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A computational study to unravel the selectivity in an iron-catalysed [3+2] cycloaddition of aziridine and heterocumulenes

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Debashis Adhikari*

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The reaction mechanism of cycloaddition between phenyl aziridine and heterocumulene catalysed by iron salts in water has been modeled computationally to trace the origin of excellent regioselectivity toward 5-substituted product formation. The calculations reveal that the Lewis-acidic iron centre activates and increases the electrophilicity of the heterocumulene upon binding, so that a nucleophilic aziridine-attack can be invoked. The preferential opening of the substituted C²-N bond in the following intermediate, dictated by the stability of an incipient carbocation is the key for such selectivity. Since the aziridine ring opening step is asynchronous, concerted in nature, the iminoazoselenolidine ring retains the stereopurity of the chiral carbon of aziridine.

Introduction

Aziridines are very valuable, strained heteroatomic synthons used in preparative organic chemistry based on their ring-opening to a wide variety of synthetic applications.¹ The heterocycles such as 2-aryl aziridines are susceptible to nucleophilic ring-opening² by a metal-catalysed or -mediated process to perform [3+2] coupling with heterocumulenes furnishing a wide range of products such as oxazolidines,³ iminothiazolidines,⁴ iminoazolidinones,⁵ and iminoimidazolidines.^{4a} In this respect, aziridines behave as masked 1,3-dipoles obtained through C-N bond cleavage. The cycloaddition reactions involving the aziridine ring expansion are very attractive owing to their most atom economical nature where no inorganic waste is generated. Recently, Punniyamurthy and co-workers have significantly expanded the scope of such [3+2] coupling reactions by a broad choice of heterocumulenes and synthesizing five-membered heterocycles including iminoazoselenolidine that display important biological⁶ and medicinal properties (eqn (1)).⁷



Their reported reactions are elegant since cheap and environmentally benign iron salts are used as catalysts, and the reactions are performed in water under mild, aerobic conditions. In contrast to the many other reported syntheses involving cycloaddition reactions of similar substrates, this reaction displays complete regio- and stereoselectivity. Despite significant success in two-component cycloadditions involving aziridine, a clear mechanistic picture which can shed light to the origin of regio- and stereoselectivity is lacking. Such an understanding is required to interrogate the role of a substituted aziridine in dictating regioselectivity and controlling stereopurity of the coupled product. In this report, a comprehensive computational study using density functional theory (DFT) has been conducted to unravel the origin of excellent regio- and stereoselectivity of reaction 1.

Computational details

All calculations were carried out using DFT as implemented in the Jaguar 8.0 suite of *ab initio* quantum chemistry programs.⁸ Geometry optimizations were performed using the M06 functional⁹ and the 6-31G** basis set. Iron was represented using the Los Alamos LACVP basis that includes relativistic effective core potentials.¹⁰ The energies of the optimized structures were reevaluated by additional single-point energy calculations of each optimized geometry using Dunning's correlation consistent triple- ζ basis set,¹¹ cc-pVTZ(-f) that includes a double set of polarization functions. All stationary points were verified to be minima or transition states by proper vibrational analysis at the double- ζ level. Solvation calculations were carried out with the 6-31G**/LACVP basis at the optimized gas-phase geometry employing a dielectric constants of $\epsilon = 80.37$ for water. Solvation energies were evaluated using a self-consistent reaction field (SCRf) approach based on accurate numerical solutions of the Poisson-Boltzmann equations.¹² For all continuum models, the solvation energies are subjected to empirical parameterization of the

atomic radii that are used to generate the solute surface. We employed the standard set¹³ of optimized radii in Jaguar for H (1.150 Å), C (1.900 Å), O (1.600 Å), Cl (1.974 Å), N (1.600 Å) and Fe (1.456 Å). Although a Born energy reported by COSMO model is a free energy, the entropic contribution accounts for perhaps 2% of the total energy. The solvation enthalpy was therefore taken as the difference between the gas-phase energy and that obtained from COSMO solvation model calculation. Analytical vibrational frequencies within the harmonic approximation were computed with the 6-31G**/LACVP basis set to confirm proper convergence to well-defined minima or saddle points on the potential energy surface. The free energy of a molecule in solution phase, $G(\text{Sol})$, is computed as follows:

