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# An Ab Initio Study of Substituent Effects on the Electrocyclization of Silyloxyazadienes

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**Keywords:** Azadienes / β-Lactams / Ab initio calculations / Electrocyclization / Nitrogen heterocycles

The electrocyclization of 4-substituted 3-silyloxy-2-azadienes to β-lactams was studied at the MP2/6-31G* level of theory and the effect of the substituents on the reactivity of the azadiene and on the stereochemistry of the cyclic products was evaluated. It was shown that the electrocyclization is favoured when the substituent in 4-position is in the (*Z*) configuration and discloses an electron-donor effect. The cyclization reactions generally lead to *trans* β-lactams, but with a basic substituent *cis* β-lactams are obtained as well.



## Introduction

In the field of the synthesis of organic natural substances and biologically interesting compounds, azadienes are known to be useful intermediates for the preparation of nitrogen-containing heterocycles.[1] In this context, the use of 3-trialkylsilyloxy-2-aza-1,3-dienes was shown to be particularly attractive.[2] These compounds, usually synthesized by the reaction of silylimines with ketenes, are stable and, following the Staudinger approach,[3] have been used to obtain β-lactams through an electrocyclic ring closure reaction.[4] However, two problems have to be taken into account: (1) With silylimines and ketenes bearing alkyl groups or no substituent at all, very stable azadienes are formed and, under the standard experimental conditions, no spontaneous electrocyclic ring closure to β-lactams is observed.[5] (2) Ring closure to *trans* β-lactams is generally achieved under reflux conditions, but with ketenes substituted by an alkoxy or an amino group, a spontaneous ring closure to *cis* β-lactams, at room temperature, is observed.[5,6] Because the reactivity of the generated azadiene and the stereochemical outcome of the ring-closure reaction strictly depend on the very nature of the substituents in the starting ketene, an ab initio computational study was undertaken. The goal of these theoretical calculations was to study the effects of the substituents in the 4-position of the azadiene skeleton on the reactivity of the related azadiene compounds and on their influence in determining the stereochemistry of the final ring. Accordingly the substituents were chosen to be representative of various electronic effects.

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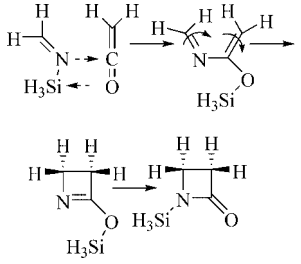
## Results and Discussion

Previous theoretical calculations,[4c,4d] performed on the reaction between unsubstituted ketene and *N*-silylimine, showed that preliminary formation of 3-silyloxy-2-azadiene takes place. The azadiene thus formed undergoes, in turn, a conrotatory ring closure to yield an intermediate 2-silyloxy-3.4-dihydroazete, which subsequently rearranges to the corresponding 1-silylazetidin-2-one (Scheme 1).

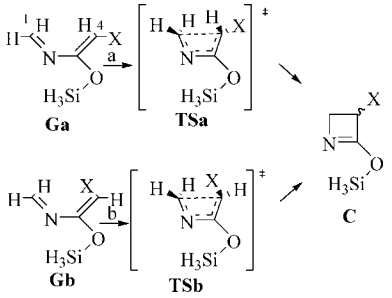


Scheme 1.

The greater stability of the final product, as a result of the strain relief going from an endocyclic to an exocyclic double bond, provides the driving force for the whole process. Nevertheless it is the value of the activation energy of azetidine closure that is responsible for the easiness of the cyclization and, therefore, only the dependence of this energy value from substituents was investigated. The substituents were placed on the ketene moiety of the azadiene skel-

eton (Scheme 2), and both (*Z*)-configured **Ga** (respectively *outward* in transition state **TSa**) (path **a**) and (*E*)-configured **Gb** (respectively *inward* in transition state **TSb**) (path **b**) were considered. The OH, OCHO, $NH_2$, NHCHO and SH substituents were taken as a model. In an oversimplification, the information thus obtained may be extended to the above-groups characterized by further substitution represented by an alkyl or an aryl moiety displaying, in principle, the same electronic effect.




