JOC Article

A DFT Study of the Boulton−Katritzky Rearrangement of (5*R*)-4-Nitrosobenz[*c*]isoxazole and Its Anion: Pseudopericyclic Reactions with Aromatic Transition States

Angeles Peña-Gallego,[†] Jesús Rodríguez-Otero,*,[†] and Enrique M. Cabaleiro-Lago[‡]

Departamento de Química Física, Facultade de Química, Universidade de Santiago de Compostela, Avda das Ciencias s/n. 15782, Santiago de Compostela, Spain, and Departamento de Química Física, Facultade de Ciencias, Universidade de Santiago de Compostela, Campus de Lugo, Avda Alfonso X El Sabio s/n, 27002 Lugo, Spain

qftjesus@usc.es

Received May 19, 2004

The nature of the Boulton−Katritzky rearrangement of (5*R*)-4-nitrosobenz[*c*]isoxazole and its anion was studied employing three methodologies: calculation of magnetic properties (magnetic susceptibility, magnetic susceptibility anisotropy, and the nucleus-independent chemical shifts), the natural bonding orbital analysis, and the ACID (anisotropy of the current-induced density) method. The deep analysis of the results indicates a pseudopericyclic character for these reactions despite the aromaticity of the transition states.

Introduction

The Boulton−Katritzky rearrangements (BKR) of (5*R*)-4-nitrosobenz[*c*]isoxazole and its anion were proposed to be pseudopericyclic reactions by Rauhut.[1] The Boulton−Katritzky rearrangement is an important reaction in heterocyclic chemistry.[2,3] Parry and Rees classified the bicyclic BKR as a [1,9]-sigmatropic rearrangement,[4,5] on the basis of experimental studies of 7-acetyl-3-methylanthranil. However, Rauhut has indicated that the bicyclic BKR should not be classified as a [1,9]-sigmatropic rearrangement but rather as a pseudopericyclic reaction.

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 co-workers have studied a large number of pseudopericyclic reactions.[8−15] They have found three common characteristics: very low or zero activation energies, planar transition states, and a pseudopericyclic reaction is always orbital symmetry allowed, regardless of the number of electrons involved.

Other studies[16] 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,[17−21] and the orbital disconnection in the pseudopericyclic reactions prevents this aromaticity. So, pericyclic reactions exhibit markedly increased aromaticity in the vicinity of transition structures while pseudopericyclic reactions do not show such aromaticity, due to the disconnection of the atoms involved. However, it is necessary to study the cyclization process as a whole and not only the transition states.[22−24] Moreover, aromaticity and its quantification remain

---

* To whom correspondence should be addressed. Fax: +34-981-595012.

[†] Facultade de Química.

[‡] Facultade de Ciencias.

(1) Rauhut, G. *J. Org. Chem.* **2001**, *66*, 5444.

(2) Bailey, A. S.; Case, J. R. *Tetrahedron* **1958**, *3*, 113.

(3) Harris, K. R.; Katritzky, A. R.; Majid-Hamid, A. *J. Chem. Soc.* **1963**, 197.

(4) Parry, K. P.; Rees, W. C. *J. Chem. Soc., Chem. Commun.* **1971**, 833.

(5) Balli, H.; Gunzenhauser, S. *Helv. Chim. Acta* **1978**, *61*, 2628.

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

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

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

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

(19) Jiao, H.; Schleyer, P. v. R. *J. Org. Chem.* **1946**, *11*, 655.

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

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

(22) Rodriguez-Otero, J.; Cabaleiro-Lago, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1147.

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

10.1021/jo0491509 CCC: $27.50 © 2004 American Chemical Society
Published on Web 09/21/2004

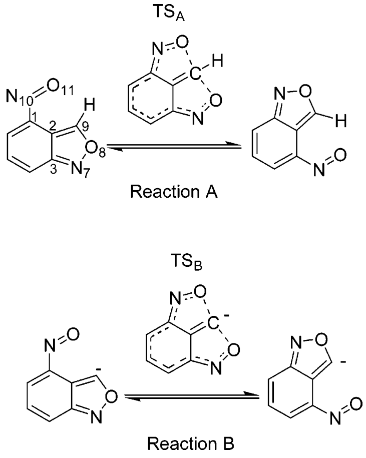


FIGURE 1. Reaction schemes for the two reactions: reaction A is the Boulton−Katritzky rearrangement of 4-nitrosobenz[*c*]isoxazole and reaction B is the Boulton−Katritzky rearrangement of 4-nitrosobenz[*c*]isoxazole anion.