$$G(\text{Sol}) = G(\text{gas}) + G^{\text{soliv}} \quad (2)$$

$$G(\text{gas}) = H(\text{gas}) - TS(\text{gas}) \quad (3)$$

$$H(\text{gas}) = E(\text{SCF}) + ZPE \quad (4)$$

$$\Delta G(\text{Sol}) = \sum G(\text{Sol}) \text{ for products} - \sum G(\text{Sol}) \text{ for reactants} \quad (5)$$

where $G(\text{gas})$ is the free energy of the molecule in the gas phase; G^{soliv} is the free energy of solvation as computed using the continuum solvation model; $H(\text{gas})$ and $S(\text{gas})$ are the enthalpic and entropic components of the molecule in the gas phase, respectively; T is the temperature (298.15 K); $E(\text{SCF})$ is the self-consistent field energy, i.e., the "raw" electronic energy as computed from the SCF procedure; and ZPE is the zero point energy. Note that by entropy here we refer specifically to the translational/rotational/vibrational entropy of the solute(s); the entropy of the solvent is implicitly included in the dielectric continuum model. The energy of the species in the potential energy surface diagram has been reported in solvation-corrected free-energy terms.

To locate transition states, the potential energy surface was first explored approximately using the linear synchronous transit (LST) method,¹⁴ followed by a quadratic synchronous transit (QST) search¹⁵ that uses the LST transition state as an initial guess. In QST, the initial part of the transition state search is restricted to a circular curve connecting the reactant, initial transition state guess, and the product, followed by a search along the Hessian eigenvectors tangential to this curve. *N*-Methyl-phenylaziridine has been chosen as a model for the aziridine substrates instead of the *N*-Pr group used under experimental conditions, to save some computational cost. It is assumed that such a small change will not affect the mechanistic course of the reaction. The iron-complex possesses a sextet spin ground-state and maintains the spin state throughout the entire reaction.

Under the experimental reaction condition, iron-salts are dissolved in water, whereas the organic reactants float on the surface of water.⁷ The present work focuses on explaining the regioselective outcome of the reaction using standard computational protocols, rather than addressing the dynamics of oil-water interface.

Results and discussion

Given the propensity of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ for generating multiple iron-containing species upon dissolution in water, selecting the active form of the catalyst is challenging. At a low concentration of iron salt used under the experimental conditions, $\text{FeCl}_3(\text{H}_2\text{O})_3$

should be the predominant species and can be chosen as an active catalyst, as reported from detailed speciation studies by X-ray diffraction.¹⁶ Fig. 1 and 2 summarize our computational probatation for reaction 1, by extensive computational modelling (DFT), employing M06 density functional.¹⁷ The pseudooctahedral $\text{FeCl}_3(\text{H}_2\text{O})_3$ loses a labile water ligand to form pentacoordinate iron(III) species which can easily bind to the phenyl isoselenocyanate substrate. Upon binding of this heterocumulene, the electrophilicity of the isoselenocyanate carbon is increased and facilitates the attack of a phenyl aziridine to generate intermediate **4**. This intermediate **4** retains the three-membered aziridine ring intact, which is opened by an internal selenide nucleophile preferentially to the phenyl-substituted carbon to form a 5-substituted iminoazoselenolidine. The preferential bond cleavage of the substituted C–N bond in phenyl aziridine by an intramolecular attack of the internal nucleophile in a concerted, asynchronous fashion is responsible for the observed complete regioselectivity (Fig. 1). The novelty of this mechanism lies in two steps: The Lewis-acidic and Lewis-basic interaction between the Fe^{III} -catalyst and phenyl isoselenocyanate, and the intramolecular ring opening of a pendant aziridine by a selenide nucleophile exclusively derived from phenyl isoselenocyanate.

