A Density Functional Theory Study of Novel Catalysts for the “Green” Synthesis of Aziridines

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Abstract: Density functional theory calculations were used to elucidate the mechanism of aziridination involving ethylene and model catalytic nitrenoids, Cl-M-NH-Cl (M = Ti – Zn). Using the BP86/CEP-31G(d) level of theory, the Gibbs free energy changes for each reaction step were calculated, and transition states were found for the proposed mechanisms. It was concluded that the metal plays a key role in determining the reaction pathway. The “late” 3d metals Zn and Cu undergo a two-step mechanism while the “middle” 3d metals (Ni, Co, Fe) undergo a three-step mechanism including an additional isomerization. Surprisingly, these middle 3d metals also exhibit two competitive pathways: the “imide” pathway and the “amide” pathway. Overall, this research suggests that the model catalysts are promising candidates for olefin aziridination under mild conditions and worthy of further investigation.

Introduction

Aziridines are the smallest nitrogen-containing heterocycles¹ and exhibit considerable ring strain, leading to their key reactive roles in the synthesis of larger, more complex molecules, such as anti-tumor agents. Additionally, they are a major part of several chemotherapeutic drugs by acting as alkylating agents through a process called bioreductive activation. In this process they serve as DNA cross-linking agents via nucleophilic ring-opening of the aziridine by purines or the DNA phosphate backbone, thus preventing the cell from reproducing. Aziridines can be used to treat several different types of cancers including leukemia,² lymphoma, Hodgkin disease, multiple myeloma, and sarcoma,³ as well as lung, breast, and ovary cancers.

Figure 1. a) General structure of the parent aziridine. b) Thiotepa, an example of a drug in the aziridine class

Aziridines are also involved in the synthesis of several classes of useful organic molecules including amines, amino acids, amino alcohols, and other derivatives, all of which have several applications in industry and medicine.¹ These versatile molecules are additionally used to set stereocenters in large molecules such as complex drugs, a procedure of high importance due to the poor performance and adverse effects different conformations of the same molecule may have. Thus, aziridines are especially necessary in order to synthesize vital drugs and functional groups that are used to treat various diseases through a more affordable, efficient, and environmentally friendly method.

Despite the prevalence of the aziridine motif in bioactive molecules and its obvious advantage over protected derivatives, there are few practical ways of synthesizing aziridines. Aziridines are currently synthesized in three main synthetic routes: 1) by addition of nitrenes or nitrenoids⁴ to the appropriate olefin, 2) by transfer of carbon to imines, and 3) by intramolecular cyclization.⁵ Traditionally, aziridines have been synthesized by the cyclization of amino alcohols through the Wenker synthesis,⁶ by the addition of carbenes to imines through the Jacobsen and Finney reaction,⁷ and by the addition of ylides to the appropriate ketone, aldehyde, imine, or enone through the Corey-Chaykovsky method,⁸ aza-Darzens reaction,⁹ *etc.* However, these reactions have several drawbacks in that they require harsh reaction conditions, require several steps, and lack stereoselectivity.¹⁰ In recent years, transition metal-catalyzed synthesis of aziridines using various nitrene and nitrenoid sources¹¹ has received growing research attention due to its increased stereoselectivity. Early on, Evans *et al.*¹² made an important discovery with the use of bis (oxazoline) copper (I) catalysts for the aziridination of alkenes. Later researchers followed, such as Che *et al.*,¹³ who reported a ruthenium catalyst used to mediate nitrene-transfer reactions, and Müller,¹⁴ who determined a Rh^{II} catalyst that

underwent a concerted mechanism during the transfer of the nitrenoid to the olefin. Sukbok *et al.* studied TRANSITION-METAL-CATALYZED (Rh(III), Ir(III), AND Cp*Ir(III)) DIRECT C–H AMINATION OF ORGANIC AZIDES RATHER THAN THE CONVENTIONAL C–N CROSS-COUPLED REACTIONS.^{15,16} Following this study, Musaev and Du Bois and their groups focused on experimental and computational studies of diruthenium catalysts for intramolecular allylic C–H amination proceeding through a hydrogen-atom abstraction/radical recombination.¹⁷⁻¹⁸ Further study by the Du Bois, Berry, and Musaev groups investigated dirhodium-catalyzed C–H amination and reported nitrene intermediates; interestingly, the mechanisms differed with the different spin states involved.¹⁹

