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Ellipticity: A Convenient Tool To Characterize Electrocyclic Reactions

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Abstract: The ellipticity of the electron density is proposed as a convenient tool to characterize electrocyclic reactions. The study of the electron density offers several advantages since it is an experimental observable. This simple topological index has proven powerful and robust for the characterization of a wide variety of electrocyclic and pseudoelectrocyclic processes. This property is sensitive to changes in the anisotropy of the electron density in the bond-forming region and provides an insightful description of the events occurring along the reaction coordinate.

Keywords: atoms in molecules theory · electrocyclic reactions · electron density · ellipticity · pseudopericyclic reactions

Electrocyclic reactions[1] are the subset of pericyclic reactions that involve the cyclization of an n–π electron system to an $(n-1)$–π + 1–σ electron system and the reverse process. Electrocyclization/ring-opening reactions are enjoying renewed interest by the synthetic community and have been recently used as steps in cascade pericyclic reactions for the construction of complex natural products.[2–5] From a theoretical perspective, pericyclic reactions are usually characterized by means of descriptors related with the aromatic character of their transition states, in line with Zimmermann's model[6,7] (Table 1). In this regard, magnetic susceptibility and nucleus independent chemical shifts (NICS)[8] have been widely used to identify reactions involving transition states that exhibit aromaticity.[9,10] Natural bond orbital (NBO)[11] analysis has also become a general method for characterizing pericyclic reactions.[9,10,12–16]

Controversy arises when the computed values of the above magnitudes lie in borderline regions, which is common for non-prototypical-hydrocarbon systems, leading to ambiguous characterizations.[9,16] Estimation of aromaticity by means of magnetic criteria would be one of the most convenient tools to describe these reactions, but the way to interpret the current calculations of aromaticity is still subject to debate.[17–20] Other widely employed tools such as population analysis present the problem of the arbitrary partitioning of the density matrix. Furthermore, an analysis based on localized orbitals is far from adequate to describe transition structures whose orbitals are essentially diffuse. Thus, no unambiguous criteria has been published to ascertain the nature of several of these intriguing rearrangements.[21]

Here we propose that the ellipticity, which is obtained by topological analysis of the electron density and therefore reliant on a non-arbitrarily modified physical observable, is an unambiguous tool to characterize the nature of electrocyclic reactions. This method is based on the topological analysis of the electron density[22] along the reaction pathway. Critical points of the electron density unequivocally define positions of the space associated with nuclei, bonds, rings, and cages depending on the rank and the signature of the matrix of the second derivatives of $\rho(\boldsymbol{r})$ (i.e. the Hessian of $\rho(\boldsymbol{r})$).

Critical points whose Hessian satisfies rank = 3 and signature = −1 define bonds (BCP, bond critical points).[22] These mathematical requirements merely reflect the chemist's intuitive view of how the density develops around a bond. At the BCP the electron density is a minimum along the line linking both atoms (the bond direction) and maxima in the remaining two normal directions (Figure 1). Ellipticity, ε, is defined as Equation (1), where λ_1 and λ_2 are the negative ei-

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Table 1. Characteristic properties of pericyclic and pseudopericyclic electrocyclizations.[a]

Reaction type	Aromaticity	Barrier	π-orbital array	Ellipticity profile	Ellipticity value
pericyclic di-rotatory	high	variable	0 disc.	max	large (>4)
pericyclic mono-rotatory	medium	variable	1 disc.	max	medium (~1)
pseudopericyclic	low	very low	2 disc.	no max	small (<0.5)

[a] Conventional indexes used to characterize pericyclic and pseudopericyclic reactions (presence of aromaticity at the transition state, activation barrier, and number of disconnections in the cyclic array of overlapping orbitals), together with the ellipticity descriptors for these reactions proposed in the present work.

