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The influence of BF$_3$ on the reaction path of the [4 + 2] cycloaddition of vinylketene with formaldimine. A computational study.

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Abstract: A comprehensive B3LYP/6-31+G* study of the influence of BF$_3$ on the [4 + 2] cycloaddition of vinylketene with formaldimine was conducted. For this purpose, the complete pathway was determined and changes in different magnetic properties (magnetic susceptibility, χ, magnetic susceptibility anisotropy, χ_{anis}, and the nucleus-independent chemical shifts, NICS) were monitored along the reaction profile with a view to estimating the aromatization associated to the process. We have also applied the ACID (anisotropy of the current-induced density) method with the same intention.

Introduction

Since Staudinger discovered ketenes in 1905,[1] their structures, reactions and use in organic synthesis are been widely studied.[2] The [2 + 2] cycloadditions of ketenes have been of great utility in synthetic methodology. An example for this is the cycloaddition with imines in order to obtain *β*-lactam antibiotics.[3] In the last years, the [4 + 2] cycloadditions where the ketene has a dienophile behavior have been investigated. Yamabe et al. have provided NMR evidence for [4 + 2] cycloadditions involving the carbonyl of the ketene with dienes.[4]

Birney et al.[5] have found a concerted pathway for the reaction of vinylketene with formaldimine at B3LYP/6-31G* level. They concluded a pericyclic nature of this cycloaddition on the basis of the geometric and electronic structure of the transitions state and the energy barrier.

Pseudopericyclic reactions were originally defined by Lemal as concerted transformations whose primary changes in bonding compass a cyclic array of atoms, at one (or more) of which nonbonding and bonding atomic orbital interchange roles.[6,7] This interchange means a disconnection in the cyclic array of overlapping orbitals. The problem of this definition seems to be in that the orbital description is not unique.

Birney and coworkers have studied a large number of pseudopericyclic reactions.[8-14] They have found three common characteristics: very low activation energies, planar transition states, and a pseudopericyclic reaction is always orbital symmetry allowed, regardless of the number of electrons involved.

Other studies[15] have employed the aromatic character of the transition states as an argument to explain the difference between pericyclic and pseudopericyclic reactions. The cyclic loop of pericyclic reactions is known to give rise to aromatic transition states,[16-20] and the orbital disconnection in the pseudopericyclic reactions prevents this aromaticity.

However, an aromatic character of a transition state does not imply the impossibility of pseudopericyclic reaction, as we have demonstrated in a previous paper.[21] This affirmation indicates the need to study the whole process and not only the transition structure in order to define a process as pericyclic or pseudopericyclic. In addition, we have stood out the importance of the study of the

magnetic properties along the reaction profile in this controversial matter.[22] For this reason, this work carries out a comprehensive study of the aromaticity along the reaction profile of the whole process of [4+2] cycloaddition of formaldimine with vinylketene. This aromaticity was examined in terms of magnetic susceptibility, χ, magnetic susceptibility anisotropy, χ_{anis}, and the nucleus-independent chemical shifts, NICS, reported by Schleyer.[23]

Herges and Geunich[24] have recently developed a method based on magnetic properties which seems to be a good tool in order to distinguish between coarctate and pseudocoarctate and pericyclic and pseudopericyclic as we have indicated in other papers.[21,22,25] This method is referred as ACID (anisotropy of the current-induced density) method and it has be employed in this study.

Moreover, we are interested in the effects of BF_3 on the behavior of this reaction. The BF_3, as Lewis acid, can form complex chemicals containing Oxygen, Nitrogen, Sulfur, and other electron pair donors. In this case, we have studied two possible complexations: with the oxygen or with the π cloud of the vinylketene.

Results and discussion

1. Computational methods:

Geometries were optimized at the Density Functional Theory (DFT) level with the 6-31+G* basis set. Becke's three-parameter exchange functional (B3)[28] was employed in conjunction with the Lee-Yang-Parr correlation functional (LYP).[29]All points were confirmed as minima or transition states by calculating the harmonic vibrational frequencies at B3LYP/6-31+G* level, using analytical second derivatives. In addition, the path for the reaction was obtained using the intrinsic reaction coordinate (IRC)[28-30] at same theoretical level.

