J. Org. Chem. **1997,** *62,* 7033−7036 **7033**

In-Plane Aromaticity in 1,3-Dipolar Cycloadditions

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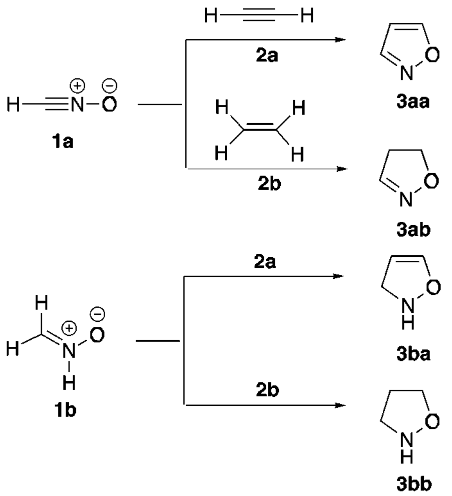
Received February 25, 1997

In spite of its epistemological concerns, aromaticity is a cornerstone in chemistry.[1] Recently, there has been a renewed interest in the precise definition and characterization of this concept, and several criteria have been proposed.[2] On the other hand, since in 1938 Evans et al.[3] recognized the analogy between the six π-electrons of benzene and the six electrons participating in the transition state of the Diels−Alder reaction, aromaticity has been closely related to the development of the theory of pericyclic reactions.[4] In this respect, the magnetic criteria have proved to be very useful in the characterization of not only aromatic compounds but also transition structures of thermally allowed reactions.[5]

Within this context, we would like to communicate our findings on the aromatic character of transition states associated with 1,3-dipolar cycloadditions. Reactions of this type are of great synthetic significance,[6] and their mechanism has been the subject of a vivid debate over the years.[7]

Scheme 1



We have selected the four transformations depicted in Scheme 1 as model reactions. Of these four, only one, namely, the interaction between fulminic acid and acetylene to yield isoxazole **3aa**, leads to an aromatic product. The remaining reactions lead to the formation of nonaromatic five-membered heterocycles. All reactants and products included in Scheme 1 and the corresponding transition structures **TSaa-bb** were fully optimized using the GAUSSIAN 94 suite of programs.[8] In order to take into account, at least partially, electron correlation, the MP2[9] and B3LYP[10] methods have been used. Since it was expected that some of the zwitterionic character of the dipoles was retained in the transition structures, the 6-31+G* basis set[11] was used because of its superior ability to accommodate negative charges. We have computed the synchronicity (S_y) of the reactions shown in Scheme 1 using the previously reported[12] formula

$$S_y = 1 - \frac{\displaystyle\sum_{i=1}^{n} \frac{|\delta B_i - \delta B_{av}|}{\delta B_{av}}}{2n - 2} \tag{1}$$

where n is the number of bonds directly involved in the reaction and δB_i stands for the relative variation of a given bond index B_i at the transition state (TS), according to the following formula:

$$\delta B_i = \frac{B_i^{TS} - B_i^{R}}{B_i^{P} - B_i^{R}} \tag{2}$$

where the superscripts R and P refer to the reactants and the product, respectively. The average value of δB_i, denoted as δB_{av} is therefore

$$\delta B_{av} = n^{-1}\sum_{i=1}^{n}\delta B_i \tag{3}$$

The Wiberg bond indices[13] B_i have been computed using the natural bond orbital (NBO) method.[14]

Our calculated energies of activation and reaction for the four processes indicated in Scheme 1 are reported in Table 1. Unfortunately, the corresponding experimental

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S0022-3263(97)00347-2 CCC: $14.00

Table 1. Activation Energies[a] (ΔE_a, kcal/mol), Energies of Reaction[a] (ΔE_{rxn}, kcal/mol), and Synchronicities[b] (S_y) Computed for the Reaction between Dipoles 1a,b and Dipolarophiles 2a,b

	ΔE_a		ΔE_{rxn}		S_y	
reaction	MP2[c]	B3LYP[d]	MP2[c]	B3LYP[d]	MP2[c]	B3LYP[d]
1a + **2a** → **3aa**	8.06	15.05	−74.36	−75.16	0.81	0.80
1a + **2b** → **3ab**	7.52	14.60	−38.16	−37.07	0.80	0.79
1b + **2a** → **3ba**	11.44	19.87	−42.67	−42.14	0.82	0.92
1b + **2b** → **3bb**	11.43	16.57	−29.39	−23.20	0.90	0.92

[a] Zero-point vibrational energies (ZPVE), scaled by 0.97 and by 0.98 for the MP2/6-31+G* and B3LYP/6-31+G* results, respectively, have been included. [b] See ref 12. [c] MP2(FC)/6-31+G* data. [d] B3LYP/6-31+G* data.