controversial subjects. For this reason, this work carries out a comprehensive study of the whole BKR process in (5*R*)-4-nitrosobenz[*c*]isoxazole and its anion. The aromaticity was examined in terms of magnetic susceptibility, χ, magnetic susceptibility anisotropy, χ_{ani}, and the nucleus-independent chemical shifts (NICS) reported by Schleyer.[25] We have also studied the reactions employing the natural bonding orbital (NBO) analysis.[26−28]

Although the pseudopericyclic character of the BKR of (5*R*)-4-nitrosobenz[*c*]isoxazole and its anion was previously proposed,[1] it seems interesting to apply the criterion recently developed by our group to differentiate a pseudopericyclic reaction from a pericyclic reaction based on the magnetic properties along the reaction path.[22−24] This will be a new proof of the validity of this magnetic criterion.

Herges and Geunich[29] have recently developed a new method based on magnetic properties. This method, named ACID (anisotropy of the current-induced density), has been used to study several pericyclic reactions and to distinguish between coarctate and pseudocoarctate reactions.[30,31] We have employed this method in a previous study, and it seems to be a good tool to distinguish between pericyclic and pseudopericyclic reactions.[23]

It is necessary to indicate the presence of two rotamers in our systems due to the orientation of the nitroso group. All the calculations are made for the most stable rotamer, which is shown in Figure 1.

Computational Methods

Geometries of all stationary points were obtained from density functional theory (DFT) calculations (specifically B3LYP functional)[32,33] employing the 6-31+G* basis set. The DFT method was selected on the basis of the good results obtained in DFT calculations for other pericyclic and pseudopericyclic reactions.[12,24,34] With regard to the basis set, structural and energetic data obtained with 6-31+G* are in agreement with data obtained with a bigger basis set (activation energy for the neutral species with zero point energy correction is 46.28 kcal/mol with our basis set and 46.24 with the 6-311+G** basis set).[1] All points were confirmed as minima or transition states by calculating the harmonic vibrational frequencies, using analytical second derivatives. In addition, the path for the two reactions was obtained using the intrinsic reaction coordinate (IRC)[35−37] with mass-weighted Cartesian coordinates at the same theoretical level. Magnetic properties, nucleus-independent chemical shift (NICS), magnetic susceptibility (χ), and magnetic susceptibility anisotropy (χ_{ani}), 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)) as recommended. To obtain the NICS at the B3LYP/6-31+G* level, we have employed the GIAO (gauge-independent atomic orbital) method,[38] but this method does not provide information about magnetic susceptibility, so χ, and χ_{ani} were calculated using the IGAIM (individual gauges for atoms in molecules) method,[39,40] which is a slight variation of the CSGT (continuous set of gauge transformations) method.[39−41] This CSGT method at the same level of theory was employed in ACID calculations. Processes were also monitored by applying the NBO (natural bond orbital) method[26−28] along the IRC at B3LYP/6-31+G* level.

All calculations were performed with the Gaussian98 software package.[42]

Results and Discussion

Reaction Paths. Figure 2 shows the energy profiles obtained from the IRC calculations. Pseudopericyclic reactions possess low activation energies with respect to analogous pericyclic reactions.[8−15] In the BKR reactions studied, the activation barriers are quite high as compared to those for typical pseudopericyclic reactions. This may be due to the involvement of a tricyclic transition state with more ring strain than the corresponding bicyclic reactant or product. In addition, the neutral species shows a higher barrier than the anionic species. Rauhut[1] has obtained the same result and explains it

---

[24] Rodriguez-Otero, J.; Cabaleiro-Lago, E. M. *Chemistry* **2003**, *9* (8), 1837.

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

[26] Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211.

[27] Reed, A. D.; Curtiss, L. A.; Weinhold, F. *Chem. Rew.* **1988**, *88*, 899.