Building on these studies, this research employed density functional theory to elucidate the mechanism of and assess the viability of the aziridination reaction involving ethylene and model metal-stabilized nitrene catalysts of the structure L-M-NH-X, in which M = Ti – Zn, L = X = Cl (L = supporting ligand and X = substituent.) These third row (3d) metals were chosen because they are “green” metals, meaning that they are both Earth-abundant and inexpensive, two important characteristics for sustainable catalysis. By substituting these different first-row transition metals, the effect of the metal on the reaction pathway was determined, the energetics of critical steps were delineated, and resulting trends were investigated. Computationally modeling the reaction allowed for study of highly reactive intermediates (which are difficult to study using experimental methods alone), the testing of diverse reaction variables such as substituting different metals, and the determination of possible reaction mechanisms before conducting experimental studies.

Computational Methods

All density functional theory computations were conducted using the Gaussian 09 package.²⁰ Past studies and computational calibrations suggested that the BP86/CEP-31G(d) level of theory provided results most consistent to the more computationally expensive MP2 and CCSD(T) calculations.²¹ Consequently, all calculations were run using the BP86/CEP-31G(d) level of theory. The calculations included the parameters of being in the gas phase, and all free energies assumed 298.15 K and 1 atm. The free energies are reported in kcal mol⁻¹. All species were modeled as neutrals and each reasonable spin multiplicity was tested. According to calculated energy Hessians, optimized ground states contain no imaginary vibrational frequencies and optimized transition states contain exactly one imaginary vibrational frequency.

Results and Discussion

The transition metals modeled in this research can be divided into three distinct categories: (1) the “late” 3d metals zinc (Zn) and copper (Cu), (2) the “middle” 3d metals nickel (Ni), cobalt (Co), and iron (Fe), and (3) the “early” 3d metals manganese (Mn), chromium (Cr), vanadium (V) and titanium (Ti).

Late 3d Metals: Zinc (Zn) and Copper (Cu)

Late 3d metals have been previously researched and are currently used in aziridination catalysis.^{22,23} Hence, they are discussed only briefly below and are included for the sake of completeness. In general they are known to be more Lewis acidic than earlier transition metals assuming the same formal oxidation state. Simulations indicate that for the two late 3d metals, zinc and copper, the two-step reaction proceeds through an initial carbometalation and a subsequent ring closure step.

Scheme 1. BP86/CEP-31G(d) computed reaction mechanism for the late 3d metals Zn and Cu.

Zinc

The rate determining step (RDS) for the Zn catalyst model is the ring closure. The initial carbometalation has a $\Delta G^\ddagger$ of 6.8 kcal mol⁻¹ while the following step, ring closure, has a $\Delta G^\ddagger$ of 21.1 kcal mol⁻¹.

Copper

The rate determining step for the Cu catalyst is the carbometalation. This initial step has a $\Delta G^\ddagger$ value of 15.8 kcal mol⁻¹ while the ring closure has a $\Delta G^\ddagger$ value of 9.4 kcal mol⁻¹. Interestingly, these results suggest that even for these late 3d metals that the metal controls the rate determining step, as it is carbometalation for copper and ring closure for zinc. Furthermore, the copper catalyst exhibits a rate determining step barrier of 16 kcal mol⁻¹, lower than zinc's 21 kcal mol⁻¹ barrier.

Early 3d Metals: Titanium through Manganese

The early 3d metals (Ti through Mn) amides were also investigated for their reactions with ethylene, but are not discussed here. In general, calculations indicate that these metals typically have very high reductive elimination transition state barriers to form the C-N bond of aziridine. Moreover, the isomerization of the amide form of the catalyst model, Cl-M-N(H)Cl, to the imide form, Cl₂M(=NH), is extremely exergonic (*vide infra*) and has a small free energy barrier. As a result, our simulations suggest aziridination with these early metals is less promising than for the middle series metals, iron, cobalt and, especially, nickel. Hence, this paper will focus attention on these middle series metals.