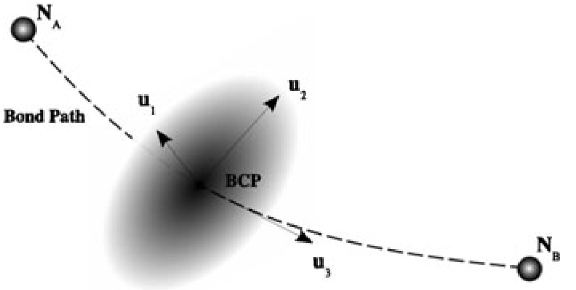


Figure 1. Schematic representation of the eigenvectors of the Hessian of $\rho(\mathbf{r})$ ($\mathbf{u}_1$, $\mathbf{u}_2$, and $\mathbf{u}_3$). The associated eigenvalues (λ_1, λ_2, and λ_3) are employed to calculate the ellipticity at the BCP between nuclei A (N_A) and B (N_B).

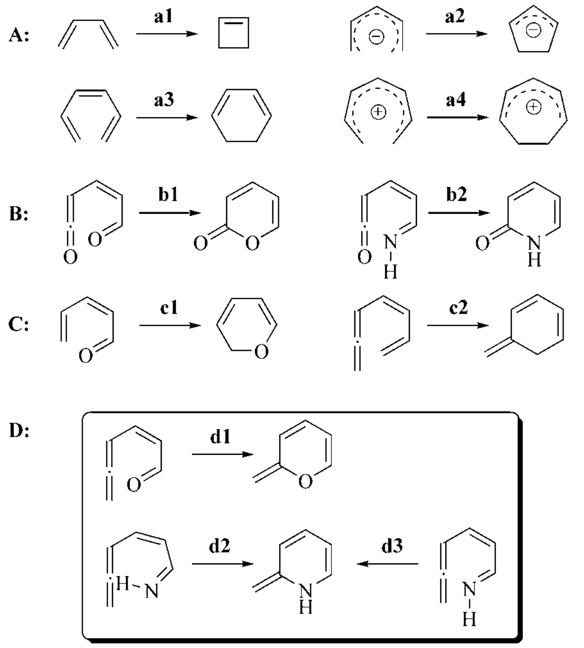
genvalues of the Hessian of the electron density at the BCP, ordered such that $\lambda_1 < \lambda_2 < 0 < \lambda_3$.

$$\varepsilon = \lambda_1/\lambda_2 - 1 \qquad (1)$$

The ellipticity at the BCP can be interpreted as a measure of the anisotropy of the curvature of the electron density in the directions normal to the bond (a zero value indicates no anisotropy), and therefore serves as a sensitive index to monitor the π character of double bonds.[23] Moreover, the ellipticity is robust since it provides sensitivity not only to directional π-bonding but also to any lateral overlap perturbing the sigma bond symmetry (Figure 1).

The changes of the electron density in the bonding region that occur in the course of a pure electrocyclic process are mainly due to the lateral overlap of π bonds,[24] whereas changes that occur in the course of a pseudopericyclic reaction are due to the in-line overlap of disconnected orbitals (see Scheme 2). The ellipticity at the bond critical point is a direct measure of the degree to which the electron density is *unequally distorted* in perpendicular directions away from the bond axis (Figure 1). Hence, in the case of a pure pseudopericyclic reaction, the in-line overlap does not produce any such unequal distortion and results in a negligible value of the ellipticity. Alternatively, for a pure electrocyclic reaction, the lateral π-bond overlap leads to a considerable excess distortion of the electron density in the direction of the π bonds, and this in turn leads to a relatively large ellipticity value. The simple physical connection afforded by the ellipticity at the bond critical point makes it a robust, intuitive index for the characterization of electrocyclic and pseudopericyclic reactions (Table 1).

The change of ellipticity along the reaction path for several selected electrocyclic reactions (Scheme 1, series: **A**, **B**, **C**, and **D**) is shown in Figure 3. Calculations were performed with Gaussian03[25] at the B3LYP/6–311+G(d,p) level.[26–28] Minima and transition states were located for all the reactions and were characterized by means of the diagonalized matrix of the second derivatives. The intrinsic reaction coordinate (IRC)[29,30] was calculated in mass-weighted Cartesian coordinates in steps of 0.1 amu$^{1/2}$bohr, and initial force constants were obtained analytically.



