Electrocyclization of (*Z*)-1,2,4,6-Heptatetraene and its Heterosubstituted Analogues: Pericyclic or Pseudopericyclic?

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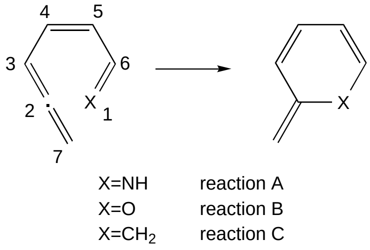
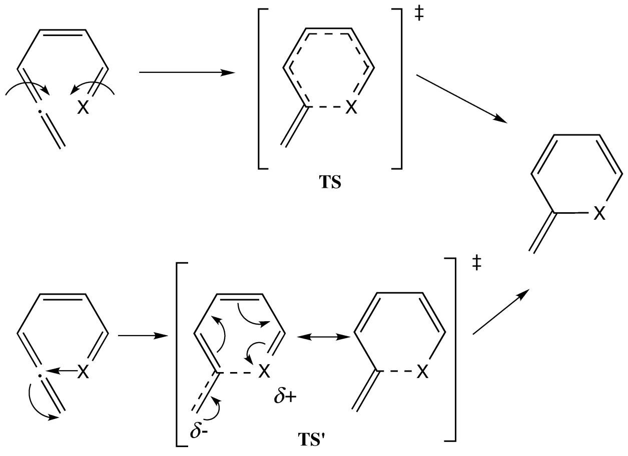
Pseudopericyclic reactions were originally defined by Lemal and co-workers as pericyclic reactions in which there is a disconnection in the cyclic array of overlapping orbitals because of the presence of orthogonal orbital systems.[1] A pseudopericyclic reaction may, therefore, be orbital symmetry allowed by a pathway that maintains the orbital disconnections, regardless of the number of electrons involved.[2] However, there is an ambiguity with the definition of Lemal and co-workers in that the orbital description is not unique.[3] One of the more salient properties of this type of reaction is the presence of very low or even no energy barriers and that of planar transition states.[4]

In a previous communication, Cossio and co-workers[5] concluded that the cyclization of (*Z*)-1,2,4,6-heptatetraene (reaction C in Scheme 1) involves a pericyclic disrotatory electrocyclization via transition state **TS** (Scheme 2), whereas those of its heterosubstituted analogues (2*Z*)-2,4,5-hexatrien-1-imine (reaction A in Scheme 1) and (2*Z*)-2,4,5-hexatrienal (reaction B in Scheme 1) involve a nucleophilic addition of pseudopericyclic nature via transition state **TS′**. To our minds, however, the evidence used to support the pseudopericyclic nature of the latter two reactions is not solid enough to warrant such an assertion. In fact, at the time the communication was published, our group was in the process of studying such reactions and the results eventually obtained further refute the hypothesis of Cossio and co-workers that the two are pseudopericyclic.



Scheme 1.



Scheme 2.

Although our density functional theory (DFT) calculations were done using a 6-31G** basis set, which was slightly smaller than that employed by Cossio and co-workers (6-31+G*), this has no effect on the ensuing discussion, as both the geometric and energetic results were virtually identical. Thus, the bond lengths provided by the two basis sets differed by only a few thousands of an angstrom at most (see Supporting Information). Also, the activation energies provided by both B3LYP computation methods (Table 1) were very similar to each other and also very close to those obtained using Møller–Pleset computations.

Table 1. Calculated energies [kcal mol^{-1}][a].

		B3LYP[b]	B3LYP[c]	MP4SDTQ[d]
reaction A	TS	13.75	14.61	13.65
	product	–33.68	–	–32.52
reaction B	TS	14.41	14.85	14.11
	product	–17.34	–	–17.34
reaction C	TS	19.97	20.56	17.20
	product	–27.00	–	–31.37

[a] Energies relative to the most stable conformer of the reactant. The values are corrected for zero-point vibrational energies (ZPE). The ZPE were scaled by 0.9806 [ZPE(B3LYP/6-31G**) 0.9806] or by 0.9608 [ZPE(MP2/6-31G**) 0.9608]. [b] B3LYP/6-31G**//B3LYP/6-31G**. [c] B3LYP/6-31+G*//B3LYP/6-31+G*.[5] [d] MP4SDTQ/6-31+G**//MP2/6-31G**.

