A DFT Study of the Concerted Cyclisation of 3-Azidopropenal to Isoxazole: Is it a Pseudopericyclic Reaction According to Its Magnetic Properties?

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

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A comprehensive B3LYP/6-31+G(2d,p) study of the nature of the concerted cyclisation of 3-azidopropenal to isoxazole 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 aromatisation associated with the process. We have also applied the ACID (anisotropy of the current-induced density) method with the same intention. Analysis of the results in depth indicates a pseudocoarctate character for this reaction.

Introduction

Fabian et al.[1] have studied the cyclisation of 3-azidopropenal (**1**) to isoxazole (**2**) (Figure 1), and have indicated that the only feasible mechanism appears to be the concerted one. In the same investigation, they considered a pseudopericyclic nature of the process, on the basis of the geometric and electronic structure of the transition state. In previous papers we have demonstrated the necessity to study the whole process and not only the transition state in order to define a process conclusively as pericyclic or pseudopericyclic.[2–5] In addition, we have emphasised the importance of studying the magnetic properties along the reaction profile in this controversial matter.[5]

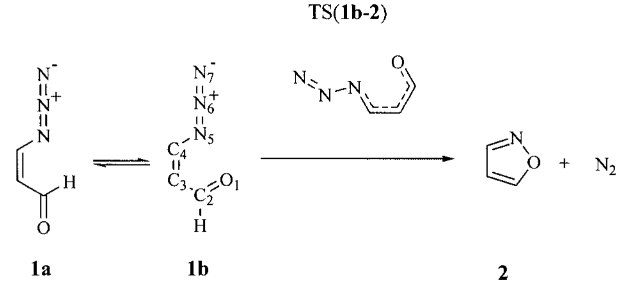

Figure 1. Reaction scheme.

Azides are useful in organic chemistry as initial substances for a variety of synthetic transformations;[6] heteroaryl azides with unsaturated groups in *ortho*-positions, for example, cyclise to bicyclic and polycyclic heteroaromatics, some of them with potential biological activity. Knowledge of the natures of these processes should be very interesting in synthetic design, and it would be very interesting in this sense to find a pseudopericyclic pathway, because of the existence of an energy barrier lower than that involved in the corresponding pericyclic process.

Herges[7] has characterised a special class of concerted reactions: the coarctate reactions. Pericyclic reactions were defined by Woodward and Hoffmann[8] as "reactions in which all first-order changes in bonding relationships take place in concert on a closed curve": that is, the bonds are made and broken in a cyclic array. In contrast, an acyclic but contiguous delocalised system (constricted or coarctate cycle) is characteristic of a coarctate reaction. Herges[7] has thus defined such coarctate reactions as reactions that proceed through the breaking and making of two bonds at one or more atoms at a time. Like the pericyclic reactions, they form an independent and coherent class of concerted reactions. We have studied the inclusion of the cyclisation of 3-azidopropenal to isoxazole in this group.

Pseudopericyclic reactions were originally defined by Lemal as concerted transformations in which the primary changes in bonding encompass a cyclic array of atoms, at one (or more) of which nonbonding and bonding atomic orbital interchange roles.[9,10] This interchange means a disconnection in the cyclic array of overlapping orbitals. The problem of this definition seems to lie in that the orbital description is not unique.

Birney and co-workers have studied a large number of pseudopericyclic reactions.[11–18] They have found three

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[a] Departamento de Química Física, Facultade de Química, Universidade de Santiago de Compostela,
Avda. das Ciencias s/n, 15782 Santiago de Compostela, Spain
Fax: +34-981-595012
E-mail: qftjesus@usc.es
[b] 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
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common characteristics: very low activation energies, planar transition states, and a pseudopericyclic reaction always being orbital symmetry allowed, regardless of the number of electrons involved.