Scheme 2. X = Me, Ph, $CF_3$, F, Cl, OH, OCHO, $NH_2$, NHCHO, SH.

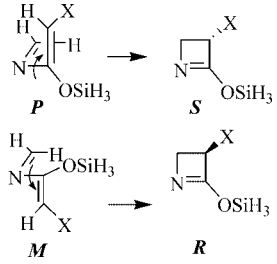
The thermodynamic stabilities of the substituted azadienes, the *outward* and *inward* activation energies of the ring closure and the difference between the energies of the *inward* and *outward* transition states are reported in Table 1, taking as zero energy in every row, the energy of the corresponding (*Z*)-substituted azadiene.

Table 1. Relative energies [kcal/mol] of paths a and b in Scheme 2.

| X [a] | $\Delta E_G$[a] | $\Delta E^{\neq}_a$ [b] | $\Delta E^{\neq}_b$ [c] | $\Delta E^*$[d] |
|---|---|---|---|---|
| Me | 2.4 | 30.4 | 34.3 | 6.3 |
| Ph | 2.7 | 28.6 | 33.3 | 7.4 |
| $CF_3$ | 0.3 | 31.3 | 32.9 | 1.9 |
| F | –0.7 | 24.8 | 39.5 | 14.0 |
| Cl | 1.6 | 27.1 | 38.6 | 13.1 |
| OH | –1.2 | 23.5 | 40.7 | 16.0 |
| OCHO | 0.7 | 25.4 | 37.9 | 13.2 |
| $NH_2$ | 5.3 | 25.6 | 38.2 | 17.9 |
| NHCHO | 6.1 | 27.6 | 36.1 | 14.6 |
| SH | 0.9 | 27.7 | 38.3 | 11.5 |

[a] $\Delta E_G = E_{Gb} - E_{Ga}$. [b] $\Delta E^{\neq}_a = E_{TSa} - E_{Ga}$. [c] $\Delta E^{\neq}_b = E_{TSb} - E_{Gb}$. [d] $\Delta E^* = E_{TSb} - E_{TSa}$.

As far as the stability of the azadienes is concerned, the (*Z*) substitution is generally favoured, whereas (*E*) substitution is favoured only when a small substituent, with strong electron-withdrawing character, is at the 4-position. In this case, the formation of electrostatic interaction between the substituent and the partially positive iminic carbon stabilizes the (*E*) form. Taking into account the cyclization step, since the *s-cis* form of the azadiene skeleton is not planar (dihedral angle C1–N2–C3–C4 = ±40°, 50° depending upon the substituent; see Supporting Information) two enantiomeric conformations, ***P*** for the positive value and ***M*** for the negative one, must be considered. The case of (*Z*) substitution is reported in Scheme 3. In order that ring closure occurs, the central C–N bond rotates towards an eclipsed arrangement following the principle of the least motion and simultaneously the two double bonds perform a clockwise rotation for the *P* conformation and an anticlockwise one for the *M* conformation.[7] The two rotation paths are equienergetic so that, consequently, a couple of enantiomeric transition states **TSa** is obtained. Analogously, a couple of enantiomeric transition states **TSb** is obtained with (*E*) substitution. The two enantiomeric couples **TSa** and **TSb** are different in structure and energy but give rise to the same couple of enantiomeric azetidines **C**. It is evident from the data reported in Table 1 that the activation energies and the energies of the transition states of the (*E*)-substituted molecules are always greater than those of (*Z*) ones. Computations show that *outward* transition states have a similar skeleton structure for all the examined substituents and the same happens in the *inward* series. For this reason, the structures of *outward* and *inward* transition states of the chlorine derivative reported in Figure 1 are representative of all the *outward* and *inward* transition states (for details see Supporting Information).




Scheme 3.