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The first argument used by Cossio and co-workers was that "the harmonic analysis of **TSa** reveals that the nuclear motion corresponding to the imaginary frequency of its diagonalized Hessian matrix has no component associated with the rotation of the N1-H group with respect to the N1–C2 bond being formed". This is the case not only with **TSa** but also with the transition state **TSc**, the disrotatory nature of which is unquestionable. Also, instead of focusing on this rotation, it is seemingly more simple and illustrative of the process to focus on that about the X1–C6 bond, which reflects changes in the H-X1-C6-C5 dihedral angle, for example. The animation of nuclear motion clearly shows that the dihedral angle changes in both **TSc** and **TSa**. To further support this assertion, we computed the path for the two reactions (using the intrinsic reaction coordinate (IRC) method with mass-weighted cartesian coordinates) and examined geometric changes along the reaction coordinate. Figure 1a shows the variation of the above-mentioned dihedral angle: the torsion in the H-N-C-C dihedral angle in reaction A is compared with that in the H-C-C-C dihedral angle in reaction C (by considering the appropriate proton of the methylene group in the latter case). As can be seen, the changes were very similar in both cases: the initial angle was close to 180° and a rotation was observed that increased along the reaction coordinate and peaked near the transition state. Only at the end of the reaction path did any easily interpreted differences arise; in fact, while C1 exhibits sp^3 hybridization at the end of reaction C, N1 will eventually adopt sp^2 hybridization (with the proton in the plane) in reaction A. As a result, the dihedral angle regained a value in the region of 180°. In summary, the most salient conclusion from this graph is that the rotations in reactions A and C are similar. We conducted a natural bond orbital (NBO) analysis at different points along the reaction path to provide more conclusive support for this assertion. This calculation allows one to determine the directionality of the electron lone pair (Lp) on the N atom and hence the variation of the Lp-N1-C6-C5 dihedral angle along the reaction coordinate. Figure 1b compares such a variation with the H-C-C-C torsion angle in reaction C by focusing on the appropriate proton of the methylene group (that is, the internal proton). As can be seen, the situation was very similar; this, together with the results of Figure 1a, clearly suggests there is rotation about the N1–C6 bond in reaction A.

In regard to the rotation of exocyclic H-C7 groups with respect to the C2–C7 bond, Cossio and co-workers stated that "this rotation corresponds to the rehybridization of the C2 atom and therefore it is not associated with disrotatory motion". At no time was this assertion supported with actual data, so we believe it constitutes no evidence; although it cannot be categorically rejected, the mere observation of the nuclear motion corresponding to the imaginary frequency of the transition state suggests no appreciable difference—as regards the rotation of these H-C7 groups—among the transition states **TSa**, **TSb**, and **TSc**. Figure 2 illustrates the similarity in the rotation of the C7-H_2 group in the three transition states.

One other argument used by Cossio and co-workers was the charge distribution in the transition states. Without questioning the dubious value of point charges in this type of study, the sole parameter utilized was the presence of a charge of -0.22e on the C7 atom in **TSa**; this value was obtained by NBO analysis and assumed to support the hypothesis of a nucleophilic addition mechanism involving **TS′** (Scheme 2). We could not reproduce the reported charge. In fact, by using the same method, we obtained a negative charge of -0.55e on C7; the divergence was not a result of using a different basis set, as the charge provided by that employed by Cossio and co-workers (6-31+G*) was virtually the same (-0.56e). This divergence aside, the truly important finding was a negative charge (-0.50e) on C7 in **TSc** (and -0.53e in **TSb**). We believe such slight differences cannot be used to discern between two potentially different reaction mechanisms.