Middle 3d Metals: Nickel (Ni), Cobalt (Co), and Iron (Fe)

The middle 3d metals Ni, Co, and Fe have been much less researched for aziridination as compared to copper and zinc catalysts. After running exploratory calculations on these metals it was determined that the previously discussed pathways for Cu and Zn did not correspond with the calculated results of these middle series metals. Instead, the middle series metals proceeded through a three-step reaction mechanism consisting of an initial isomerization, followed by [2+2] addition, and reductive elimination. Furthermore, the aziridination mechanism follows two pathways: the “imide” pathway and the “amide” pathway. To clarify, imide and amide are two isomers of the same MCl₂NH molecular formula (**Figure 2**). There are two important chemical differences between the amide and imide isomers. First, the imide possesses a formal metal-nitrogen multiple bond, necessitating the

breaking of a π bond in order for a reaction with ethylene to occur. On the other hand, the amide possesses only a metal-nitrogen single bond; hence, it is necessary to break a stronger (in relation to the corresponding π bond) metal-nitrogen σ bond to react with ethylene. This suggests that the imide should be a much more reactive isomer if it indeed stable. Second, the two isomers differ in the oxidation state of the metal. In the case of the amide catalyst, the metal exhibits a formal

Figure 2. Structural representation of model **amide** (left) and model **imide** (right).

Scheme 2. The BP86/CEP-31G(d) computed reaction mechanism for the middle 3d metals Ni, Co and Fe.

oxidation state of +2, while in the case of the imide, the metal has a +4 oxidation state. Thus, the isomerization from amide to imide formally oxidizes the metal center.

The middle series 3d metals undergo two possible pathways: what is termed the “imide” pathway and the “amide” pathway (**Scheme 2**). The starting molecule is an amide in both cases. When following the imide pathway (the top pathway in the scheme), the amide first undergoes an isomerization in which the chlorine transfers from the nitrogen to the metal, thus producing the imide Cl₂M=NH. The imide then goes on to react with ethylene to form the imide-ethylene adduct. Next, the adduct undergoes a [2+2] addition in which the M=N double bond is added to the C=C bond of ethylene, forming the four-centered amide-C₂ intermediate. Thereafter, reductive elimination occurs, breaking both the metal-C bond and metal-N bond while creating the N-C bond of the aziridine. This leads to an aziridine adduct, also known as the successor complex, in which the products, metal dichloride and aziridine, are weakly associated by a dative bond. In the last step the two components dissociate to form the final products.

In the amide pathway, the starting amide catalyst reacts with the ethylene to form an amide-ethylene adduct before the former isomerizes. The precursor then undergoes a [2+2] addition to create the amine-C₂ intermediate (**Scheme 2**). This intermediate undergoes an isomerization that transfers the chlorine on the nitrogen to the metal, thus forming the amide-C₂ intermediate. The remainder of the amide pathway is identical to the imide pathway. Hence, the imide and amide pathways differ in the order of addition of ethylene and the migration of Cl from metal to nitrogen.

Nickel (Ni)

The rate-determining step for the Ni amide pathway (**Scheme 3**) is the [2+2] addition. The initial [2+2] addition has a $\Delta G^\ddagger$ value of 17.8

kcal mol⁻¹. The intermediate isomerization, has a $\Delta G^\ddagger$ value of 8.3 kcal mol⁻¹. The reductive elimination has a $\Delta G^\ddagger$ value of 6.4 kcal mol⁻¹. **Figure 3** (next page) depicts an optimized transition state for the

intermediate isomerization from the amine-C₂ to the amide-C₂ for nickel.

Scheme 3. Free energy diagram of the **amide** pathway for the **Ni catalyst**: BP86/CEP-31G(d) at STP. Calculated ΔG (kcal mol⁻¹) for each step in the mechanism are reported along with calculated $\Delta G^\ddagger$ values (kcal mol⁻¹).

Figure 3. The BP86/CEP-31G(d) optimized geometry (and schematic representation) of the intermediate isomerization transition state of the Ni to N chlorine transfer for the azametallacyclobutane intermediate.

