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A Hetero Diels–Alder Concerted vs. Aldol Stepwise Mechanism in the Cyclization of Silyloxyazadienes with Aldehydes: A Theoretical Study

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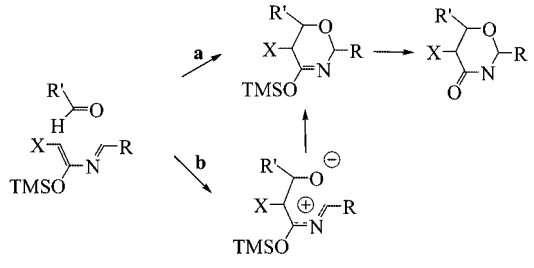
The Diels–Alder reaction of 3-silyloxy-2-azadiene with formaldehyde has been studied at the B3LYP/6-31G* level of theory and the role played by a Lewis acid evaluated. It is shown that the reaction is preferred when the Lewis acid coordinates to the aldehyde oxygen. This coordination allows for a concerted as well as a stepwise mechanism for the cyclization.

Introduction

The hetero Diels–Alder (HDA) reaction with carbonyl compounds as dienophiles is a very useful method to construct heterocyclic rings that is widely used in the synthesis of natural products,[1] and the use of activated 3-trialkylsilyloxy-2-aza-1,3-dienes has found many applications since its introduction.[2] The reaction with aldehydes gives rise to tetrahydrooxazinones with various substitution patterns (Scheme 1) and takes place in neutral conditions[3] or in presence of a stoichiometric amount of boron trifluoride etherate.[4] According to previous calculations performed on a similar substrate[5] the cyclization reaction is considered to happen by a concerted HDA mechanism (Scheme 1, path a) through the formation of an oxazinic ring, but, in analogy with what is known for similar reactions,[6] a stepwise mechanism with the formation of an aldol-type intermediate cannot be ruled out (Scheme 1, path b).



Scheme 1.

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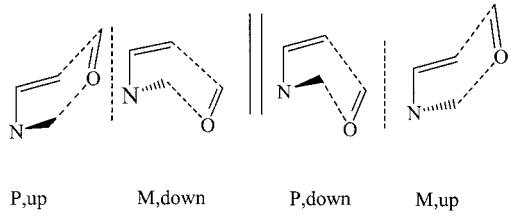
With the aim of gaining a deeper insight into this subject we performed a DFT computational study on both the uncatalyzed and Lewis acid (LA) catalyzed reaction. The results are presented below.

Results

Uncatalyzed Cyclization

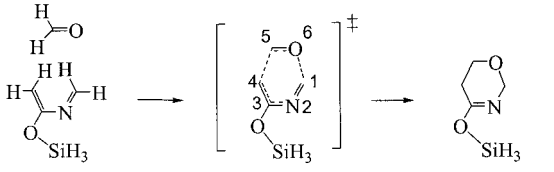
In order to determine the preferred pathway for the cyclization reaction, the calculations were performed using the unsubstituted 3-silyloxy-2-azadiene and formaldehyde as model starting compounds and the sum of their energies (–652.35675 hartrees) was taken as the zero point. As the *s-cis* form of the azadiene skeleton is not planar (C1–N2–C3–C4 = +42° for the P conformation and –42° for the M conformation)[7] the approach of formaldehyde to one or the other side of azadiene can lead, in theory, to the formation of two enantiomeric couples of transition states (Scheme 2). For the sake of easy reading we define the up approach as that identified by a negative sign of the dihedral angle N2–C3–C4–C5 and the down approach as that identified by a positive sign of the same dihedral angle. Moreover, in this theoretical study only one regioisomer has been considered according to the experimental results obtained from previous studies.[4a,5]



Scheme 2.