The ketene object of our study presents different conformations. The reactant for the cycloaddition is the *s-cis* conformation (*cis-1*)

Magnetic properties: nucleus-independent chemical shift (NICS), magnetic susceptibility (χ) and magnetic susceptibility anisotropy (χ_{anis}) were calculated at different points along the IRC. In the

magnetic susceptibility calculations, the NMR shielding tensors have been computed with a larger basis set (6-311+G(2d,p)). In order to obtain the NICS along the reaction path at B3LYP/6-31+G* level, we have employed the GIAO (Gauge-Independent Atomic Orbital) method[31] but this method does not provide information about magnetic susceptibility, so χ, and χ_{anis} were calculated using the IGAIM (Individual Gauges for Atoms in Molecules) method,[32,33] which is a slight variation of the CSGT (Continuous Set of Gauge Transformations) method.[32-34] Finally, CSGT method at B3LYP/6-31+G* level of theory was employed in ACID calculations.

All calculations were performed with the Gaussian98 software package.[35]

2. Reactions paths:

The relevant stationary points found in the potential energy surfaces are presented in Scheme 1 and their energies are indicated in Table 1. As we can observe at B3LYP/6-31+G* level we have found a two stepwise process.

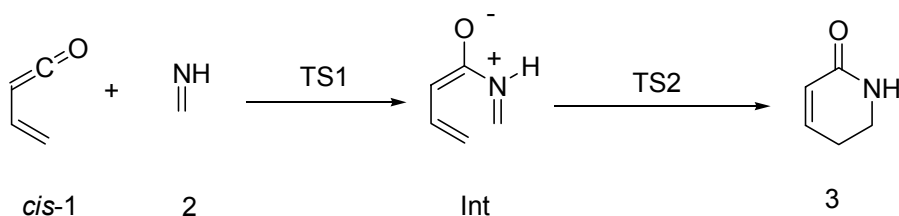**Scheme 1. Reaction paths for the process.**

Figure 1 shows the differences in the reaction path when BF_3 is included in the reaction. Without BF_3, the higher energy barrier corresponds to the nucleophilic attack of the imine nitrogen on the ketene, but for the complexes with BF_3, the electrocyclic ring closure has a higher barrier. When we have included the ZPE energy the barriers for the nucleophilic attack and the ring closure are respectively: 9.27 and 3.38 kcal mol^{-1} without BF_3, 3.58 and 4.91 kcal mol^{-1} in the π-BF_3 case, and 3.71 and 11.87 kcal mol^{-1} in the O-BF_3 case. It is worth pointing out the stabilization of the zwitterion by complexation with BF_3, specially in the O-BF_3 case.

TABLE 1. Calculated relatives energies in kcal mol^{-1} of the stationary points. The values are relative to the reactive conformation of reactants and the values in parenthesis are corrected with ZPE.

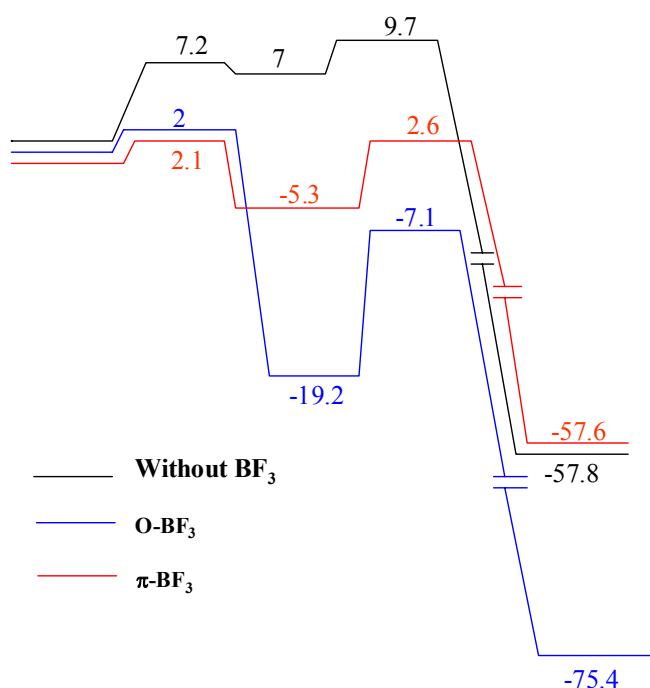| Structure	Relative energy		
	Without BF$_3$	π-BF$_3$	O-BF$_3$
TS1	7.23 (9.27)	2.13 (3.58)	2.05 (3.71)
Int	6.98 (9.69)	-5.30 (-1.01)	-19.16 (-14.33)
TS2	9.70 (12.65)	2.58 (3.90)	-7.08 (-2.46)
3	-57.83 (-51.13)	-57.60 (-50.92)	-75.40 (-67.38)

FIGURE 1. Energy profiles for the three cycloadditions. The energy values are in kcal mol^{-1} and referred to reactant.