[28] Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO 3.1 Program Manual*, **1988**.

[29] Herges, R.; Geuenich, D. *J. Phys. Chem. A* **2001**, *105*, 3214.

[30] Herges, R.; Papafilippopoulos, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4671.

[31] Kimball, D. B.; Weakley, T. J. R.; Herges, R.; Haley, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 13463.

[32] Lee, C.; Yang, W.; Parr, R. J. *Phys. Rev. B* **1988**, *37*, 785.

[33] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

[34] Rodriguez-Otero, J. *J. Org. Chem.* **1999**, *64*, 6842.

[35] Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363.

[36] Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.

[37] Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5223.

[38] Wolinski, K.; Hilton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.

[39] Keith, T. A.; Bader, R. F. W. *Chem. Phys. Lett.* **1993**, *210*, 223.

[40] Keith, T. A.; Bader, R. F. W. *Chem. Phys. Lett.* **1992**, *194*, 1.

[41] Cheeseman, J. R.; Frisch, M. J.; Trucks, G. W.; Keith, T. A. *J. Chem. Phys.* **1996**, *104*, 5497.

[42] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; J. A. Montgomery, J.; Stratmann, R. E.; Burant, J. C.; pprich, 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.; Baboul, A. G.; 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 98 (Revision A.9), Gaussian, Inc. Pittsburgh, PA, **1998**.

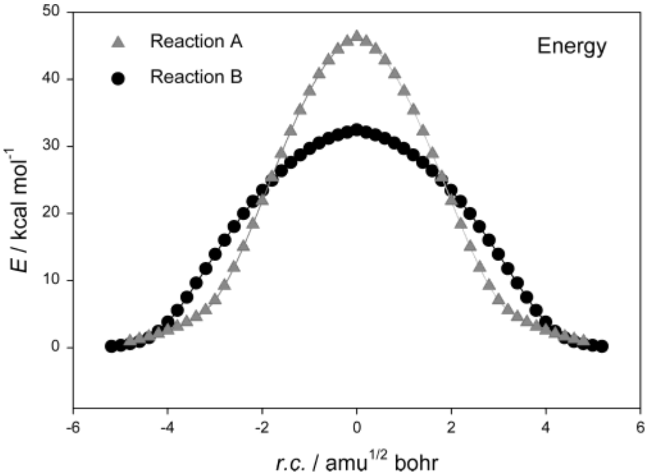


FIGURE 2. Energy profile for the reactions.

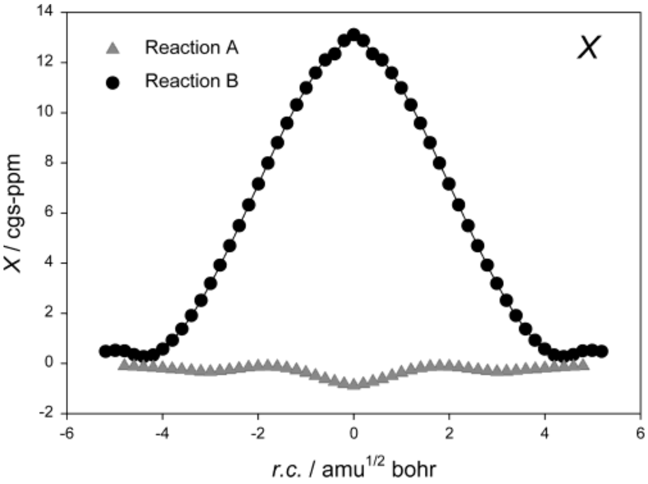


FIGURE 3. Variation of magnetic susceptibility relative to the reactant.