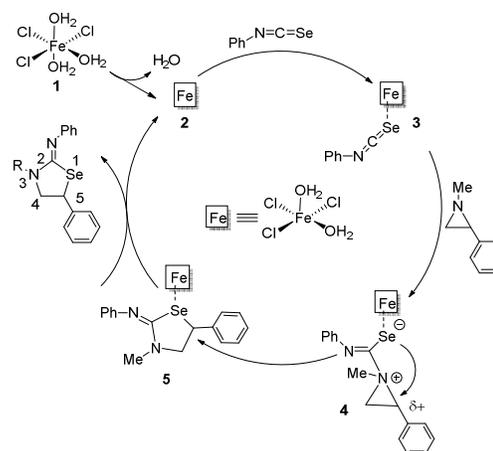


Fig. 1 Proposed mechanistic cycle for Fe^{III} -catalyzed coupling of phenyl aziridine and phenyl isoselenocyanate, which has been investigated computationally (DFT, M06 level of theory).

As mentioned earlier, the catalytically competent iron species in water is pseudo-octahedral $\text{FeCl}_3(\text{H}_2\text{O})_6$, **1**, that forms upon dissolution of iron chloride salt in water. Since both chloride and water are weak field ligands, iron possesses a spin sextet ground-state in this molecule and retains the same spin-state throughout the entire reaction. The catalyst **1** loses one molecule of water to open a vacant coordination site engendering **2** for further substrate binding. The intermediate **2** is slightly higher in energy ($1.1 \text{ kcal mol}^{-1}$) than the reference state of the reaction where the catalyst and all substrates are infinitely separated (Fig. 2). The creation of a vacant coordination site is followed by the isoselenocyanate binding to **2** through the selenium. Although this binding is weak and slightly thermodynamically uphill (by $2.9 \text{ kcal mol}^{-1}$), this is sufficient to activate the heterocumulene for

further attack by a nucleophile. This activation becomes evident both from elongation of the C–Se bond (by 0.04 Å compared to unbound isoselenocyanate) as well as the increase in electrostatic-potential-fitted (ESP) charge at the carbon by 0.09 e. Notably, the binding of phenyl aziridine to the Fe^(III) centre is an unproductive mode but can be competitive with the isoselenocyanate binding. Although the phenyl aziridine becomes activated by donation of the nitrogen lone pair to the Lewis-acidic Fe^(III) centre, the simple binding is not sufficient to augment the spontaneous ring-opening process (*vide infra*). The *N*-methyl-phenyl aziridine then attacks the activated isoselenocyanate carbon to result intermediate **4**, where the isoselenocyanate is inserted between the iron and aziridine. This aziridine mediated nucleophilic attack overcomes an energy barrier of 19.3 kcal mol⁻¹. The charge transfer (CT) index for **3-TS**, computed from the natural population analysis (NPA) is 0.08 e.¹⁸ As expected, the successful formation of intermediate **4** by the nucleophilic attack of an aziridine will depend on the nucleophilicity of the nitrogen lone pair of the heterocycle. Indeed, no coupling product was observed experimentally where benzoyl (Bz) and *tert*-butyloxycarbonyl (Boc) groups were used as *N*-substituents.⁷ This can be attributed to heavy delocalization of nitrogen lone pair to the *N*-substituents, reducing the nucleophilicity of the nitrogen lone pair considerably. The intermediate **4** is significantly zwitterionic in character, as supported from the calculated CT index as 0.51 e.¹⁸ In the intermediate **4**, the Lewis-acidic activation of the phenyl aziridine through an isoselenocyanate moiety becomes very prominent as shown from the following N–C bond length comparison (Fig. 3).