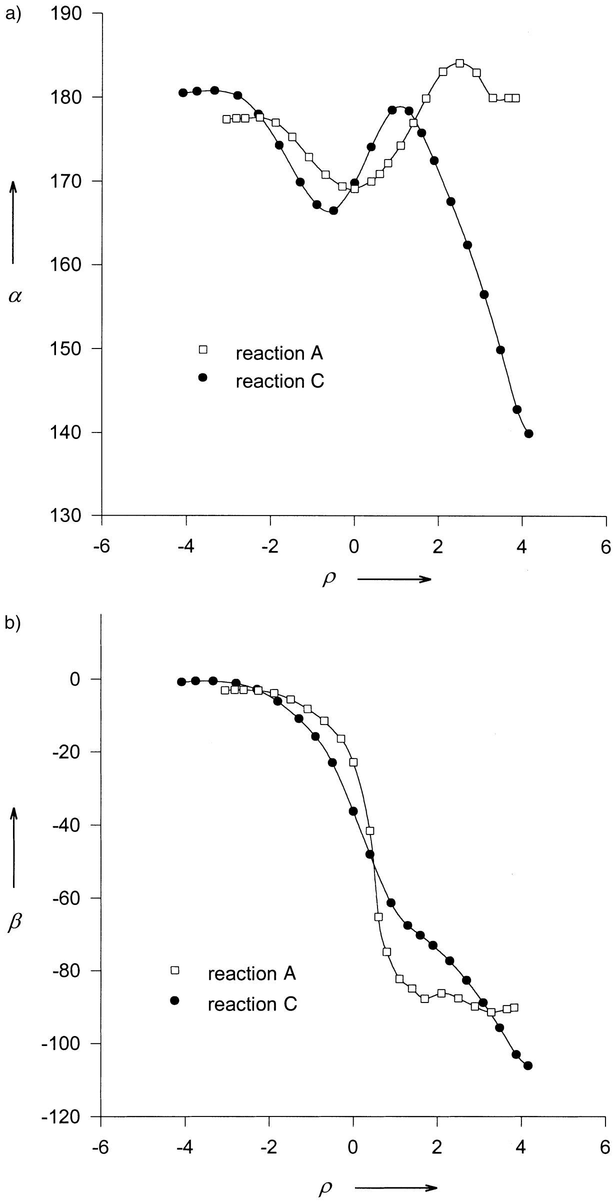
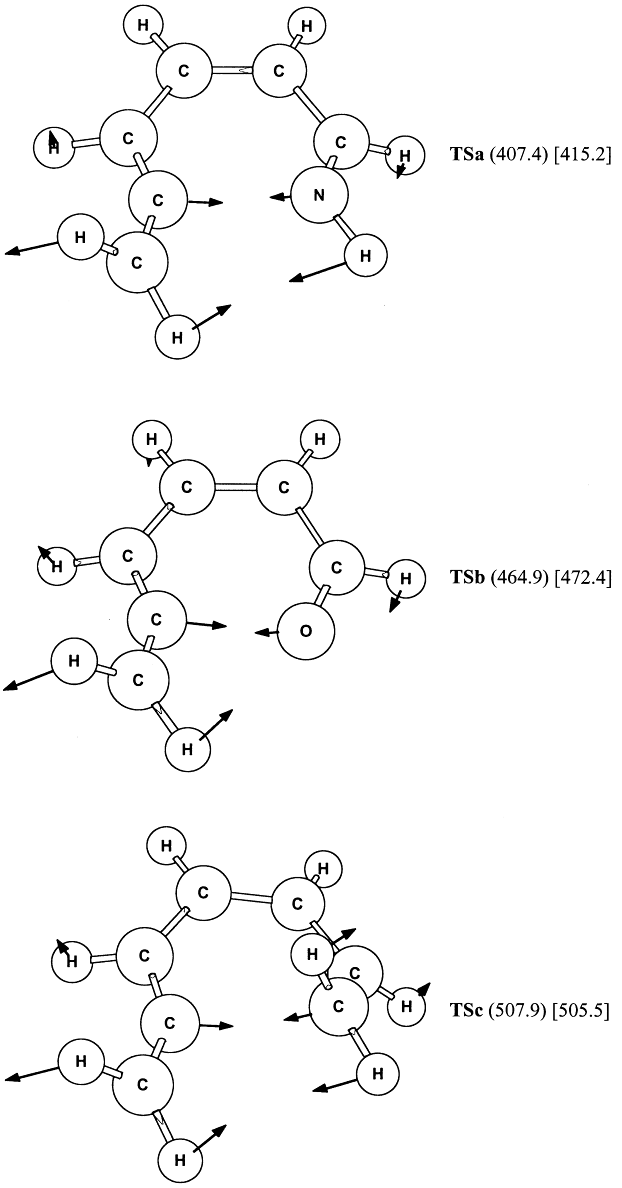


Figure 1. Modification of the H-X1-C6-C5 (a) and Lp(H)-X1-C6-C5 (b) torsion angles for reactions A and C along the reaction path ρ (amu$^{1/2}$-bohr). α = H-X1-C6-C5°; β = Lp(H)-X1-C6-C5°.