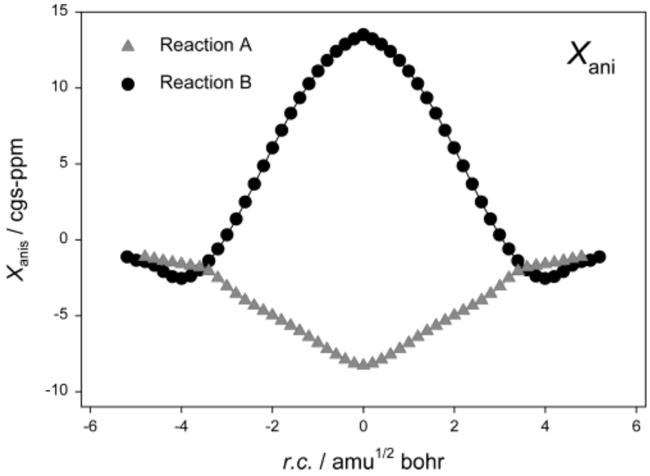


FIGURE 4. Variation of anisotropy of the magnetic susceptibility relative to the reactant

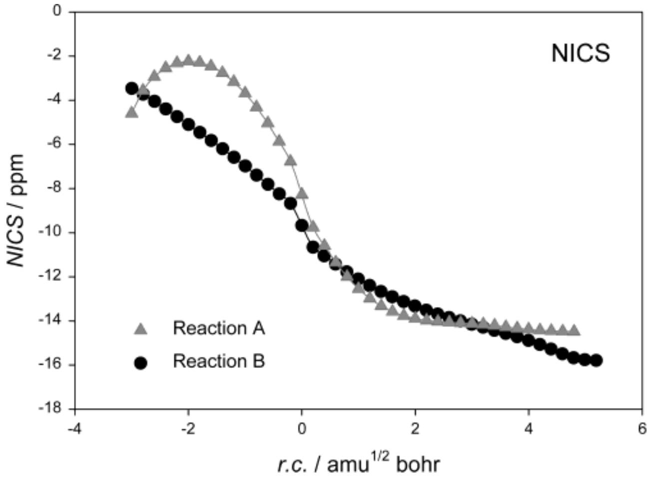


FIGURE 5. Variation of NICS along the IRC.

since the proton hinders the pseudopericyclic in-plane reaction. However, he indicates that the BKR rearrangement must be considered as a pseudopericyclic reaction and this reaction may be accelerated by deprotonation. In this work, the pseudopericyclic character will be proved on the basis of magnetic properties.

Magnetic Properties along the Reaction Path: Susceptibility, Anisotropy, and NICS. Figures 3 and 4 show the variation of magnetic susceptibility (χ) and magnetic susceptibility anisotropy (χ_{ani}) during the reaction process. For the (5*R*)-4-nitrosobenz[*c*]isoxazole anion, both graphics have the typical shape for a pseudopericyclic reaction, namely these properties do not have a minimum near the transition state. On the contrary, the graphics exhibit a maximum near the transition state, indicating a less aromatic character of the transition state than reactant and product. For the (5*R*)-4-nitrosobenz[*c*]isoxazole, the susceptibility is nearly constant along the reaction path but the anisotropy shows a minimum near the transition state.

Figure 5 collects the nucleus-independent chemical shift (NICS) values for several points in the path reaction at the (3 + 1) ring critical point of electron density as defined by Bader[43] in the forming cycle (C1−C2−C9−O11−N10). In this case, both graphics exhibit a similar behavior without a minimum in the vicinity of the transition states. On the basis of this behavior, the reactions should be classified as pseudopericyclic.

The graphics of magnetic susceptibility anisotropy and nucleus-independent chemical shift for the neutral species may seem contradictory. But we have to realize that χ_{ani} is a property of the whole molecule while the NICS is obtained for only the forming cycle. Thus, the behavior of the NICS along the IRC will be the most important property to study the cyclization process.

We have also investigated the aromatic character of the transition states for both reactions by computing the NICS values in points above and below the plane of the molecule (*z*-axis). As we can observe in Figure 6, the variation of the NICS along the *z*-axis is very similar for both reactions with very negatives values. This behavior is in agreement with a π^2 aromaticity.[44,45] In the usual π aromaticity the maximum diamagnetic shielding takes place at a certain distance above and below the molecular

---

[43] Bader, R. F. W. *Atoms in Molecules-A Quantum Theory*; Clarendon Press: Oxford, 1990; pp 13−52.

[44] de Lera, A. R.; Alvarez, R.; Lecea, B.; Torrado, A.; Cossio, F. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 557.

