference of 5.0 (3.8) kcal/mol in the phenyl-substituted catalyst, these results suggest that the larger the substitutes are, the better the enantioselectivity for this reaction is. That is to say, the phenyl rings play a key role in governing the enantioselectivity for this asymmetric reaction.

Step 3: Proton Transfer

Trost and Yeh proposed that formation of C—C bond would result in a nitroalkoxide, which can undergo protonation by a new nitromethane coordinated to Zn2. Such a proton transfer can generate a new reactive nitronate, and restart the catalytic cycle.

We found from our calculations that on the coordination of the other nitromethane, the S-complex (Int4S) is 1.6 kcal/mol higher than R-complex (Int4R). The optimized transition states for the proton transfer (TS3S and TS3R) are shown in Fig. 7. The barriers of the reactions are 4.6 (5.2) kcal/mol and 4.1 (5.1) kcal/mol relative to Int4S and Int4R, respectively (Fig. 8). In the TS3R, the transferred proton is sandwiched between the nitroalkoxide oxygen and the nitromethane carbon, with the O—C0 and C—C0 distance of 1.238 Å and 1.373 Å, respectively. The main part of the TS3R geometry is quite similar to that of TS3S, with the corresponding O—H and C—H distance of 1.238 Å and 1.373 Å, respectively. At the end, the products complexed with the catalyst (PrS and PrR, see SI) are formed, with a hydrogen bond between the nitronate oxygen and 2-nitro-1-phenylethanol. It was noted that an additional intermediate Int5S (see SI) lies between TS3R and PrS, with a hydrogen bond between the nitronate carbon and 2-nitro-1-phenylethanol. From Int5S to PrS, we find a new transition state which is named as TS4 (see SI). It corresponds to the formation of a new hydrogen bond. The energy barrier is only 0.2 kcal/mol (Fig. 8), which suggests that the transformation is very fast.
Because the catalytic cycle contains just step 2 and step 3, our calculations suggest that step 2 determines the reaction kinetics, which is consistent with experimental results for the main product is S-configuration.

Conclusions

In the present paper, we have investigated the reaction mechanism and the enantioselectivity of the reaction of benzaldehyde and nitromethane catalyzed by the dinuclear zinc complex 1. The potential-energy profiles were calculated by means of DFT methods. Our calculations strongly support the experimentally proposed catalytic cycle as shown in Scheme 2 (See Scheme 4 for the calculating steps and energetics of some steps and involved species). The detailed mechanisms for all three steps are discussed, especially the enantioselectivity determining C–C bond formation step.

For step 1, two plausible proton transfer channels involving the retention (I_A) and the inversion (I_B) of the configuration have been considered, with I_A slightly preferred. For the C–C bond formation step, three possible pathways (pathways A, B, C) have been found. Pathway A is energetically preferred over other two pathways. Both zinc ions are involved in stabilizing the negative charge in the transition states and intermediates. The enantioselectivity mainly comes from the steric repulsion between the benzaldehyde and the phenyls of the catalyst. The preferred S-product is in agreement with the experimental findings. In the following step, the proton transfer between the nitroalkoxide and a new nitromethane can generate the product nitroalcohol and a new reactive species ready for the next catalytic cycle. For the reaction cycle, the C–C bond formation step is rate limiting.

We can speculate that this dinuclear zinc complex may catalyze other transformations through similar mechanistic issues. Theoretical studies of other catalytic C–C bond formation reactions are in progress.

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