Scheme 1. Series of ring-closure reactions studied by means of the ellipticity of the electron density at the BCP between the termini atoms. Series **A** presents classical electrocyclizations, whereas series **B** includes reactions previously described as pseudopericyclic. Series **C** groups cyclizations of molecules that show one disconnection in the array of overlapping orbitals. Series **D** presents three controversial reactions

Hydrocarbon electrocyclic ring closures (Scheme 1, series **A**) involve the formation of a new σ bond by lateral overlap of two rotating atomic p orbitals. The electron density is therefore highly asymmetric at the BCP at the early stages of the reaction. Moreover, this lateral overlap is the major contribution to the electron density as opposed to the product energy minima, for which the σ bond is the largest component to the total electron density. Hence, the ellipticity is expected to be much larger at these stages of the reaction where the p orbitals initiate their rotation than in the minima (Figure 2). As a bond develops the density at the BCP gains σ character and the values of the ellipticity are

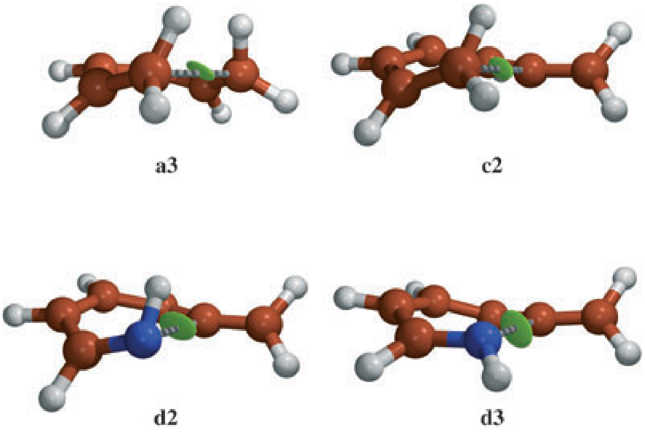


Figure 2. Representation of the anisotropy of the electron density at the bond critical point (BCP) for structures **a3**, **c2**, **d2**, and **d3** corresponding to the reaction coordinate value of $-1\,\mathrm{amu}^{1/2}\mathrm{bohr}$. The green ellipse shown at the BCP between the bonding atoms reflects the anisotropy of the Hessian of $\rho(\boldsymbol{r})$ (the magnitude of the elliptical axes are proportional to the eigenvalues of the Hessian).

expected to decrease rapidly as the reaction progresses (see Figure 3, structure **a3**). Consistent with this analysis, the ellipticity at the BCP of the forming σ bond shows a defined maximum (8.1 for **a2**, 15.4 for **a3**, and 3.9 for **a4**)[31] before reaching the transition state. This general feature is independent of the rotational preference (disrotatory in **a2**, **a3**, and **a4**, and conrotatory in **a1**) of the cyclizing termini of the reactant.[32]

Pseudopericyclic reactions have been defined by Lemal et al[33] as concerted transformations whose primary changes in bonding encompass a cyclic array of atoms, at one (or more) of which nonbonding and bonding atomic orbitals interchange roles. The expression *interchange roles* means a *disconnection* in the cyclic array of overlapping orbitals due to orthogonality (Scheme 2), and therefore these reactions would be neither symmetry-allowed nor forbidden. From a theoretical point of view, precise differentiation of pericyclic and pseudopericyclic reactions proved challenging, since both are concerted in nature, proceed with no intermediates, and involve a shift in the π pattern of the reactant. In previous studies of these processes, Birney and co-workers concluded that the prototypical pseudopericyclic reactions exhibit three main features (Table 1):[34]

1) A pseudopericyclic reaction may be orbital-symmetry allowed via a pathway that maintains the orbital disconnections, regardless of the number of electrons involved.
2) Barriers to pseudopericyclic reactions can be very low, or even nonexistent.
3) Pseudopericyclic reactions will have planar transition states if possible.[35]