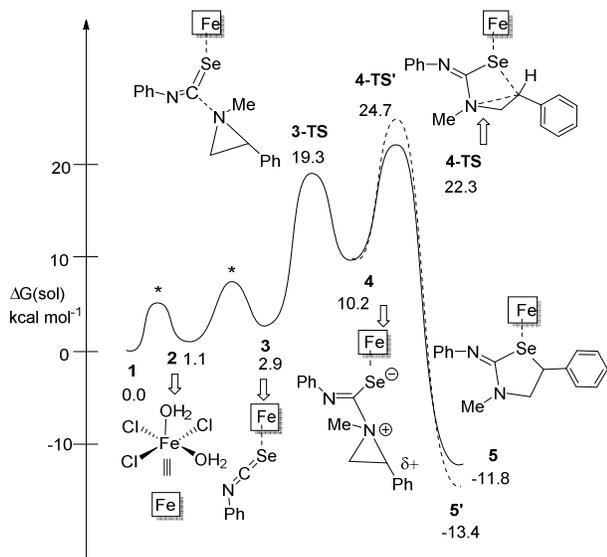


Fig. 2 The free-energy landscape for reaction 1 using FeCl₃(H₂O)₆ as the model catalyst system and [*N*-Me-phenyl aziridine + phenyl isoselenocyanate] as the model substrate pair. TSs with * symbol are for illustration purpose only and were not located.

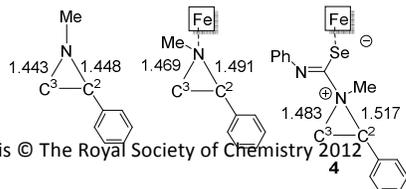


Fig. 3 The computed structures of *N*-methyl-phenylaziridine (left), Fe^{III}-bound aziridine (middle) and intermediate **4** (right) at the M06/LACVP** level of theory. The middle structure, although not a part of the catalytic cycle, is shown for comparison. Bond lengths are shown in Å. A difference in elongation of phenyl-substituted (N–C²) vs unsubstituted (N–C³) bond is evident from intermediate **4**.

As the difference in elongation of two C–N bonds in **4** suggests, the ring-opening will be preferentially facilitated at the C² carbon where the presence of a phenyl substitution can stabilize a developing carbocation. Furthermore, the ESP charge separation between C² and C³ carbons (0.44 e) corroborates well with the difference in two C–N bond activation of aziridine in **4**. In intermediate **4**, the selenide nucleophile¹⁹ is appropriately oriented to attack the C² carbon of the tethered aziridine to form a five-membered iminoazoselenolidine. The large strain energy, 27 kcal mol⁻¹, contained within the three-membered ring²⁰ of aziridine and the required orientation of the nucleophile makes the molecule susceptible for nucleophile-driven ring-opening reaction (Fig. 4). The transition state, **4-TS**, leading to the major product formation was located at an energy barrier of 22.3 kcal mol⁻¹.²¹ Interestingly, the **4-TS** is concerted, asynchronous in nature where C–N bond cleavage slightly precedes the C–Se bond formation. The respective bond distances at the TS are 2.19 and 3.17 Å (Fig. 5, left). The asynchronicity of the TS was further quantified by using eqn 6 where δB_i is the bond index for every bond *i* involved in a chemical reaction. The δB_{av} provides a measure of the degree of advancement of the transition state along the reaction path, and *n* is the number of bonds that undergo a change during the reaction.²²

$$A = \frac{\sum_{i=1}^n \frac{|\delta B_i - \delta B_{av}|}{\delta B_{av}}}{2n-2} \quad (6)$$