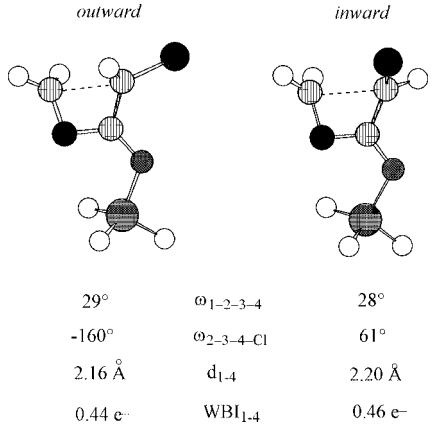
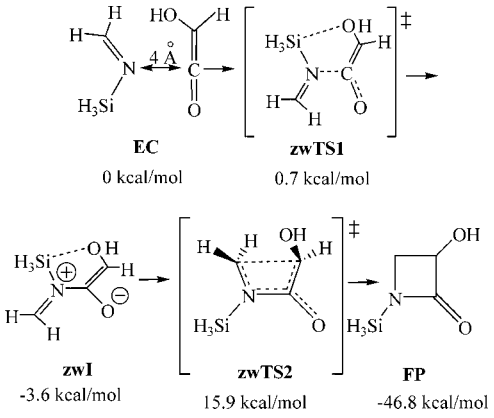



Figure 1. Gauss view of the structures of the chlorine transition state.

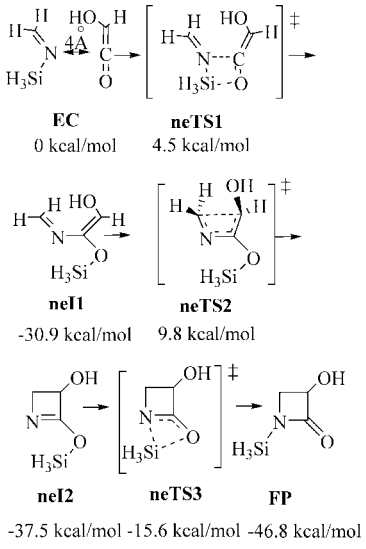
The geometry of the azadiene skeleton and the nature of the incipient 1–4 bond are similar in the *outward* and *inward* structures, the real difference between them being the orientation of the substituent, which is pseudoequatorial in the *outward* structure and pseudoaxial in the *inward* one. Therefore, it is the different orientation of the substituents that is responsible for the energy difference between the two transition states. This behaviour can be correlated to the classic