3. Magnetic properties along the reaction path: susceptibility, anisotropy and NICS:

In the ring closure step, we can study the possible development of aromaticity and the pericyclic or not nature of the cyclization. This is the reason why we have only monitored the variation of magnetic properties in this part of the reaction profile. Figure 2 shows the variation of magnetic susceptibility (χ), magnetic susceptibility anisotropy (χ_{anis}), and nucleus-independent chemical shift

(NICS) during the electrocyclation process. For pericyclic reactions, a marked minimum is observed near the transition structure, indicating its special aromaticity.

In our case, the graphics for susceptibility and its anisotropy seem to lead us to different conclusions. This contradicting behavior between isotropic magnetic susceptibility and anisotropy can be a consequence of the different role the *zz* component of the magnetic susceptibility tensor plays in both properties. The shielding associated with aromatization is mainly due to the *zz* (perpendicular to the molecular plane) component of magnetic susceptibility. The anisotropy responds more readily to changes in zz component than mean magnetic susceptibility does, probably leading to the differences thus noted.

In any case, it should be remembered that some caution must be present when analyzing results from magnetic susceptibility, since they correspond to global properties, and effects not directly involved in aromatization could distort the observed behavior.

For this reason, we have also employed another way of measuring aromaticity: the NICS index proposed by Schleyer, which is defined as the negative value of the magnetic shielding.[23] This property can be evaluated at a single point of the molecule, avoiding some of the problems related to global properties as susceptibility and anisotropy. In our case, The NICS values were calculated in the geometric center of the forming ring.

For the studied reactions, minimum close to transition state is not present in the NICS curves, appearing even a marked maximum for the reaction without BF_3 and O-BF_3. This fact indicates the absence of special aromaticity in the transition state. On the basis of this behavior the reactions should be classified as not pericyclic.
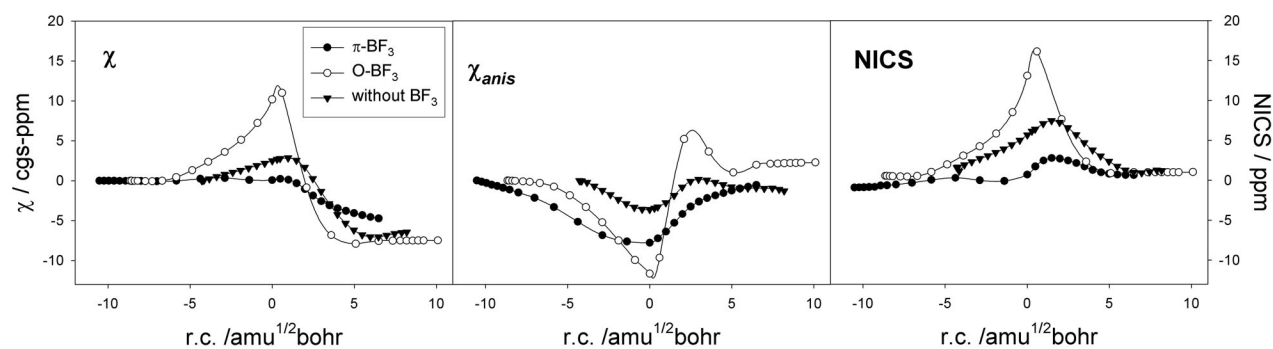
FIGURE 2. Variation of magnetic properties along the reaction path.