The last argument used by Cossio and co-workers involved the aromaticity of the transition states (as determined using


TSa (407.4) [415.2]

TSb (464.9) [472.4]

TSc (507.9) [505.5]

Figure 2. Transition structures and normal mode eigenvectors for the coordinate frequency. The value of the imaginary frequency (cm^{-1}) is given in each case: (B3LYP/6-31G**) [B3LYP/6-31 + G*].

the method of Schleyer et al.[6]); in fact, pericyclic reactions are known to exhibit aromatic transition states.[7, 8] While the maximum nucleus-independent chemical shift ($NICS_{max}$) is certainly much less negative for the transition states **TSa** and **TSb** than for **TSc** ($\delta = -13.64$), which indicates that the latter is more aromatic than the former two, the values for **TSa** ($\delta = -7.75$) and **TSb** ($\delta = -6.80$) also reveal a certain aromatic character; for example, benzene possesses a slightly larger NICS value ($\delta = -9.7$).[6] In addition, recent studies have shown that aromaticity is seemingly a multidimensional property,[9] so its quantitative determination requires the use of several criteria. One other criterion frequently employed in this context is the magnetic susceptibility anisotropy (χ_{anis}). By using the B3LYP/6-311 + G(2d,p) method in combination with IGAIM (a slight variation on the continuous set of Gauge transformations (CSGT) method), we obtained an χ_{anis} value of -36.54 and -31.37 cgs ppm for **TSa** and **TSb**, respectively, neither of which is very different from that for pyrrole (-41.8 cgs ppm)[10] or from that for the transition state of the Diels–Alder reaction (-43.1 cgs ppm).[7] The corresponding value for **TSc** was -46.44 cgs ppm, which suggests that this transition state is more aromatic than **TSa** and **TSb**; however, this does not necessarily mean that these two states cannot be aromatic or that their respective reactions take place in a pseudopericyclic manner. Both the NICS and χ_{anis} values are susceptible to local effects other than aromaticity and therefore the absolute values should not be used to quantify aromaticity properly.

Now that the arguments used by Cossio and co-workers have been discussed, we introduce some additional points, which cast even more doubt on them. If reactions A and B are assumed to take place via **TS′** (Scheme 2), then, on the basis of the structure of this transition state, **TSa** and **TSb** should exhibit an appreciably lengthened C7–C2 bond as this loses (at least in part) its double bond character. However, the results contradict this assumption: the bond lengths obtained for the three transition states are similar and, paradoxically, **TSc** exhibits the longest bond (1.325 Å for **TSa**, 1.322 Å for **TSb**, and 1.328 Å for **TSc**). In addition, the Wiberg bond orders provided by the NBO analysis (namely, 1.90 for **TSa**, 1.93 for **TSb**, and 1.89 for **TSc**) suggest that the double bond remains virtually intact in the three cases. The behavior of that bond along the reaction path is very similar for the three reactions (see Supporting Information).

There is solid evidence that pseudopericyclic reactions take place via planar or nearly planar transition states.[3] It is true that the rings in **TSa** and **TSb** are less strained than those in **TSc**. However, the structure of these rings is far from planar. In fact, if we add up the differences from 0.0° (in absolute value) of the six dihedral angles in the ring, we obtain 86.9° for **TSa**, 100.3° for **TSb**, and 129.8° **TSc**, all at the B3LYP/6-31G** level. The B3LYP/6-31 + G* values are very similar and those provided by MP2/6-31G** suggest an even greater loss of planarity.

Let us now examine our NBO results for the transition states in greater detail. Figure 3 illustrates the directionality of

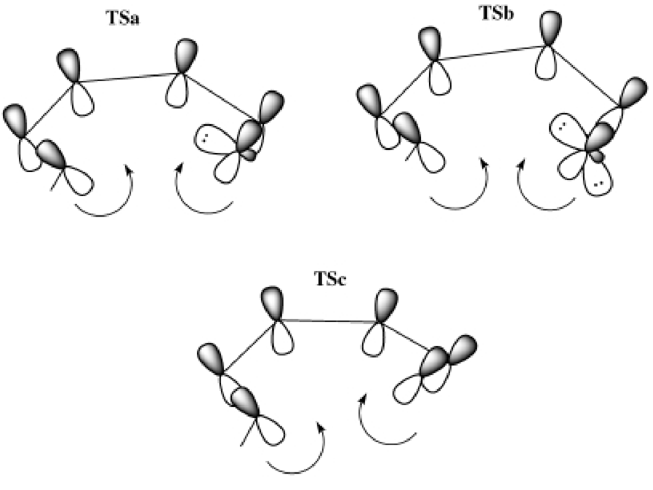


Figure 3. Schematic depiction of the directionality of the NBOs most strongly involved in the transition states **TSa**, **TSb**, and **TSc**.