torquoelectronic effect observed by Houk in the conrotatory opening–closure of four-membered rings.[8] The torquoelectronic effect is due to an interaction between the p orbitals of the substituent and the σ-forming bond in the transition state, and it is destabilizing when a donor group is placed in the *inward* position and stabilizing when a donor group is placed in the *outward* position.[9] In fact, in Table 1 the relative energies point out a decrease in the *outward* transition state energy (and related activation energy) and an increase of the *inward* transition state energy (and related activation energy) going from the trifluoromethyl group, which has the minimum donor effect in the series, to the amino group, which has the maximum donor effect. As a consequence, an easier cyclization is to be expected with a (*Z*) substituent presenting a lone pair of electrons, which can afford a mesomeric effect, and a more difficult cyclization with other substituents or with substituents in the (*E*) position. When two substituents, one on silylimine and one on ketene, are present, a *trans* β-lactam is generally obtained.[2] It was supposed[4c,4d] that, for steric reasons, the approach of silylimine to ketene leads to a (1*E*, *3Z*)-1,4-substituted azadiene, which, by a conrotatory rotation, must give rise to a *trans*-cyclized compound. In fact, in the cases in which the structure of the azadiene intermediate was been investigated, a (1*E*, *3Z*) configuration was observed.[4a,4e] In some cases, however, when the ketene is substituted with alkoxy or amino groups and the silyilimine with alkyl or aryl groups, a *cis* β-lactam is obtained.[5,6] In these cases, the reaction is very fast and it is not possible to isolate the azadiene intermediate. From the stereochemistry point of view, to have a *cis* product it is necessary for the azadiene to be (1*E*,3*E*)- or (1*Z*,3*Z*)-substituted. In the light of previous experimental results, where acyloxy or amide substituted ketenes furnished only *trans* β-lactams,[4c] the possibility that the 1-position is (*Z*)-aryl,alkyl-substituted may be, at least for steric reasons, excluded. The other possibility is therefore that the 4-position is (*E*)-alkoxy or -amino substituted. It was supposed that the basic oxygen or nitrogen atom in the 4-position could stabilize the (*E*) configuration through the formation of a weak interaction with the electrophilic carbon in the 1-position.[6] However, the present calculations show that the *inward* closure activation energy is much higher than the *outward* one, and, therefore, a very slow reaction should be expected, associated with a possible isolation of the azadiene intermediate. As this does not happen, it is conceivable that, for these substituents, the mechanism of the reaction is different from that described in Scheme 1. A possibility is that the approach of an alkoxy- or amino-substituted ketene to a silylimine is driven by an electrostatic interaction between the basic group on the ketene and the imine silyl group. On the basis of this hypothesis, theoretical calculations were performed, the results being depicted in Scheme 4. For the sake of comparison, in Scheme 5 are reported the calculations for a ketene *endo* attack according the reaction profile reported in Scheme 1. In both of the schemes, the zero energy is that of the same electrostatic complex **EC** between hydroxyketene and silylimine.




Scheme 4.




Scheme 5.

In Figures 2, 3 and 4, the structures of some critical points in the two schemes are reported. In Scheme 4, the interaction of the hydroxy group with the silyl group leads to transition state **zwTS1** in which the silyl group is on the other side of the ketene carbonyl group.

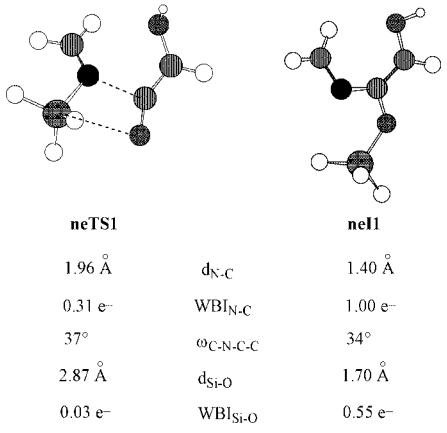



Figure 2. Gauss view of the structures of **neTs1** and **neI1** (Scheme 5).

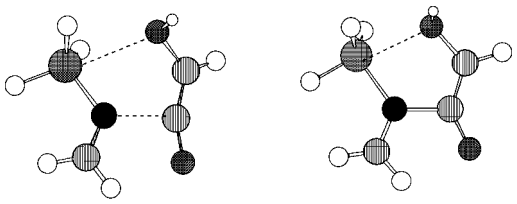



Figure 3. Gauss view of the structures of **zwTS1** and **zwI** (Scheme 4).

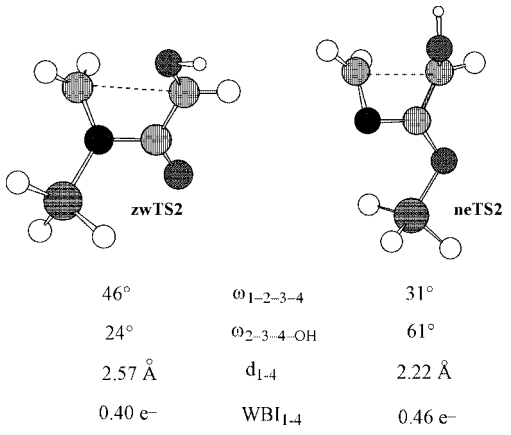



Figure 4. Gauss view of the structures of **zwTs2** (Scheme 4) and **neTS2** (Scheme 5).