Other studies[19] 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,[20–24] whilst the orbital disconnection in pseudopericyclic reactions prevents this aromaticity. However, an aromatic character of a transition state does not imply the impossibility of a pseudopericyclic reaction, as we have demonstrated in a previous paper,[5] so it is necessary to study the cyclisation process as a whole and not only the transition states. For this reason, this work reports a comprehensive study of the magnetic properties along the reaction profile of the whole cyclisation of 3-azidopropenal.[2–4] The aromaticity was examined in terms of magnetic susceptibility (χ), magnetic susceptibility anisotropy (χ_{anis}) and the nucleus-independent chemical shifts (*NICS*) reported by Schleyer.[25]

Birney[15] found that disconnections can also occur in coarctate reactions, similarly to pseudopericyclic reactions. Kimball et al.[26] have termed these reactions pseudocoarctate.

Herges and Geunich[27] have recently developed a method based on magnetic properties that seems to be a good tool with which to distinguish between coarctate and pseudocoarctate and pericyclic and pseudopericyclic processes, as we have indicated in other papers.[3,5] This method is referred as the ACID (anisotropy of the current-induced density) method and has been employed in this study.

Results and Discussion

Reaction Pathways

Figure 2 shows the energy profiles obtained from the IRC calculations. Birney and co-workers have cited a low or almost vanishing activation barrier, always lower than the barrier for the analogous pericyclic reactions, as a characteristic of pseudopericyclic reactions.[11–18] In this reaction, despite the exothermic character of the reaction (presumably due to the formation of the very stable N_2 fragment), the activation barrier is high in relation to those for typical pseudopericyclic reactions. We may explain this behaviour in terms of a fairly early transition state. Fabian et al. have proposed that the cyclisation of 3-azidopropenal to isoxazole should be regarded as a pseudopericyclic reaction on the basis of structural features and a natural bond order (NBO) analysis.[1] In this work the nature of the reaction is analysed on the basis of magnetic properties.

Magnetic Properties along the Reaction Pathway: Susceptibility, Anisotropy and NICS

Figure 3 shows the variation of the three magnetic properties that form the object of our study [susceptibility (χ), magnetic susceptibility anisotropy (χ_{anis}) and nucleus-independent chemical shift (*NICS*)] during the reaction process. The graphics for susceptibility and magnetic susceptibility anisotropy do not present the minimum (maximum of aromaticity) near the transition state characteristic of pericyclic reactions. On the contrary, the graphics exhibit maxima near the transition state, indicating a less aromatic character for the transition state than for the reactant and product.

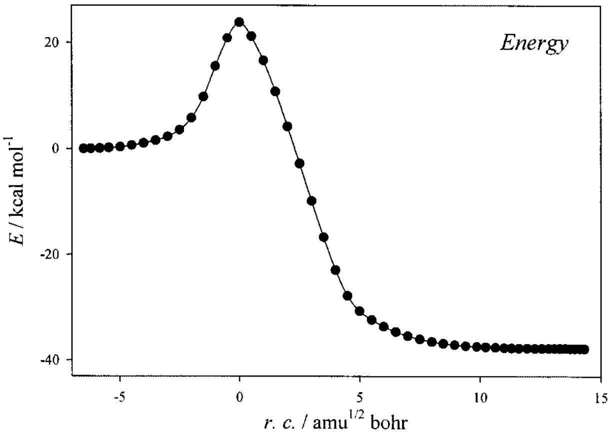

Figure 2. Energy profile for the reaction.

The nucleus-independent chemical shift (*NICS*) values were obtained for several points in the reaction pathway at the (3,+1) ring critical point of electron density as defined by Bader[28] in the forming cycle. Despite the negative value of the *NICS* in the transition state (–4.25 ppm), the graphic shows behaviour similar to that of the magnetic susceptibility (χ) and the magnetic susceptibility anisotropy (χ_{anis}), with no minimum in the vicinity of the transition state. The lack of a minimum (maximum of aromaticity) near the transition state permits it to be stated that this reaction is not a pericyclic reaction.

As in other cases,[5] study of the whole reaction and not only the transition state is necessary to rule on pericyclic or pseudopericyclic behaviour, because the value of the *NICS* at the transition state is negative, indicating certain aromaticity, and this may result in the reaction being erroneously classified as pericyclic.