4. ACID (anisotropy of the current-induced density) method:

In order to carry out a deeper study of the nature of this reaction, the ACID method[24] was employed. This is a recently published method to investigate the delocalisation and conjugation effects in molecules. It provides a powerful way to visualize the density of delocalised electrons and quantify conjugation effects. The ACID approach has several advantages: it is a scalar field which is invariant with respect to the relative orientation of the magnetic field and the molecule, it is not a simple function of the overall electron density, it has the same symmetry as the wave function, and it can be plotted as an isosurface. Some examples have demonstrated the applicability of this method to distinguish between pericyclic/pseudopericyclic and coarctate/pseudocoarctate reactivity.[21,22,24,25,36,37]
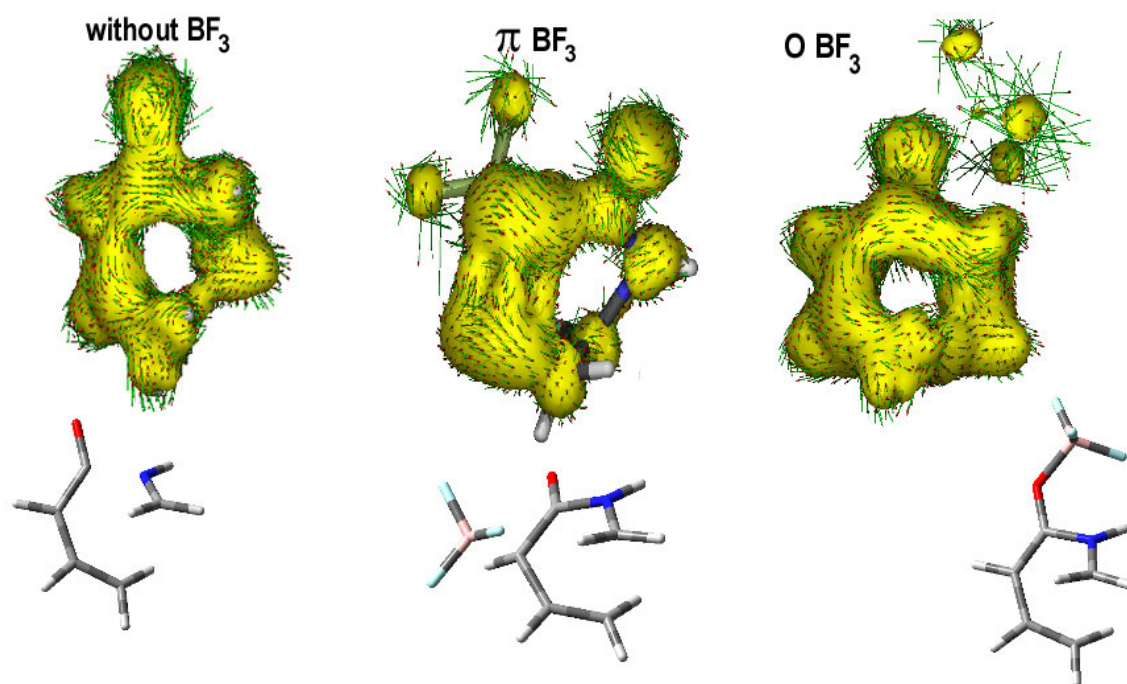
FIGURE 3. ACID plots for the transition structures of the studied reactions.

Figure 3 presents the ACID isosurface of the transition states for these reactions at an isosurface value of 0.05 au. Current density vectors are plotted onto the ACID isosurface. Figure 3 shows paratropic ring current for the transition state of the reaction without BF$_3$ and O-BF$_3$, indicating its antiaromatic character. Fot the π case, we can observe a disconnection in the ring current. Both behavior are in agree with the no- pericyclic character of the reactions. We have to indicate that when the BF$_3$ attacks to π cloud, the antiaromatic character of the transition state disappear. This fact can also be observed in the NICS graphic.

Conclusions

The main conclusion of this work is the stepwise and no-pericyclic nature of the [4 + 2] cycloaddition of vinylketene with formaldimine and when the vinylketene is complexed with BF$_3$.

We have observe the important differences in the reaction profile by complexation with BF$_3$, specially the stabilization of the zwitterion intermediate in O-BF$_3$ case.

We have demonstrated the necessity to study the whole process and not only the transition state in order to define a process as not pericyclic. The variation of magnetic properties, specially NICS,

along the IRC does not present a minimum near the transition state structure. This minimum (maximum of aromatic character) is a characteristic of the pericyclic reaction and an important distinction between pericyclic and pseudopericyclic processes.

The ACID isosurfaces of the transition states do not have the diatropic cyclic topology which characterized to aromatic structures. In this case, the isosurfaces for transition states of the reactions without BF_3 and $O-BF_3$ present a paratropic ring current, indicating an antiaromatic character and the complexation of BF_3 and the π cloud of the transition state produce the loss of this character. This a new example of the applicability of the ACID method in order to distinguish pericyclic and pseudopericyclic reactions.