[45] Alajarin, M.; Sánchez-Andrada, P.; Cossio, F. P.; Arrieta, A.; Lecea, B. *J. Org. Chem.* **2001**, *66*, 8470.

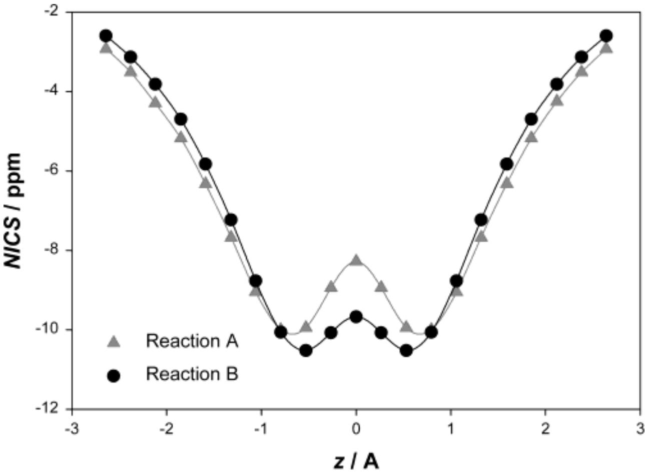


FIGURE 6. Plot of NICS versus *z* for the transition structures.

TABLE 1. Wiberg Bond Orders at Reactant and Transition State for the Most Remarkable Bonds

	A	TS_A	B	TS_B
N_7-O_8	1.08	1.49	0.94	1.50
O_8-C_9	1.14	0.44	1.22	0.29
C_9-O_{11}	0.02	0.44	0.01	0.29
$N_{10}-O_{11}$	1.78	1.49	1.77	1.50
C_2-C_9	1.47	1.65	1.32	1.66
C_1-N_{10}	1.15	1.33	1.14	1.31
C_3-N_7	1.51	1.33	1.52	1.31

plane, as our case. This effect can be described by means of two ring currents circulating at a certain distance from the molecular plane.

We have also calculated the NICS values at the geometric center of the six-membered ring in the reactant/product and transition state for both reactions. In the two cases, the NICS values are more negative (more aromatic character) for the reactant/product (−4.892 and −5.023 ppm for neutral and anion species, respectively) than for the transition state (−2.818 and −2.126 ppm for neutral and anion species, respectively). This is a small variation, and it seems to have a little repercussion for the global process.

So, in these pseudopericyclic reactions we can observe aromatic transition states but the aromatic character decreases from transition state to product and do not have a minimum near the transition state. As was indicated, some authors differentiate pericyclic and pseudopericyclic reactions on the basis of aromatic or no aromatic character of the transition states. But our case shows that the study of the whole reaction and not only the transition state is necessary to deduce a pericyclic or pseudopericyclic behavior.

NBO Analysis. The transition state and the whole path for each reaction were subjected to a comprehensive NBO analysis. Table 1 collects the Wiberg bond order at the reactants and transition states for the most important bonds in these reactions. As we can observe, the C_9-O_{11} bond is forming at same time that the O_8-C_9 bond is breaking, and in the transition state the bond order is the same for both bonds. Moreover, the N_7-O_8 bond order is increasing as the $N_{10}-O_{11}$ bond order is decreasing to same value in the transition state (1.49 for the neutral species and 1.50 for the anion). The C_1-N_{10} and C_3-N_7 bond orders are also changing to same value in the transition state.

As expected for a pseudopericyclic reaction,[6,7] the NBO analysis along the IRC indicates that the reaction involves the exchange between nonbonding and bonding orbitals (a lone pair in the O_{11} becomes the C_9-O_{11} bonding). This means a disconnection in the cyclic array of overlapping orbitals.

ACID Method. To obtain more proof of the pseudopericyclic behavior, the ACID method[26] was employed. This is a recently published method to investigate the delocalization and conjugation effects in molecules. It provides a powerful way to visualize the density of delocalized 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.[27−29]

Figure 7 presents the ACID isosurface of the transition states for both reactions at an isosurface value of 0.03 for A and 0.02 for B. We may observe the aromaticity of the transition state. For comparison, in the same figure, the ACID isosurfaces of the reactants (or products) are presented. This seems to be a new proof of the pseudopericyclic nature of both processes, showing the transition state is an intermediate step in the development of the aromatic character from open cycle to closed cycle.