In order to obtain a more visual representation of the *NICS* values, we also calculated the *NICS* values, for the reactant, transition structure and product, in a three-dimensional grid (64000 points) around the molecule. The limits of this grid of points in the x and y axis are 1 Å up and down the maximum and minimum x and y of the structure, respectively, and the limits in the z axis (perpendicular to the five-membered ring) are 2.5 Å up and down the maximum and minimum z. Figure 4 shows the spatial representation of these calculation over a 0.05 au. isodensity surface for the reactant, the transition state and the product. This figure is a clear demonstration that the product in the cyclisation of 3-azidopropenal to isoxazole has more aromatic character than the reactant and the transition state. The figures for reactant and transition state are very similar.

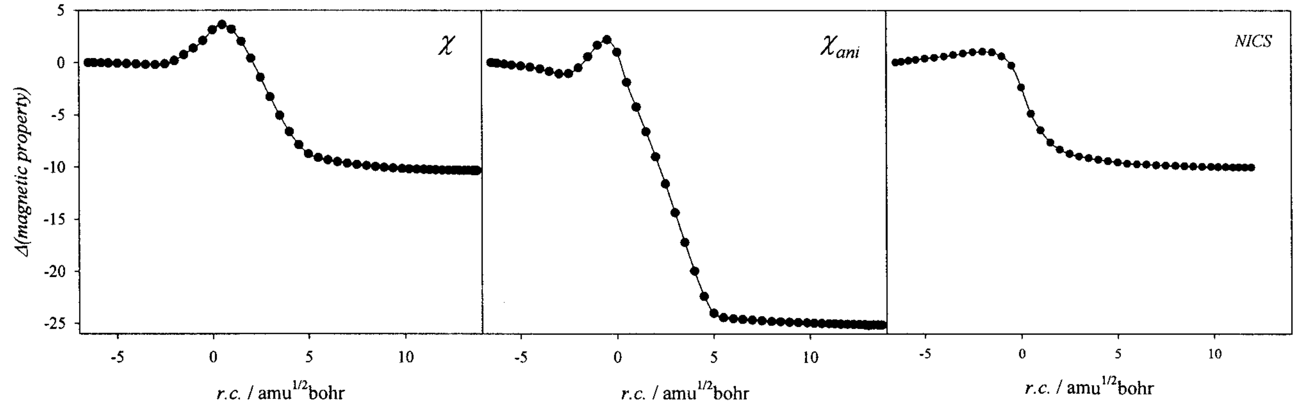

Figure 3. Variation of magnetic properties relative to the reactant. The units of χ and χ_{ani} are cgs-ppm and the units of *NICS* are ppm. The *NICS* were calculated at the (3,+1) ring critical point of electron density as defined by Bader.

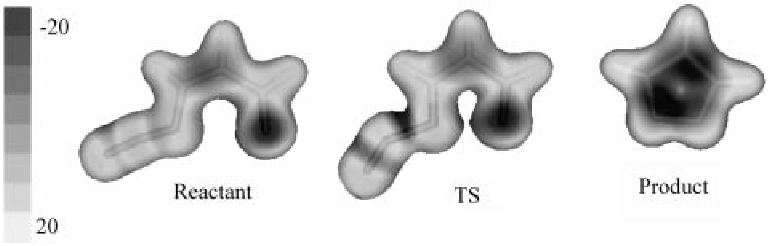

Figure 4. Three-dimensional plots of NICS values over a 0.05 au. isodensity surface for the reactant, transition structure and product of this reaction.

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[27] was employed. This is a recently published method to investigate delocalisation and conjugation effects in molecules, providing a powerful way to visualise the density of delocalised electrons and to quantify conjugation effects. The ACID approach has several advantages: it is a scalar field 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 distinguishing between pericyclic/pseudopericyclic and coarctate/pseudocoarctate reactivity.[3,5,26,27,29]

Figure 5 presents the ACID isosurface of the reactant, product and transition state for this reaction at an isosurface value of 0.05 au. Current density vectors are plotted onto the ACID isosurface. This figure shows a strong diatropic ring current for the product, indicating its aromatic character. In contrast, the reactant and transition state each exhibit a density of delocalised electrons confined to six bonds and do not have the cyclic topology typical for aromatic structures such as pericyclic or coarctate transition states.