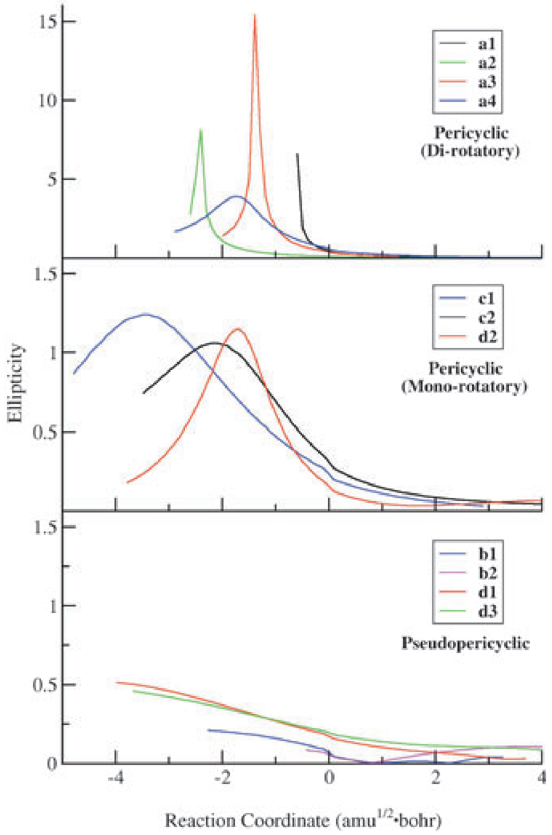
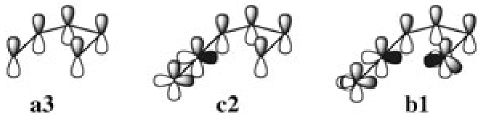


Figure 3. Ellipticity along the reaction coordinate of the concerted ring-closures depicted in Scheme 1: di-rotatory pericyclic (top), mono-rotatory pericyclic (middle), and pseudopericyclic (bottom). Note the scale of the upper plot (di-rotatory electrocyclizations, series **A**) is ten times that of the lower two plots below it (mono-rotatory electrocyclizations and pseudopericyclic reactions).



Scheme 2. Schematic representations of the π-orbital arrays in reactants of series **A**, **B**, and **C**. The disconnections (see text) between orthogonal orbitals are shown in black.

Electrocyclizations depicted in series **B** of Scheme 1 contain two orthogonal disconnections in the cyclic array of π orbitals. The ring closure of **b1** has been previously characterized as pseudopericyclic,[36] and the isoelectronic system **b2** was expected to display analogous features. These reactions are conceived to proceed through the in-line overlap of two disconnected orbitals that are conveniently oriented in the reactant. Regarding the electron density, pseudopericyclic reactions may be visualized as processes with higher cylindrical symmetry in the bond formation region compared to those described above. Ellipticity is expected to be small in these reactions because of the predominant in-line overlap which preserves the cylindrical symmetry of the electron density along the full reaction path. Indeed, the values displayed in Figure 3 for series **B** of cyclizations are very small (lower than 0.5) compared to those for classical electrocyclic reactions in series **A**. Furthermore, as the bond is being formed, overlapping orbitals from both cyclization termini gradually gain more σ character, thus ellipticity values decrease almost monotonically along the reaction coordinate.

The presence of a heteroatom or a cumulene carbon atom (series **C**) at only one of the cyclizing termini implies the introduction of one disconnection (either a lone pair or an orthogonal π bond, according to Lemal's definition) in the array of orbitals (see Scheme 2). The consequence is a considerable lowering of the ellipticity values along the IRC relative to those of the prototypical series **A** (values being lower than 1.25 for reactions in series **C**, whereas they are greater than 4 for all the structures in series **A**). The behavior of the ellipticity within these reactions can be readily explained by the nearly cylindrical electron density around the cumulene carbon atom or heteroatom. The result is a variation of the electron density in the directions normal to the bond path reduced relative to electrocyclic series **A**.