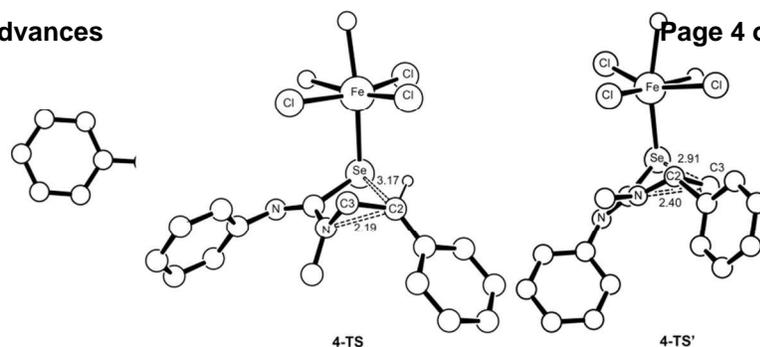
The asynchronicity index (*A*) for the major **4-TS** is found to be 0.73, which further suggests that the C–N bond cleavage and C–Se bond formation events are not concomitant. The single-bond development index for C–Se bond is calculated to be 0.42, which further ascertains that the TS is late with respect to the new bond formation.²³ At the transition state, the loss of energy due to C–N bond cleavage is partly compensated by the electron donation from the selenide nucleophile to the LUMO of the substituted carbon as the delocalization energy from second order perturbation (from NBO analysis) was calculated to be 5.6 kcal mol⁻¹.²⁴ At the TS, the C² carbon bearing the phenyl substitution is almost planar, as reflected by the angle around it (359.8 °) and slight increase in bond order of the C²–Ph bond (from 0.21 to 0.26). It is imperative that the aziridine ring-opening will be preferred at the C² centre owing to the stability enjoyed by the incipient carbocation. This type of stabilization due to phenyl substitution closely mirrors the allylic²⁵ or the β-silicon stabilization^{3a} of the aziridine

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carbon during the ring-opening process. Excellent regioselectivity in favour of 5-substituted oxazolidinone formation from the (salen)Cr^{III}Cl-catalyzed CO₂ and aryl aziridine coupling reaction has also been reported recently, where such a preferential ring-opening of the aryl aziridine seems operative.²⁶ Since the C²-N bond elongation results an incipient carbocation, rather a fully developed one, the stereochemical description of the chiral carbon of aziridine should be retained in the product iminoazoselenidine. This proposition is completely consistent with the experimental observation: (*S*)-Ph substituted aziridine reacts with phenyl isoselenocyanate to give optically active iminoazoselenolidine.⁷

Fig. 4 The transition state structure, **3-TS** (left) and resulting intermediate **4** (right), as obtained computationally. For clarity all of the hydrogens have been removed.

Interestingly, the TS leading to the minor product formation, **4-TS'** (not observed experimentally, reported by NMR detection) is also concerted, asynchronous in character where the developing C---Se and cleaving C---N bond distances are 2.91 and 2.40 Å respectively.²⁷ The solvation-corrected free-energy difference between these two transition states is 2.4 kcal mol⁻¹, which correctly reproduces the experimental trend. The asynchronicity index for **4-TS'** was calculated to be 0.69 that signifies the minute C-Se bond formation compared to C-N bond cleavage at the TS. Further scrutiny of **4-TS'** structure reveals that the transient carbocation generated from the unsubstituted C³ carbon, being primary in nature, is so electron-deficient that the phenyl group from the adjacent C² carbon participates via anchimeric assistance²⁸ to confer stability (Fig 5. right). The participation of the phenyl group to impart stability is evident both from the C²-Ph and C³-Ph bond lengths (1.60 and 1.75 Å respectively) as well as a slight change in hybridization (pure sp² to sp³) for the phenyl carbon to assist better orbital overlap with C³ (see ESI†, section S1). The validity of both the TSs, **4-TS** and **4-TS'** were further authenticated by their smooth connection to the intermediate **4** and the final products comprising a 5-membered iminoazoselenolidine ring connected to the Fe^(III) centre. Finally, the bound five-membered product is replaced by another molecule of isoselenocyanate and thus the process remains catalytic. Notably, the lack of minor product formation under experimental conditions reiterates the importance of incipient carbocationic stabilization by the presence of phenyl or aryl rings in the aziridine molecule.²⁹ The stability enjoyed by the incipient carbocation from the presence of a -Ph group is critical for the excellent regioselectivity, since alkyl substituted aziridines have been reported to exhibit poor regioselectivity under Lewis-acid mediated- or catalysed conditions.³⁰ Given the discussed stability of the phenyl substituted carbon, it can be hypothesized that the incorporation of more electron donating groups at the *para*-position of the phenyl ring will increase the incipient