The calculations show (Scheme 3) the preliminary formation of a stabilizing electrostatic complex (**EC1**) with a

mean distance of 3 Å between the two molecules. Only one couple of enantiomeric transition states is located (**TS1**, Figure 1), with an energy 12.6 kcal mol^{-1} higher than that of the electrostatic complex. This transition state is characterized by the same sign of the two dihedral angles C1–N2–C3–C4 and N2–C3–C4–C5 of ±10° and ±53°, respectively, and these values allow us to assign the configuration P,down (both positive) or M,up (both negative) to the enantiomeric **TS1**. The strong planarization of the azadiene skeleton in the transition state (10° against 41° in the **EC1**) allows an easy inversion of the skeleton when the approach of the formaldehyde is of the M,down or P,up type, therefore no transition states of this type could be identified in the calculations. Other features of the transition state include a neat pyramidalization of C1, C4, and C5 (150–160°), the equality of the lengths of the two forming bonds C4–C5 and C1–O6 (2.14 and 2.15 Å), and the values of their bond orders (0.32 and 0.17 e$^-$). These geometric features are very similar to those found for the transition structure of concerted pathways in related reactions[8] and are good evidence for a synchronous pericyclic reaction. An HDA-type cyclized compound, characterized by the presence of a localized C3=N2 double bond in the ring, originates from the transition state. The strong exothermicity of the cyclization reaction provides the driving force for this process. No transition state suggestive of a stepwise reaction was found. All attempts to form a zwitterionic aldol-type structure starting from the *s-cis* or *s-trans* azadiene form resulted either in the formation of **TS1** or in separation to the reactants.



Scheme 3.

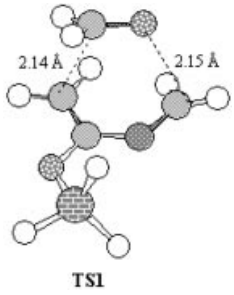
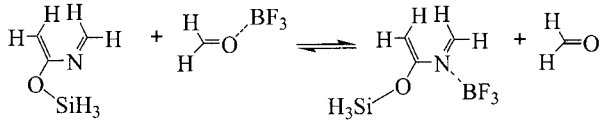


Figure 1. Gauss view of the optimized structure of **TS1**.

Lewis Acid Catalyzed Cyclization

The addition of a Lewis acid such as BF_3 can lead to different reactions pathways depending on where the LA coordinates. In such reactions BF_3 is generally regarded as coordinating the aldehyde oxygen,[1] although it is known that azadiene can coordinate to BF_3 through the imine nitrogen.[9]

Calculations show that BF_3 can coordinate to both sites with a length and bond order of 1.92 Å, 0.23 e$^-$ and 1.70 Å, 0.43 e$^-$ respectively. In the isodesmic reaction shown in Scheme 4 the right-hand part is 5.8 kcal mol^{-1} more stable, thus showing that the azadiene nitrogen must be considered to be preferred coordination site. As a consequence, cyclization would occur between the complexed azadiene and the free aldehyde. On the other hand, and according to frontier molecular orbital (FMO) theory,[10] the cycloaddition of carbonyl dienophiles with 2-aza-1,3-dienes has been shown to be a $LUMO_{dienophile}$ – $HOMO_{diene}$ controlled process.[4a,5] In order to analyze the effect of the coordination of BF_3 on such orbitals, we report in Table 1 the calculated energies for uncomplexed and complexed formaldehyde and azadiene.



Scheme 4.

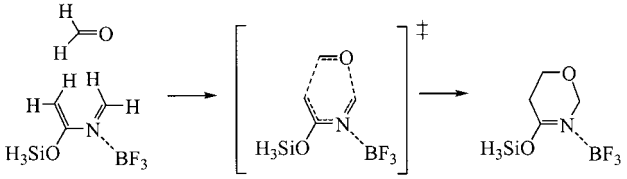
An analysis of the values shows that the strong electron-withdrawing effect exerted on the substrate by BF_3 causes a lowering in energy of the orbitals of both substrates. Upon comparing the energies of the involved interacting orbitals it becomes clear that the cyclization via formaldehyde complexation should be strongly favored with respect to that via azadiene complexation (ΔE = 3.52 and 6.20 eV, respectively), whilst the uncatalyzed cyclization (ΔE = 5.04 eV) would be just in the middle. As the acid–base equilibrium in Scheme 4 would favor the *N*-complexed cyclization path whilst FMO theory would favor the *O*-complexed cyclization path, calculations were performed for both cases. For the sake of comparison, the sum of the energies of the three free molecules (–976.89741 hartrees) is taken as a common zero point.