Conclusions

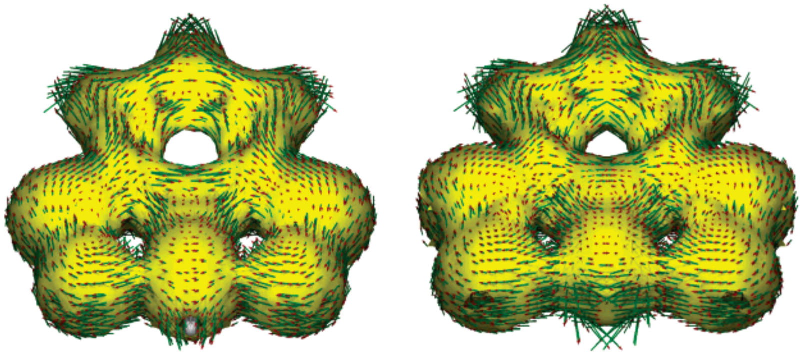
The three methodologies employed in this work show the same result: the studied reactions have a pseudopericyclic nature.

The variation of magnetic properties, in particular NICS, along the IRC indicates a continuous increase of the aromatic character during the formation of the cycle (C1−C2−C9−O11−N10) without a maximum of aromaticity near the transition state structure. The lack of a minimum in the NICS graphic (maximum of aromatic character) is a characteristic of the pseudopericyclic reaction and an important distinction between pericyclic and pseudopericyclic processes.

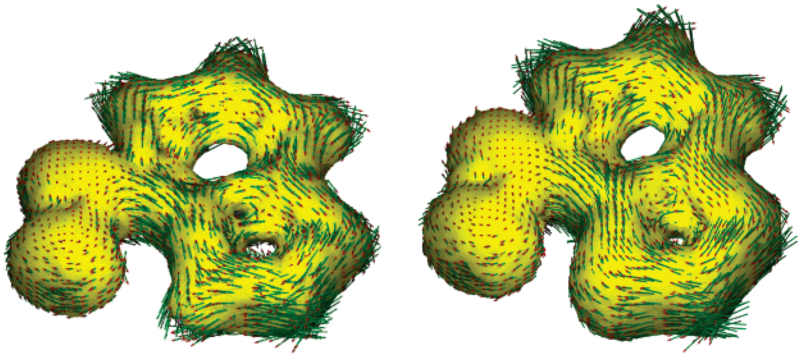
The NBO analysis along the IRC indicates that the reaction involves the exchange between nonbonding and bonding orbitals. This interchange means a disconnection in the cyclic array of overlapping orbitals and it is in perfect agreement with the Lemal's definition of pseudopericyclic reaction.[6,7]

The comparison of the ACID isosurfaces of the transition states and reactants (products) for both reactions demonstrate the applicability of the ACID method in distinguishing between pericyclic and pseudopericyclic reactions.

We have shown that these reactions have transition states with characteristics of pericyclic reactions, namely they are aromatic and have high energy barriers, but the methods used here show the pseudopericyclic nature of the reaction. We emphasize the importance of the study



TS_A: Isosurface value 0.03 TS_B: Isosurface value 0.02



$Reac_A$: Isosurface value 0.03 $Reac_B$: Isosurface value 0.02

FIGURE 7. ACID plots for the transition states and reactants of the BKR rearrangement of the nitrosobenz[*c*]isoxazole and its anion.

of the magnetic properties along the reaction profile in distinguishing between a pericyclic and a pseudopericyclic process.

Acknowledgment. We thank the Xunta de Galicia (Project PGIDIT02PXIA20901PR) and the Ministerio de Ciencia y Tecnología (BQU2003-01104) for financial support. We express our deep gratitude to Dr. Herges for his assistance and for the ACID program. A.P.-G. thanks Xunta de Galicia for a "Isidro Parga Pondal" contract. We are also thankful to the Centro de Supercomputación de Galicia (CESGA) for the use of their computers.

Supporting Information Available: Geometries, energies, and frequencies of all the structures obtained at the B3LYP/6-31+G* theoretical level. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0491509