carbocationic stability,³¹ thus increasing the rate of the ring-opening process. This is indeed observed computationally, as the incorporation of a highly electron donating *p*-OMe group in the same ring decreases the electronic barrier of the step by 6 kcal mol⁻¹ (see ESI,† Fig. S1).

Fig. 5 The transition states leading to major and minor products (not observed experimentally), **4-TS** (left) and **4-TS'** (right) obtained through a concerted, asynchronous pathway. The lengths for both C---Se and C---N bonds (in Å) are indicated in the structure. For clarity, all of the hydrogens have been removed except for that on the C² carbon in **4-TS**, where C-Se bond formation is taking place.

To further ascertain the generality of the proposed mechanism, cycloaddition reactions involving different heterocumulenes were also investigated. Gratifyingly, the heterocumulenes such as phenyl isocyanate and phenyl isothiocyanate exhibit the similar concerted, asynchronous transition states (see ESI,† Fig. S2) leading to major product formation and can be located at reasonable energy barriers (Table 1). The higher reaction energy barrier for these two heterocumulenes compared to that in isoselenocyanates also correlates well with the increasing reaction temperature required for similar [3+2] coupling reaction involving them.

Table 1 Computed TS-energy for the major product giving pathway for different heterocumulenes

Entry	Heterocumulene	TS-energy (kcal mol ⁻¹)
1	Ph-isoselenocyanate	22.3
2	Ph-isocyanate	28.5
3	Ph-isothiocyanate	31.4

Since **4-TS** is concerted, asynchronous in character, a true carbocation is never generated during the cycloaddition reaction. As already discussed, stereochemically pure 5-membered iminoazoselenolidine product from stereochemically pure aziridine was indeed observed experimentally. A true carbocation generation should result in the racemization or significant erosion of stereopurity as observed by others in the case of aziridine ring-opening mediated by a strong Lewis acid.^{3b, 32} Our proposed mechanism is reminiscent of Alper's S_Ni type reaction in a Pd-catalysed ring-opening cycloaddition of aziridines and ketenimines, where a concerted reaction was also invoked as an explanation for the stereochemical retention at the chiral carbon

of aziridine^{4a, 33}. However, it is noteworthy that the suggested double inversion at the chiral centre for the retention of stereochemistry as proposed by Lee in a chloromethylformate mediated oxazolidinone formation reaction cannot happen in this system.³⁴

Conclusions

The computationally investigated mechanistic course of the cycloaddition reaction between phenyl aziridine and phenyl isoselenocyanate reveals that the activation of aziridine happens through a molecule where the selenocyanate is inserted between catalyst Fe^(III) and aziridine. The preferential opening of the aziridine C–N bond at the phenyl-substituted carbon occurs by an internal selenide nucleophile that is responsible for exhibiting excellent regioselectivity. The stereochemical retention of the asymmetric carbon in aziridine to cycloaddition product is a result of the concerted nature of the reaction where a fully developed carbocation is never generated.

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Department of Chemistry, Indiana University, Bloomington, Indiana 47405, USA. Tel: 01-812-855-6779. E-mail: dadhikar@indiana.edu

†Electronic Supplementary Information (ESI) available: TS structures, Cartesian coordinates and vibrational frequencies of the structures studied. See DOI: 10.1039/x0xx000000x/

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