values are not available. Only for the **1a** + **2a** → **3aa** reaction have two estimates based on experimental data been reported. According to the first one,[15] the activation energy for this reaction should be of 8−12 kcal/mol, a value in the range of our MP2(fc)/6-31+G*+ΔZPVE and B3LYP/6-31+G*+ΔZPVE results. The other estimate[16] is based upon bond energies and suggests an activation energy of *ca.* 15 kcal/mol. This value is in perfect agreement with our value computed at the B3LYP/6-31+G*+ΔZPVE level (see Table 1). On the other hand, several energies of activation and secondary kinetic isotopic effects[17] computed using the B3LYP hybrid functional for other pericyclic reactions suggests that this method yields quantitatively accurate results. On the basis of these arguments, we think that our B3LYP results are probably closer than the MP2 ones to the real values.

It is also noteworthy that the four reactions studied are found to be close to the perfect synchronicity,[12] the computed values of S_y being in the range 0.8−0.9 (see Table 1). Therefore, if we assume that the bonding equalization criterion for aromaticity[2] is related to the synchronicity associated to a cyclic transition structure, the four saddle points depicted in Figure 1 fulfill reasonably well this geometric requisite of aromaticity.

In Table 2 we have reported the magnetic susceptibility anisotropies of structures depicted in Figure 1, as well as the relative variation of the χ_{anis} values of these stationary points with respect to the reactants. These values have been computed according to the following equation:

$$\chi_{anis} = \chi_{zz} - \frac{1}{2}\left[\chi_{xx} + \chi_{yy}\right] \qquad (4)$$

where χ_{zz} is the out-of-plane and χ_{xx} and χ_{yy} are in-plane components of the magnetic susceptibility tensor. Although it is known that magnetic anisitropy is not entirely due to nonlocal effects,[18,19] large negative values of χ_{anis} are usually associated with aromatic character.[2] Isoxazole **3aa** is the only cycloadduct for which experimental data of χ_{anis} are available. The reported[20] isotropic magnetic susceptibility of isoxazole is −38.0 ppm cgs, a value with which our computed value of −33.8 ppm cgs (CSGT-SCF/6-31+G*//B3LYP/6-31+G* result) agrees quite well. The computed χ_{anis} values for the saddle points **TSaa-bb** are higher in absolute value than those of either reactants or products including the aromatic isoxazole (see Table 2). Therefore, we can conclude that these 1,3-dipolar reactions are concerted processes which take place through highly synchronous and aromatic transition structures.

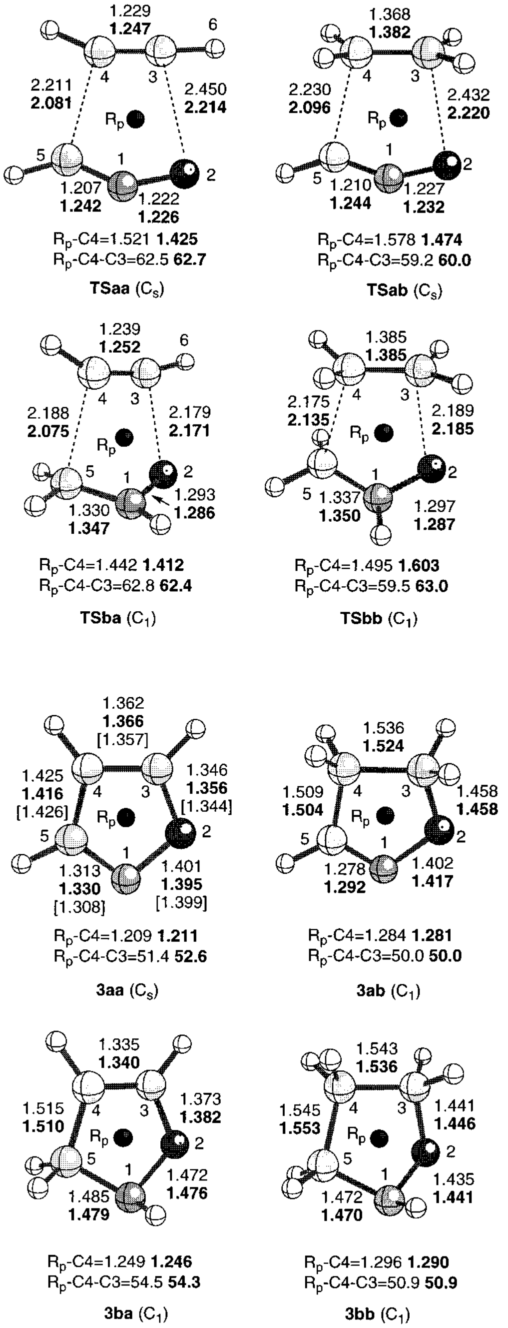

Figure 1. Calculated B3LYP/6-31+G* (plain numbers) and MP2(fc)/6-31+G* (bold numbers) and experimental (numbers in brackets, see ref 7b) geometries of transition structures **TSaa-bb** and cycloadducts **3aa-bb**. Bond distances and angles are given in angstrom and degrees, respectively. R_p denotes the (3,+1) ring point of electron density.