We have demonstrated that this reaction is not pericyclic but should be classified as pseudopericyclic or pseudocoarctate. For this it is necessary to realise that the elimination of nitrogen is exocyclic, so the delocalised system of electrons features N_6 exocyclic to the five-membered ring in the ACID plot and in the three-dimensional plot of the *NICS* at the transition state. This is the characteristic topology of coarctate transitions states.[26] However, as the current density vectors do not describe a circle in the forming heterocyclic ring (there is a disconnection), the reaction should be classified as pseudocoarctate.

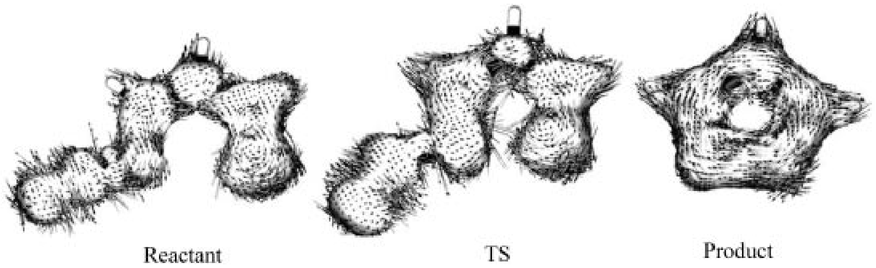

Figure 5. ACID plots for the reactant, transition structure and product of this reaction at an isosurface value of 0.05 au.

Conclusions

The main conclusion of this work is the pseudocoarctate nature of the cyclisation of 3-azidopropenal to isoxazole. This behaviour may be very interesting for investigation of the characteristics of this group of reactions, due to the scarcity of examples in the literature.

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

In this study we have employed a new method to show the *NICS* values for the reactant, transition state and product structures, in the form of the three-dimensional pictures of the *NICS* values in a three-dimensional grid (64000 points) around the structures. It is a very visual way to observe the more aromatic character of the product with respect to reactant and transition state and seems to be a good tool for other studies of aromaticity.

The comparison of the ACID isosurfaces of reactant, transition states and product is a new example of the applicability of the ACID method for distinguishing between coarctate and pseudocoarctate reactions and pericyclic and pseudopericyclic reactions. The disconnection of the delocalised system of electrons between the O_1 and N_5 atoms indicates pseudocoarctate behaviour.

We wish to emphasise the importance of the study of the magnetic properties along the reaction profile in the controversial matter of the difference between pericyclic, pseudopericyclic, coarctate and pseudocoarctate processes.

Experimental Section

Computational Methods: Figure 1 shows the minima and transition state of this reaction. As can be observed, the formyl group in the 3-acylpropenal can adopt either an *s-trans* (1a) or an *s-cis* (1b) conformation. Geometries of all stationary points were obtained from density functional theory (DFT) calculations (specifically, Becke3LYP functional)[30,31] by employment of the 6-31+G(2d,p) basis set. All points were confirmed as minima or transition states by calculation of the harmonic vibrational frequencies, by use of analytical second derivatives. In order to probe the quality of the B3LYP/6-31+G(2d,p) calculations, we also carried out optimisations at the MP2 level with the same basis set. The geometries of the most significant points (1a, 1b, TS(1b-2) and 2) are presented in Table 1, which compares the results at B3LYP/cc-pVDZ,[1] B3LYP/6-31+G(2d,p) and MP2/6-31+G(2d,p) levels. The energies obtained for the different points are shown in Table 2. In addition, the pathway for this reaction was obtained by employment of the intrinsic reaction coordinate (IRC).[32–34]

Table 1. Distances (in Å) and angles (in degrees) of the main stationary points at: A) B3LYP/cc-pVDZ,[a] B) B3LYP/6-31+G(2d,p) and C) MP2/6-31+G(2d,p) theoretical levels.