Figure 4. The BP86/CEP-31G(d) optimized geometry (and schematic representation) of the isomerization transition state for Cl transfer for the isomerization between amide and imide is shown to the right. Bond lengths (Å) and angles (°) of interest are labeled.

Scheme 4. Free energy diagram of the **imide** pathway for the **Ni catalyst**: BP86/CEP-31G(d) at STP. Calculated ΔG (kcal mol⁻¹) for each step in the mechanism are reported along with calculated $\Delta G^\ddagger$ values (kcal mol⁻¹).

The rate-determining step for the Ni imide pathway (**Scheme 4**) is the amide to imide isomerization. This initial isomerization has a $\Delta G^\ddagger$ of 10.9 kcal mol⁻¹. The [2+2] addition has a $\Delta G^\ddagger$ of 3.0 kcal mol⁻¹. The reductive elimination has a $\Delta G^\ddagger$ of 6.4 kcal mol⁻¹. **Figure 4** shows an optimized transition state for the initial isomerization from the amide to the imide for nickel.

In the case of nickel, the imide pathway has a lower rate determining step of 10.9 kcal mol⁻¹ when compared to the 17.8 kcal mol⁻¹ barrier of

the amide pathway. However, both pathways may be competitive due to the Curtin-Hammett principle, which states that a reaction with a pair of reactants that interconvert rapidly, will have a product ratio that depends on the difference in energy between the two ground state conformers and the free energy of the transition state barrier of each product. Due to the 5.5 kcal mol⁻¹ difference (and low energy isomerization barrier of 10.9 kcal/mol) between the amide and imide forms, it is likely interconversion will occur. Thus, the concentration of product depends

more on the amide-imide concentration at equilibrium than on each complex's respective reactivity. Assuming a Boltzmann distribution, the nickel amide and imide free energies at 298.15 K imply that the amide **Cobalt (Co)**

concentration would be $\sim 10^4$ times more prevalent than the imide. This suggests that although the imide pathway has a lower RDS barrier of 11 kcal mol⁻¹, due to the much higher concentration of the amide, it is far

Scheme 5. Free energy diagram of the **amide pathway** for the **Co catalyst**: BP86/CEP-31G(d) at STP. Calculated ΔG (kcal mol⁻¹) for each step in the mechanism are reported along with calculated $\Delta G^\ddagger$ values (kcal mol⁻¹).

Scheme 6. Free energy diagram of the **imide pathway** for the **Co catalyst**: BP86/CEP-31G(d) at STP. Calculated ΔG (kcal mol⁻¹) for each step in the mechanism are reported along with calculated $\Delta G^\ddagger$ values (kcal mol⁻¹).

more likely for the reaction mechanism to follow the amide pathway. However, the likelihood of each respective pathway also depends on another variable—the concentration of ethylene—as a higher concentration of ethylene may further enhance the likelihood of the amide pathway. Regardless, both of these computed pathways are promising as they exhibit reasonably low barriers.

Moving on to the next 3d metal, cobalt, the rate determining step for the Co amide pathway (**Scheme 5**) is the [2+2] addition. The [2+2] addition has a $\Delta G^\ddagger$ value of 17.5 kcal mol⁻¹. The intermediate isomerization has a $\Delta G^\ddagger$ value of 0.7 kcal mol⁻¹. The reductive elimination has a $\Delta G^\ddagger$ value of 6.5 kcal mol⁻¹. The above values for the Co amide pathway compare to the following $\Delta G^\ddagger$ values from the Ni amide pathway: 17.8 kcal mol⁻¹ for the [2+2] addition, 8.3 kcal mol⁻¹ for the intermediate isomerization, and 6.4 kcal mol⁻¹ for the reductive elimination.

The rate determining step for the Co imide pathway (**Scheme 6**) is undetermined due to the energetically similar transition state barriers for

all three steps. This means that all three steps equally determine the efficiency of the catalyst. The initial [2+2] addition, intermediate isomerization, and reductive elimination all have a low $\Delta G^\ddagger$ value of approximately 6 kcal mol⁻¹. The above values for the Co imide pathway compare to the following $\Delta G^\ddagger$ values from the Ni imide pathway: 10.9 kcal mol⁻¹ for the isomerization, 3.0 kcal mol⁻¹ [2+2] addition, and 6.4 kcal mol⁻¹ for the reductive elimination.