Table 1. B3LYP/6-31G* energies [eV] of FMO orbitals and electronic charges [e$^-$] of terminal groups.

	HOMO	LUMO	$q(CH_2)1$	$q(CH_2)4$	$q(CH_2)5$	qO6
Formaldehyde	–	–1.15	–	–	+0.323	–0.323
Formaldehyde·BF_3	–	–2.67	–	–	+0.446	–0.326
Azadiene	–6.19	–	+0.196	–0.106	–	–
Azadiene·BF_3	–7.35	–	+0.315	–0.056	–	–

N-Complexation

The complexation of the azadiene with BF_3 does not change the geometry of the azadiene skeleton[9] substantially and, consequently, the behavior of the system is very similar to that of the uncatalyzed cyclization. The calculations (Scheme 5) show the preliminary formation of a stabilizing electrostatic complex (**EC2**) with a mean distance of 3 Å between the two molecules. A transition state was located (**TS2**, Figure 2) with an energy 16.4 kcal mol^{-1} higher than that of the electrostatic complex.



Scheme 5.

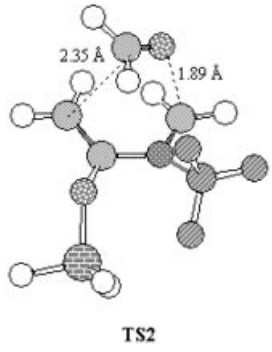


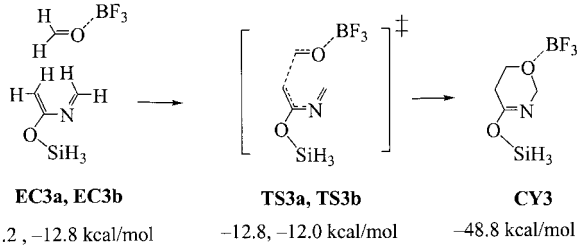
Figure 2. Gauss view of the optimized structure of **TS2**.

The transition state **TS2**, which has the same configuration as **TS1** (M,up or enantiomeric P,down), is characterized by a minor twisting of the azadiene skeleton (9°) with respect to that in **EC2** (47°), a neat pyramidalization of C1, C4, and C5 (150–160°) and by the presence of two incipient bonds (C4–C5 and C1–O6).

The coordination with BF_3 increases the electrophilic character of C1 (Table 1) and favors the bonding to the aldehyde oxygen, as shown by the lengths and bond orders of the two forming bonds (2.35 Å, 0.28 e$^-$ and 1.89 Å, 0.41 e$^-$, respectively). However, these lengths and the overall geometry of the transition state allow us to consider this reaction as an HDA concerted reaction with a certain degree of asynchronicity. No transition state accountable for a stepwise reaction was found. All the attempts to form a zwitterionic aldol-type structure starting from the *s-cis or s-trans* azadiene form resulted either in the formation of **TS2** or in a separation to the reactants.

O-Complexation

BF_3-complexed formaldehyde can approach the *s-cis* azadiene skeleton in an *endo* or *exo* fashion. In the *endo* approach no formation of a zwitterionic or HDA-type transition state is observed due to the steric hindrance between the BF_3 and the azadiene imine bond. In the *exo* approach a preliminary formation of two tight, stabilizing electrostatic complexes (**EC3a** and **EC3b**, Scheme 6), very close in distance (2.5 Å) and with a P,up (M,down) configuration for **EC3a** and P,down (M,up) for **EC3b**, is observed.



Scheme 6.