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the orbitals most strongly involved in the reactions. As can be seen, the position of the p orbitals (99.99 % p character) are identical in **TSa**, **TSb**, and **TSc**: the X1−C6 and C2−C3 π bonds are rotated in a disrotatory manner, which is consistent with the Woodward–Hoffmann rules. Clearly, a difference exists in the involvement of the electron lone pair on the heteroatom. However, the most salient conclusion is that this lone pair does not attack C2 directly, but rather takes part in an extremely lateral overlap as the X1−C6 bond is already slightly rotated (in **TSa** the Lp-N1-C6-C5 dihedral angle is -22.9°). Thus, in **TSa** the lone pair deviates by 57° from the plane formed by the N1-C2-C3 atoms. If reaction A were pseudopericyclic, the lone pair—which would be in the N1-C2-C3 plane or very close to it—would perform a more direct attack on C2. In **TSb**, the deviation is even greater: the lone pair lies virtually normal (89°) to the O1-C2-C3 plane. Nevertheless, the role of the lone pair in **TSa** and **TSb** is very important, as judged from the energy results shown in Table 1. However, this contribution—which allows the process to take place with a reduced energy investment—does not exclude a prominent role of π orbitals in the reaction.

In conclusion, we believe that the evidence reported by Cossio and co-workers is not conclusive enough to state that reactions A and B are pseudopericyclic. Rather, the results suggest that both are essentially pericyclic even though they are favored (or assisted) by the electron lone pair on the heteroatom. As shown in a previous paper on the electrocyclization of hexatriene and its derivatives,[11] the lone pair provides a reaction path with a decreased energy investment, but the essential features of the process are typical of a disrotatory electrocyclization.

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Reply

Angel R. de Lera* and Fernando P. Cossio*

Rodriguez-Otero et al. have questioned our results on the pseudopericyclic nature of the cyclization of (2*Z*)-hexa-2,4,5-trienals and their Schiff bases. Since the electrocyclic nature of the all-carbon reaction reported in our paper (**6c**→**7c** transformation) has not been questioned by these authors, we will focus our discussion on the cyclization of compound **6a** of our article[1] to form the cyclic structure **7a**, and we shall demonstrate that the analysis of Rodriguez-Otero is incorrect.

First, we must emphasize that the nature of the imaginary vibration of **TSa** corresponds to the attack of the electron lone pair of the nitrogen atom on the terminal double bond of **6a**. Animation of this imaginary frequency (for instance, by means of the MOLDEN program[2]) clearly shows that the attack of the NH group does not involve any significant rotation around the N=C bond, although in-plane motion of the imine hydrogen atom clearly participates in the imaginary frequency. Moreover, the geometries of the points along the intrinsic reaction coordinate (IRC) pathway at the B3LYP/6-31+G* level shows only marginal variations of the H-N1=C6-H dihedral angle, denoted as ω in Figure 1, motivated by small conformational variations of the cycle being formed.

Concerning the observation of Rodriguez-Otero and Cabaleiro-Lago on the magnitude of the NBO charge of the exocyclic atom, the value of about -0.2 e included in our article has been obtained by integration of the charges on the hydrogen atoms bonded to the exocyclic carbon atom, a common practice in computational chemistry since the charge on the isolated carbon atom has no chemical meaning. The values of about -0.5 e reported by these authors correspond to the isolated C7 atom and are not relevant from a chemical standpoint.

Rodriguez-Otero and Cabaleiro-Lago also report an analysis of the bond length between the C2−C7 atoms. The authors do not take into account that, according to Scheme 3 of our paper,[1] the electronic reorganization in structure **TS′** does not necessarily imply any significant variation of the length of the C2−C7 bond. Therefore, the long discussion on this topic reported by these authors does not contribute to the elucidation of the nature of the mechanism of the cyclization.

The NBO analysis of **TSa** reported by Rodriguez-Otero and Cabaleiro-Lago is also erroneous. The most convenient tool to elucidate the nature of the reaction mechanism is to examine

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