Contrary to what happens in Scheme 5 (see Figure 2), it is not possible to have a silyl tropism from the imine to the ketene and zwitterionic intermediate **zwI** is formed (see Figure 3). A second transition state, **zwTS2** (Figure 4), directly leads to the azetidinone. It is noteworthy the similarity between the profile of this reaction and the profile of the classic Staudinger reaction as reported by Sordo and coworkers.[10]

In fact, both the reactions are characterized by the presence of two transition states and by a high-energy zwitterionic intermediate. The difference is that the reaction in Scheme 4 is competing with the reaction in Scheme 5. A

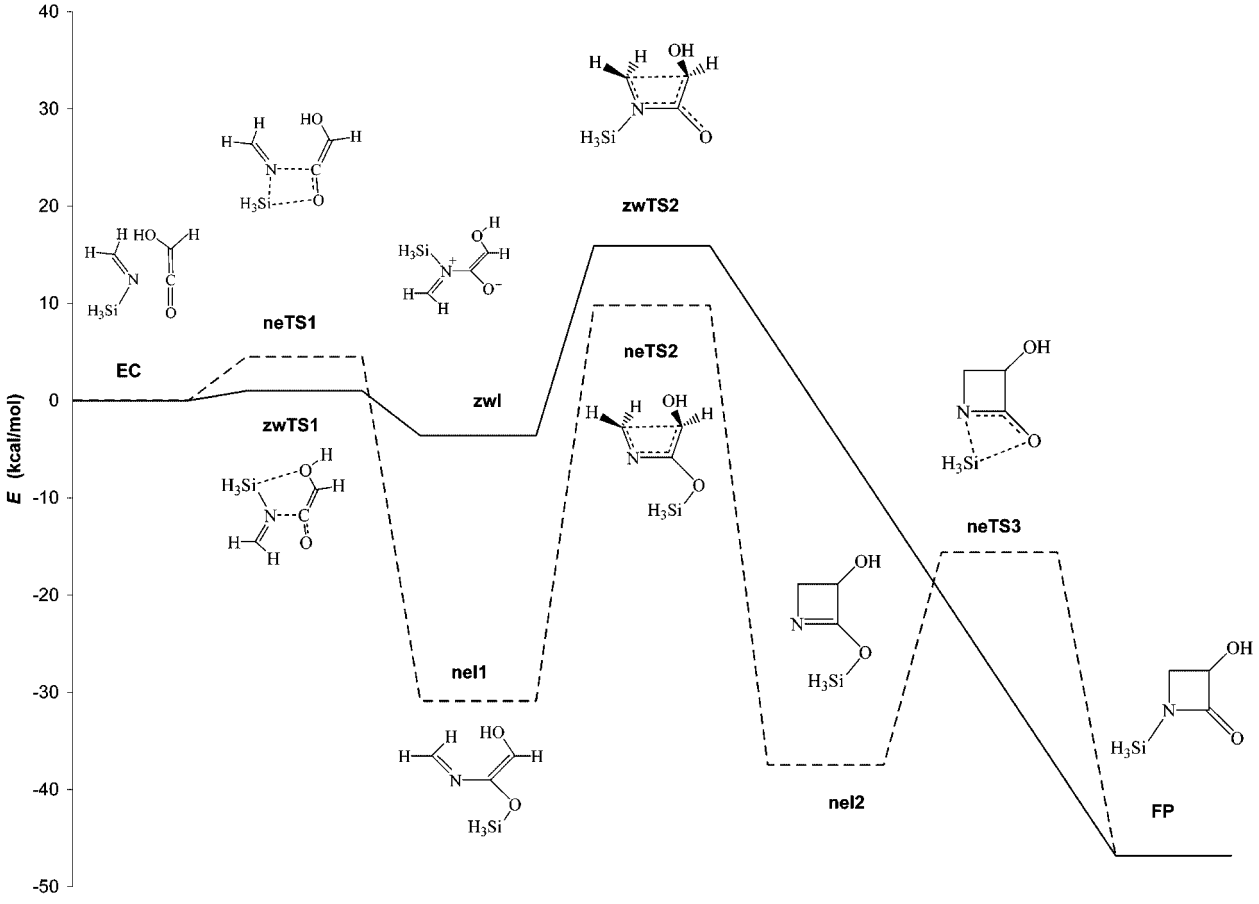



Figure 5. Path profile for zwitterionic and neutral hydroxy cyclization.