From the comparative analysis of processes **A** to **C** several conclusions can be drawn. The use of ellipticity is appropriate to distinguish between pericyclic and pseudopericyclic rearrangements (see Table 1). The wide range of reactions studied here can be divided in two distinctive groups; those that exhibit a maximum of ellipticity along the reaction pathway and those whose ellipticity decreases monotonically as the cyclization proceeds. The former is a feature which groups together all the pericyclic rearrangements, whereas the latter is exhibited by reactions previously described as pseudopericyclic.[36] It can be observed that the values of ellipticity are also clearly different. Pseudopericyclic processes show small values (always below 0.5) that decrease almost parallel to each other. In contrast, the group of pericyclic reactions present maximum values larger than 1. Classical neutral electrocyclizations show exalted ellipticity maxima compared to electrocyclic reactions of systems with one terminal cumulene or heteroatom, in which only one terminus of the reaction is required to rotate (mono-rotatory electrocyclic reactions).

Ellipticity analysis of the controversial 2(*Z*)-hexa-2,4,5-trienal and the corresponding imines (Scheme 1, series **D**) unequivocally shows that the behavior of the aldehyde **d1** and the (*E*)-Schiff base derivative **d3** fit with that of the pseudopericyclic reactions. The ellipticity shows no maximum along the reaction profile and its values are smaller than 0.5. Furthermore, representations for both **d1** and **d3** run almost parallel to classical pseudopericyclic reactions **b1** and **b2**. On the other hand, (*Z*)-imine **d2** exhibits a clear maximum of 1.15 in the ellipticity, which lies in the range displayed by molecules in series **C**. In fact, the (*Z*)-imine **d2** presents the same geometrical features as molecules in series **C**, that is, one terminus of the cyclization (the N–H substituent) has to rotate to achieve orbital overlap, whereas the other (the allene) is already adequately oriented in the reactant.

Figure 2 shows an early stage (corresponding to $-1\,\mathrm{amu}^{1/2}$-bohr to allow comparison) of the cyclization of representative systems of Scheme 1. The distortion of the electron density at the BCP is represented through an ellipse with axes proportional to the eigenvalues of $\rho(\boldsymbol{r})$. For the classical hexatriene electrocyclic reaction **a3** the rotating terminal C–H_{out} and C–H_{in} bonds are aligned with the major and minor axes, respectively. A considerably distorted electron density is also observed for the mono-rotatory process **c2** and **d2**, for which the rotating C–H_{in} and N–H bonds run almost perpendicular to the major axis of the ellipse. In contrast, cyclization of the (*E*)-imine **d3** maintains an almost circular section of the electron density and has the major axis of the ellipse nearly parallel to the N–H bond. The orientation of the terminal hydrogen atoms is consistent among the entire series of reactions in Scheme 1, and highlights the relevance of light atoms as probes for the properties of transition states of pericyclic reactions.[37]

In summary, the ellipticity of the electron density at the bond critical point has been demonstrated to be a robust, sensitive topological index for characterizing electrocyclizations. This approach has three main advantages over the evaluation of aromaticity and population analysis in the transition state. First, since the electron density is a physical observable, the present method avoids any arbitrary processing of the wave function (i.e., orbital localization or density matrix partition). Second, the electron density and its topological properties are known to be fairly independent of the basis set size.[38] Third, this method evaluates the electronic changes in the molecular complex along the full reaction pathway, not only the stationary points. Although they are the focus of most studies, very often stationary points lie quite separated on the potential energy surface and therefore many changes in the electron density of the reacting molecules that can take place between them can go unnoticed.[39] The ellipticity of the electron density at the BCP has been shown to be extremely sensitive to changes in the electron density, such as those generated by lateral or in-line overlap, thus providing an unambiguous tool to describe electrocyclic and pseudoelectrocyclic reactions.

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