In the case of cobalt, the imide pathway is computed to be the preferred reaction mechanism. The imide pathway has a lower rate determining step of 6.5 kcal mol⁻¹ when compared to the 17.5 kcal mol⁻¹ barrier of the amide pathway. Additionally, based on the Boltzmann Distribution at 298.15 K, the concentration of the imide at equilibrium is $\sim 99.9998\%$ because the imide is 7.2 kcal mol⁻¹ lower in energy. Overall, the amide pathway for cobalt has become much less competitive as compared to the nickel catalyst model just discussed.

Iron (Fe)

Scheme 7. Free energy diagram of the **amide pathway** for the **Fe catalyst**: BP86/CEP-31G(d) at STP. Calculated ΔG (kcal mol⁻¹) for each step in the mechanism are reported along with calculated $\Delta G^\ddagger$ values (kcal mol⁻¹).

Scheme 8. Free energy diagram of the **imide pathway** for the **Fe catalyst**: BP86/CEP-31G(d) at STP. Calculated ΔG (kcal mol⁻¹) for each step in the mechanism are reported along with calculated $\Delta G^\ddagger$ values (kcal mol⁻¹).

Moving to iron, the rate-determining step for the Fe amide pathway (**Scheme 7**) is the [2+2] addition. The initial [2+2] addition has a $\Delta G^\ddagger$ value of 21.7 kcal mol⁻¹. The intermediate isomerization, has a $\Delta G^\ddagger$ value of 4.2 kcal mol⁻¹. The reductive elimination has a $\Delta G^\ddagger$ value of approximately 4.6 kcal mol⁻¹. These values compare to the Ni/Co amide pathway values of: 17.8/17.5 kcal mol⁻¹ for the [2+2] addition, 8.3/0.7 kcal mol⁻¹ for the intermediate isomerization, and 6.4/6.5 kcal mol⁻¹ for the reductive elimination. Hence, for all three metals, the initial [2+2] addition has the highest barrier while isomerization and reductive elimination are relatively facile.

The rate determining step for the Fe imide pathway (**Scheme 8**) is difficult to determine from the computations because the values are all similarly computed. The initial [2+2] addition, intermediate isomerization, and reductive elimination all have a $\Delta G^\ddagger$ value of approximately 5 kcal mol⁻¹. These values compare to the Ni/Co imide pathway values of: 10.9/6.1 kcal mol⁻¹ for isomerization, 3.0/6.0 kcal mol⁻¹ for [2+2] addition, and 6.4/6.5 kcal mol⁻¹ for the reductive elimination.

In the case of iron, the imide pathway is predicted to be the preferred reaction mechanism. The amide pathway has become even less competitive, with an RDS of 22 kcal mol⁻¹ versus an RDS of 5 kcal mol⁻¹ for the imide pathway. Also, the concentration of the amide is nearly

inconsequential when compared to the concentration of the imide due to the nearly 21 kcal mol⁻¹ free energy difference between both isomers.

Imide versus Amide Comparison

One of the most interesting discoveries resulting from this research was the existence of amide and imide isomers that each played different roles in the reaction mechanism for aziridine formation. In general, the imide isomer was computed to be lower in free energy than the amide form for most of the 3d metals studied here. Fascinatingly, there was an obvious trend between the location of the metal in the periodic table and the difference in free energy between the amide and imide (**Figure 5**). The early metals tended to have a larger difference in energy between the two isomers, but the difference decreased while moving right. At cobalt the imide was 7.2 kcal mol⁻¹ lower free energy than that of the amide, but at nickel the two isomers “flipped” in relative free energy and the amide was 5.5 kcal mol⁻¹ lower than the imide. Copper and zinc, which are further right, were not included because it is not possible for either metal to have a stable formal oxidation state of +4 and they thus only exist in the amide state with its formal 2+ charge on the metal.

Figure 5. Graph comparing the free energy of the imide and amide conformations of each 3d metal.

SUMMARY AND CONCLUSIONS

In this study, DFT calculations were performed to determine the reaction pathways and to assess the effect of 3d metal upon the mechanism and energetics of aziridination of ethylene by divalent metal amides, Cl-M-N(H)Cl . Several interesting results have emerged from this research that shed light on this important transformation, of which the most essential are summarized below.