	1a			**1b**			TS(**1b-2**)			**2**		
	A	B	C	A	B	C	A	B	C	A	B	C
$r(O_1–C_2)$	1.213	1.217	1.226	1.211	1.215	1.225	1.239	1.244	1.262	1.341	1.341	1.350
$r(C_2–C_3)$	1.463	1.465	1.468	1.466	1.468	1.472	1.411	1.413	1.408	1.354	1.360	1.368
$r(C_3–C_4)$	1.342	1.348	1.351	1.345	1.351	1.354	1.377	1.383	1.386	1.420	1.424	1.418
$r(C_4–N_5)$	1.396	1.398	1.406	1.386	1.388	1.395	1.346	1.35	1.366	1.305	1.311	1.329
$r(N_5–N_6)$	1.235	1.241	1.246	1.236	1.243	1.246	1.597	1.596	1.556	–	–	–
$r(N_6–N_7)$	1.126	1.133	1.154	1.126	1.133	1.156	1.108	1.116	1.145	–	–	–
$R(O_1–N_5)$	–	–	–	–	–	–	2.194	2.178	1.995	1.397	1.397	1.392
$\theta(H–C_2–C_3)$	115.9	116.4	116.5	113.7	114.0	114.6	120.7	121.2	123.4	133.4	133.6	134.4
$\theta(O_1–C_2–C_3)$	123.2	122.9	122.8	126.0	125.9	125.9	119.6	119.2	116.8	110.5	110.5	110.1
$\theta(C_2–C_3–C_4)$	124.7	124.6	123.6	126.7	126.7	125.3	113.4	113.2	110.6	103.1	103.0	103.7
$\theta(C_3–C_4–N_5)$	122.5	122.2	121.5	123.6	123.5	122.7	120.8	120.6	119.2	112.4	112.2	112.0
$\theta(C_4–N_5–N_6)$	117.8	117.3	116.8	117.8	117.4	117.1	107.9	107.7	105.5	–	–	–
$\theta(N_5–N_6–N_7)$	172.7	172.4	172.4	171.8	171.4	171.2	143.6	143.1	143.5	–	–	–
$\tau(C_4–C_3–C_2–O_1)$	180.0	180.0	180.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$\tau(C_3–C_4–N_5–N_6)$	180.0	180.0	180.0	180.0	180.0	180.0	180.0	180.0	180.0	–	–	–
$\tau(C_3–C_4–N_5–O_1)$	–	–	–	–	–	–	0.0	0.0	0.0	0.0	0.0	0.0
$\tau(C_2–C_3–C_4–N_5)$	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0

[a] Ref.[1]

Table 2. Theoretically calculated and experimentally measured relative energies of the stationary points. The values in parentheses are corrected with ZPE.

	B3LYP/6-31+G(2d,p)	MP2/6-31+G(2d,p)	B3LYP/cc-pVTZ[a]	Exp.[a]
1a	0	0	0	0
1b	2.9 (2.8)	2.6 (2.6)	(2.7)	–
TS(**1a**–**1b**)	9.0 (8.3)	7.8 (7.2)	–	–
2+N_2	–34.6 (–35.6)	–42.0 (–43.5)	(–36.7)	–
TS(**1b**–**2**)	26.6 (24.8)	33.1 (31.3)	27.1 (25.3)	25.8

[a] Ref.[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,[35] but this method does not provide information about magnetic susceptibility, so χ and χ_{anis} were calculated by the IGAIM (Individual Gauges for Atoms in Molecules) method,[36,37] which is a slight variation of the CSGT (Continuous Set of Gauge Transformations) method.[36–38] For the reactant, transition structure and product, we also calculated the *NICS* values in a three-dimensional grid (64000 points) around the molecule in order to obtain an spatial representation of this magnetic property. This NICS values were obtained at HF/6-31+G* level because of the huge number of points. Finally, the CSGT method at the B3LYP/6-31+G* level of theory was employed in ACID calculations.

All calculations were performed with the Gaussian98 software package.[39]

Supporting Information: Geometries, frequencies, absolute electronic energies and ZPEs for the two conformations of the reactant, the transition state and the product; for supporting information see also the footnote on the first page of this article.

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