We have to stand out the importance of the study of the magnetic properties along the reaction profile in a controversial matter, namely, the difference between pericyclic and pseudopericyclic processes.

References:

(1) Staudinger, H. *Chem. Ber.* **1905**, *38*, 1735-1739.

(2) Tidwell, T. T. *Ketenes*; John Wiley & Sons: New York, 1995.

(3) Georg, G. I. *The Organic Chemistry of β-Lactams*; VCH: New York, 1992.

(4) Machiguchi, T.; Hasegawa, T.; Ishiwata, A.; Terashima, S; Yamabe, S.; Minato. T. *J. Am. Chem. Soc.* **1999**, *121*, 4771-4786.

(5) Zhou. C.; Birney, D. M. *J. Am. Chem. Soc.* **2002**, *124*, 5231-5241.

(6) Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325.

(7) Bushweller, C. H.; Ross, J. A.; Lemal, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 629.

(8) Birney, D. M.; Wagenseller, P. E.; *J. Am. Chem. Soc.* **1994**, *116*, 6262.

(9) Birney, D. M. *J. Org. Chem.* **1996**, *61*, 243.

(10) Birney, D. M.; Ham, S.; Unruh, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 4509.

(11) Birney, D. M.; Xu, X.; Ham, S. *Angew. Chem. Int. Ed.* **1999**, *38*, 189.

(12) Birney, D. M. *J. Am. Chem. Soc.* **2000**, *122*, 10917.

(13) Shumway, W.; Dalley, N. K.; Birney, D. M. *J. Org. Chem.* **2001**, *66*, 5832.

(14) Shumway, W.; Ham, S.; Moer, J.; Whittlesey, B. R.; Birney, D. M. *J. Org. Chem.* **2000**, *65*, 7731.

(15) de Lera, A. R.; Alvarez, R.; Lecea, B.; Torrado, A.; Cossio, F. P. *Angew. Chem. Int. Ed.* **2002**, *41*, 1147.

(16) Zimmerman, H. E.; *Acc. Chem. Res.* **1971**, *4*, 272.

(17) Herges, R.; Jiao, H.; Schleyer, P. v. R. *Angew. Chem. Int. Ed.* **1994**, *33*, 1376.

(18) Jiao, H.; Schleyer, P. v. R. *J. Phys. Org. Chem.* **1998**, *11*, 655.

(19) Manoharan, M.; De Proft, F.; Geerlings, P. *J. Org. Chem.* **2000**, *65*, 7971.

(20) Manoharan, M.; De Proft, F.; Geerlings, *J. Chem. Soc., Perkin Trans. 2,* **2000**, 1767.

(21) Peña-Gallego, A.; Rodriguez-Otero, J.; Cabaleiro-Lago, E. M. *J. Org. Chem.* **2004**, *69*, 7013.

(22) Peña-Gallego, A.; Rodriguez-Otero, J.; Cabaleiro-Lago, E. M. *Eur. J. Org. Chem.* **2005**, 3228.

(23) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317.

(24) Herges, R.; Geuenich, D.; *J. Phys. Chem. A* **2001**, *105*, 3214.

(25) Rodriguez-Otero, J.; Cabaleiro-Lago, E. M.; Hermida-Ramon, J. M.; Peña-Gallego, A. *J. Org. Chem.* **2003**, *68*, 8823.

(26) A. D. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(27) Lee, C.; Yang, W.; Parr, R. J. *Phys. Rev. B* **1988**, *37*, 785.

(28) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363.

(29) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.

(30) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5223.

(31) Wolinski, K.; Hilton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.

(32) Keith, T. A.; Bader, R. F. W. *Chem. Phys. Lett.* **1993**, *210*, 223.

(33) Keith, T. A.; Bader, R. F. W. *Chem. Phys. Lett.* **1992**, *194*, 1.

(34) Cheeseman, J. R.; Frisch, M. J.; Trucks, G. W.; Keith, T. A. *J. Chem. Phys.* **1996**, *104*, 5497.

(35) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox,D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, **1998**.

(36) Kimball, D. B.; Weakley, T. J. R.; Herges, R.; Haley, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 13463.

(37) Herges, R.; Papafilippopoulos, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4671.