plot of the relative energy reaction coordinates for the two reaction paths is reported in Figure 5.

Comparing the energy of zwitterionic intermediate **zwI** in Scheme 4 with that of neutral azadienic intermediate **neI1** in Scheme 5, **zwI** appears less stable than **neI1**, but it is formed 600 times faster at room temperature because of the lower energy of transition state **zwTS1** that is involved in its formation (0.7 kcal/mol against 4.5 kcal/mol for **neTS1**). Moreover, owing to the high energy of **zwI**, the cyclization step in the zwitterionic route results in a smaller activation energy than that in the neutral route (19.5 kcal/mol and 40.7 kcal/mol respectively). The high value of the last one prevents the cyclization in the neutral route, and only a cyclization as in Scheme 4 is therein allowed. The zwitterionic route is in agreement with the experimental results. The reaction is fast, no intermediate is isolated, and a cyclic derivative from an (*E*) configuration of the azadiene is obtained.

## Conclusions

The reaction of silyl imines with substituted ketenes generally leads to the formation of stable azadiene intermediates having (*E*,*Z*) stereochemistry, followed by a ring-closing reaction to *trans* β-lactams. The ring-closure kinetics follow the rules of the torquoelectronic effect, and it is as easy as the electron-donating abilities of the substituent. As a consequence, the reaction successfully happens only when the ketene is substituted with heteroatomic groups. Failing these, the reaction does not happen under relatively mild conditions and more drastic ones should be necessary. When the ketene is substituted with a basic group, the interaction of this with the silyl imine can lead to the formation of a very reactive zwitterionic intermediate having an (*E*,*E*) stereochemistry. The possibility of this alternative zwitterionic route can explain the formation of a *cis* β-lactam. The reaction path disclosed by these theoretical calculations for the formation of the 3,4-substituted *cis* and *trans* β-lactams open a vein in determining a priori the stereochemistry of the final ring by a suitable choice of the substituents on the basis of their electronic effects. In fact, the experimental results so far obtained by our group on the use of azadiene in the preparation of the β-lactam ring are in accordance with the calculations. Moreover, since azadienes have been used by us and other research groups as a diene counterpart in HDA reactions,[11] these studies are of value to help in predicting if the azadiene moiety will be stable, and whether it can be isolated or spontaneously close to a β-lactam ring. As a matter of fact, we already confronted ourselves with this problem: no azadiene could be obtained from a 2-alkoxy or 2-aryloxy ketene and a silylimine.[12] Finally, we are aware that mutual interactions between the substituents on ketene and imine could afford the mechanism and the overall kinetic of the reaction. Further studies are in progress on this subject.

## Experimental Section

**Computational Methods:** All ab initio calculations were carried out at the MP2/6-31G* level by using the GAUSSIAN 98 series of programs.[13] Geometries were fully optimized by standard gradient techniques and the final structures were checked by frequency analysis. Each transition state showed only one imaginary frequency and the corresponding vibration was associated with the nuclear motion along the reaction coordinate. Zero-point vibrational energy corrections were applied for all the examined structures without scaling. The electronic density of incipient bonds and electrostatic interactions was determined by calculation of the Wiberg bond index (WBI) with the natural bond orbital (NBO) method[14] as implemented in GAUSSIAN 98.

**Supporting Information** (see footnote on the first page of this article): Tables of energies and cartesian coordinates of all optimized structures.

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