First, as expected, it was found that the metal plays a large role in determining the aziridination pathway. Intriguingly, however, all nine 3d metals from titanium to zinc could be subdivided into three groups - late (Cu, Zn), middle (Fe – Ni), and early (Ti – Mn) - based on the preferred reaction mechanisms computed for aziridination. The late 3d metal complexes underwent aziridination of ethylene via initial carbometallation followed by subsequent ring closure. The early 3d metal complexes followed the same three step mechanism as middle series complexes, but for these metals, reductive elimination to form the second of the two C-N bonds of aziridine was prohibitive. The middle 3d metal complexes exhibited a three step reaction mechanism consisting of an additional isomerization and two competing pathways—the “imide” pathway and the “amide” pathway.

Second, perhaps the most surprising result of this project was the discovery of the competing imide and amide pathways for the catalyst models investigated. For the late 3d metal complexes of copper and zinc, the Cl transfers occurs concomitant with ring closure, consistent with previous research. Amide to imide ($\text{Cl}_2\text{M}=\text{NH}$) isomerization via chloride transfer was seen to be highly exergonic and kinetically facile

for most early and middle series 3d metals, which although expected for the former, it is nonetheless interesting that this “crossover” does not occur until cobalt and nickel. Overall, the nickel catalyst model is predicted to follow the amide pathway given the relatively large ground state free energy difference ($\Delta G = -5.5 \text{ kcal mol}^{-1}$) in favor of the amide and the low barriers to Cl transfer ($\Delta G^\ddagger = 10.9 \text{ kcal mol}^{-1}$ for the forward reaction and $5.4 \text{ kcal mol}^{-1}$ for the reverse reaction). The cobalt model catalyst will likely follow the imide pathway because of the dominance of the imide form of the catalyst ($\Delta G = 7.2 \text{ kcal mol}^{-1}$) and the facile Cl transfer barriers; similar comments can be made for the iron catalyst.

Third, the reaction pathways observed are promising in terms of the computed thermodynamics and free energy barriers. While small model ligands and substituents were chosen to focus on the role of metal identity and d-orbital occupation, the majority of the mechanistic steps were found to be downhill thermodynamically and proceed with low activation barriers. It is expected, of course, that larger, bulkier ligands and substituents than Cl may increase the barriers for the required transformations, but barriers were calculated to be quite low ($\Delta G^\ddagger < 10 \text{ kcal mol}^{-1}$), so that even with more sterically demanding ligands the reaction would be expected to proceed quickly under mild conditions.

Fourth, the most promising catalyst candidates are the middle 3d metals containing nickel, cobalt, and iron due to their low rate determining steps and favorable thermodynamics on par with, if not more promising than, current catalysts that use copper.¹⁶ Iron has the overall lowest rate determining step ($\Delta G^\ddagger \sim 5 \text{ kcal mol}^{-1}$) and holds the additional benefit of being the most cost-effective metal. Furthermore, assuming a Boltzmann distribution, the equilibrium concentration of Cl-Fe-N(H)Cl would consist almost solely of the imide isomer, $\text{Cl}_2\text{Fe}=\text{NH}$ ($\Delta G^\ddagger = 5.1 \text{ kcal mol}^{-1}$; $\Delta G = -20.7 \text{ kcal mol}^{-1}$). On the other hand, the nickel amide pathway has one obvious rate determining step (the [2+2] addition) that may be improved if necessary, while the related iron and cobalt catalyst models have three competing reactions. Thus, the nickel catalyst may be the easiest to improve in a catalyst design scenario.

Taken together, the present results suggest that low-coordinate catalysts employing Fe^{II} , Co^{II} and Ni^{II} are promising leads for synthesizing aziridines efficiently and inexpensively. Additionally, depending on the metal, and presumably the ligands and nitrogen substituents, it is quite likely that the catalysts could be tailored to operate via imide or amide intermediates.

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Graphical Abstract

DFT calculations revealed an intriguing trend between the location of the metal in the periodic table and the differences in free energy between the amide and imide pathways.