Two transition states originate from these two electrostatic complexes, namely **TS3a** and **TS3b** (Figure 3), respectively, with an energy 0.4 and 0.8 kcal mol^{-1} higher than that of the corresponding electrostatic complex. They differ only in their configuration P,up (+18° and –90°) and M,up (–33° and –68°). The azadiene skeleton is more twisted than in the previously observed transition states (18° and 33°), and, due to the coordination with BF_3, which increases the electrophilic character of the aldehyde carbon (Table 1), both the transition states are characterized by the presence of only one incipient bond between C4 and C5, as shown by the values of the bond lengths and bond orders (2.25 Å, 0.29 e$^-$ in **TS3a** and 2.20 Å, 0.32 e$^-$ in **TS3b**), by the neat pyramidalization of C4 and C5 (150–160°), and by the long distance between C1 and O6 (3.2 Å). **TS3a** and **TS3b**, which have a geometry apt to directly form a ring, close to **CY3** even though the incipient bond between C1 and O6 is failing in the transition states.

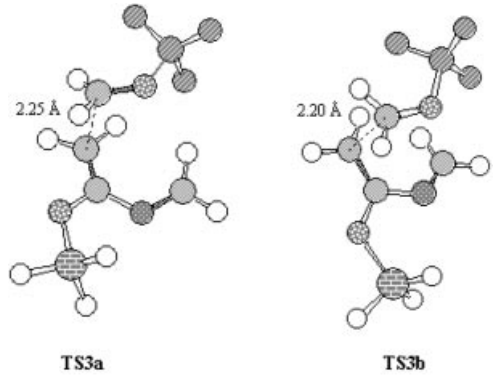
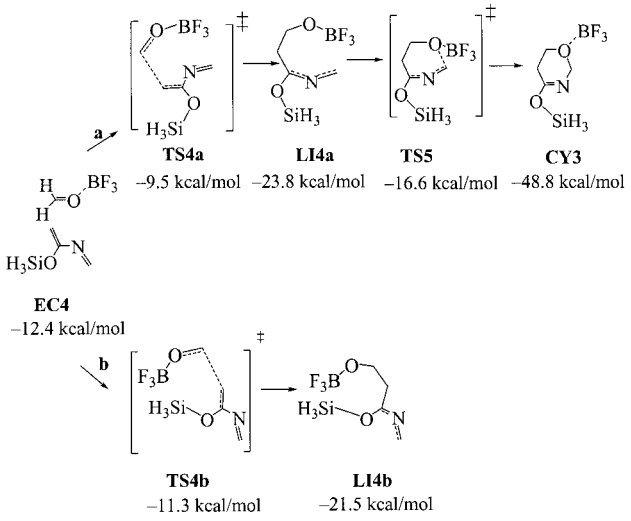


Figure 3. Gauss view of the optimized structures of **TS3a** and **TS3b**.

In contrast to what is observed in the previous cases, the attack of the complexed formaldehyde on the *s-trans* form of the azadiene is now possible. In this case a preliminary formation of a stabilizing electrostatic complex (**EC4**) with a mean distance of 3 Å between the two molecules also takes place, followed by bond formation between C4 and C5. As many orientations of the two molecules are possible

in the formation of the new bond, all the relevant geometries in discrete staggered conformations were examined, with BF_3 *endo* or *exo* to the azadiene skeleton (dihedral angles B–O6–C5–C4 of +90° or –90°, respectively). The results are shown in Scheme 7.



Scheme 7.

Only two transition states were found (**TS4a** and **TS5**; Figure 4), with an energy 2.9 and 1.1 kcal mol^{-1} higher than that of the electrostatic complex and showing only one net incipient bond between C4 and C5 (2.22 Å, 0.34 e$^-$ for **TS4a** and 2.21 Å, 0.32 e$^-$ for **TS5**). They are characterized by a different geometry around the incipient bond, with **TS4a** having the C–O bond eclipsed to the C3–C4 bond (0.1°) and BF_3 *exo* to the azadiene skeleton and **TS5** having the C–O bond in a *gauche* conformation with the C3–C4 bond (–69.5°) and BF_3 *endo* to the azadiene skeleton. In both cases an acyclic aldol-like structure is formed (**LI4** in Figure 4 and **LI5** in Figure 5) due to the stabilization effect of the LA catalyst, which neutralizes the negative charge on the oxygen through the formation of a neat O–B single bond (2.21 Å, 0.65 e$^-$).

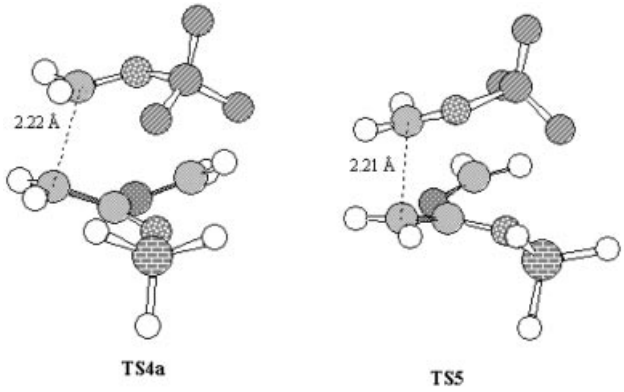


Figure 4. Gauss view of the optimized structures of **TS4a** and **TS5**.

The two structures present a different geometry that strongly affects their reactivity. In **LI5** the BF_3 and the SiH_3 groups are on the same side of the molecule, with a stabilizing interaction between the silicon atom and one of the fluorine atoms (Si···F 2.20 Å). This geometry forces the C=N bond onto the other side of the C–O bond, with the consequence that the long distance between C1 and O6 (4.50 Å) prevents a further cyclization to **CY3**. In **LI4**, however, the BF_3 and SiH_3 groups are on opposite sides of the molecule and C1 and O6 are enough close (3.41 Å) and have the right geometry to allow cyclization to **CY3**. This happens through the transition state **TS4b** (Figure 6), which is characterized by an incipient bond between C1 and O6 (2.50 Å, 0.11 e$^-$).

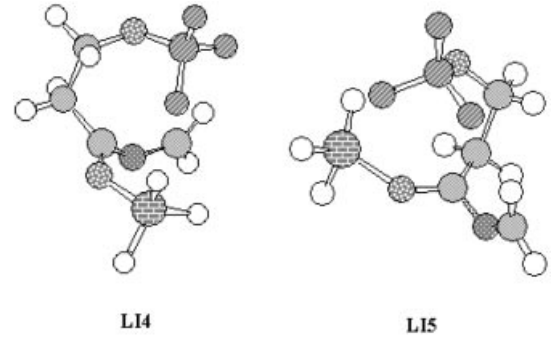


Figure 5. Gauss view of the optimized structures of **LI4** and **LI5**.

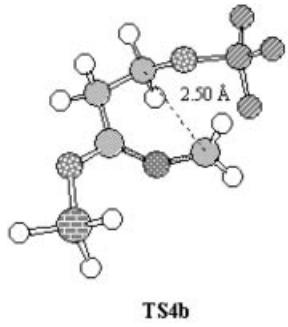


Figure 6. Gauss view of the optimized structure of **TS4b**.

Discussion

The reaction paths described in Schemes 6 and 7 deserve some comments. First of all it must underlined that the paths described in Scheme 6 are characterized by a *single* transition state, which is directly connected to the cyclization product. All the attempts to find an acyclic intermediate failed, and a separation of the reactants or a cyclization to **CY3** occurred. Therefore, even if only one incipient bond is formed in the transition state, the reactions described in Scheme 6 can be considered as one-step HDA-type reaction characterized by a high level of asynchronicity. On the contrary, the presence of two transition states and an acyclic intermediate in path a of Scheme 7 allows us to consider this path as that of an aldolic two-step cyclization, which is competitive with the reaction paths described in Scheme 6. The latter, however, are favored by the very low activation energy of their unique transition states.

A plot of the relative energy reaction coordinates for the LA-catalyzed reaction paths (Figure 7) shows that the *N*-complexation path is characterized by the highest activation energy. As a consequence, even if *N*-complexation is favored over *O*-complexation, in the process of the reaction the *O*-complexation paths 3 and 4 (Figure 7) are neatly favored. At this point we should draw attention to the activation energy values that we found for the BF_3 *O*-complexed, uncatalyzed, and BF_3 *N*-complexed HDA reactions (0.4–0.8, 12.6, and 16.4 kcal mol^{-1}), which have the same trend of the $LUMO_{dienophile} - HOMO_{diene}$ energy difference (ΔE = 3.52, 5.04, and 6.20 eV, Table 1), thus confirming the effectiveness of FMO theory in predicting the reactivity of such systems. The different observed need for the presence of a Lewis acid catalyst to perform a cyclization[3,4] can therefore be ascribed to the effect exerted on the frontier orbitals by the substituents. Accordingly, electron-donor substituents present on the azadiene substrate,[3a,3b] which increase the azadiene HOMO energy,[10] have the effect of decreasing the $LUMO_{dienophile} - HOMO_{diene}$ energy difference and the reaction proceeds without acid catalysis. The same effect may be observed when strong electrophilic aldehydes are used.[3b] In this case the decrease of the aldehyde LUMO energy[10] allows the reaction to take place without a catalyst. Finally, with electron-withdrawing or neutral substituents present on the azadiene substrate[4] the gap energy is higher and an LA catalyst is necessary in order for a reaction between the azadiene and the aldehyde moieties to take place. Under such conditions, in the absence of an acid catalyst, an electrocyclic conrotatory closure of the azadiene moiety is preferred, leading to a four-membered cyclic azetidinone.[7]

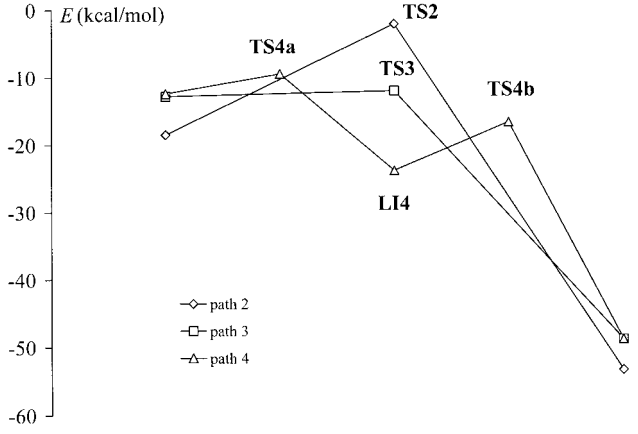


Figure 7. Path profile for LA-catalyzed reactions.

Conclusions

The uncatalyzed cyclization is a classic hetero-Diels–Alder reaction that occurs through a synchronous mechanism, as shown by the structure of the transition state. In the LA-catalyzed reaction BF_3 can coordinate to either the azadiene or the aldehyde moiety. In the first case, the reduced nucleophilicity of the azadiene strongly increases the energy activation of the HDA-type cyclization and makes this reaction path the less probable one, whereas in the second case the enhanced electrophilicity of the aldehyde leads to an easier cyclization, which can take place through an HDA asynchronous concerted mechanism or an aldolic two-step one. The presence of substituents with a different stereoelectronic character can shift the reaction towards one or the other of these possible ways. Further studies are in progress on this subject.

Experimental Section

Computational Methods: All calculations were carried out at the B3LYP/6-31G* theory level using the Gaussian 98 program.[11] The use of the hybrid B3LYP functional appears to adequately reproduce the activation energies of pericyclic reactions.[5,12] 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 Wiberg bond-orders of the incipient bonds in the transition states were calculated by the natural bond orbital (NBO) method[13] as implemented in Gaussian 98. Three transition states representative of the various aspects of the examined reactions (**TS1**, **TS2**, and **TS2b**, see above) were recalculated at the MP2 level and their geometries and energy differences found to be fully in agreement with the results obtained at the B3LYP level (see Supporting Information for further experimental details).

Supporting Information (see footnote on the first page of this article): Tables of energies and Cartesian coordinates of all the optimized structures at the B3LYP and MP2 levels.

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