We have also studied the magnetic properties of transition structures and products using the nucleus-

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Table 2. GIAO-SCF/6-31+G* Calculated NICSs (ppm) and CSGT-SCF/6-31+G* Calculated Magnetic Susceptibility Anisotropies (χ_{anis}, 10^{-6} erg/G^2 mol)

	MP2/6-31+G* [a]			B3LYP/6-31+G* [a]		
structure	NICS[b]	χ_{anis}	$\Delta\chi_{anis}$[c]	NICS[b]	χ_{anis}	$\Delta\chi_{anis}$[c]
TSaa	−25.37	−25.31	−14.23	−17.82	−21.89	−11.04
TSab	−25.47	−19.94	−10.88	−20.08	−14.58	−5.31
TSba	−19.60	−35.03	−23.49	−17.83	−18.01	−6.74
TSbb	−21.91	−25.58	−15.53	−21.20	−24.48	−14.79
3aa	−12.30	−23.30	−12.22	−12.30	−22.70	−11.85
3ab	−5.14	−11.04	−1.98	−5.15	−10.77	−1.50
3ba	−7.31	−7.93	+3.61	−7.25	−7.65	+3.62
3bb	−9.13	−3.60	+6.45	−9.24	−3.55	+6.14

[a] Level of optimization of the stationary points. [b] Computed at the corresponding (3,+1) critical point of electron density. [c] $\Delta\chi_{anis}$ is the difference between the χ_{anis} values of the corresponding stationary point and those of the reactants.

independent chemical shifts[21] (NICSs) recently introduced by Schleyer. Given the unsymmetrical character of our cyclic systems, we needed to define the inner points unambiguously. We argue that the (3,+1) ring critical point of the electron density, as defined by Bader,[22] constitutes an unambiguous choice for the calculation of the NICSs, since only at this point is the electron density a minimum with respect to motion on the ring's plane and maximum with respect to motion perpendicular to the plane defined by the ring. The position of the ring critical points of **TSaa-bb** and **3aa-bb** are indicated in Figure 1, and the NICSs at these points are reported in Table 2. We have found that the four transition structures exhibit high negative values, associated with strong diamagnetic shielding. It is also noteworthy that the magnitude of the NICSs for the transition structures is higher than that calculated for isoxazole **3aa**. For the nonaromatic reaction products **3ab**, **3ba**, and **3bb**, the NICS are considerably lower (see Table 2).

The commonly accepted magnetic criterion of aromaticity is usually attributed to ring current effects.[23] However, this model has been criticized, and some modifications and alternatives have been proposed.[24] Very recent high-level calculations seem to support, at least partially, the ring current model in organic aromatic compounds such as benzene- and nitrogen-containing heterocycles.[18,25] With these considerations in mind, a possible explanation for the high NICS values observed for the transition structures is that the six electrons involved in the cycloaddition lie approximately in the molecular plane and give rise to an appreciable ring current. In turn, this ring current promotes a strong diamagnetic shielding at the ring critical point, as is represented in Figure 2. This reasoning leads to the conclusion that these transition structures exhibit *in-plane* aromaticity.[26]

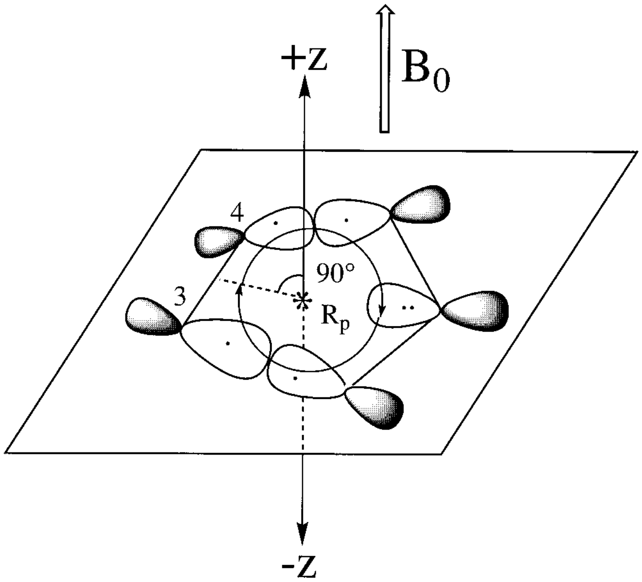

Figure 2. Schematic representation of an *in-plane* ring current induced by an external magnetic field (B_0) acting over a *supra*−*supra* transition state associated to a thermal [3 + 2] cycloaddition. The asterisk denotes the (3,+1) ring point of electron density (R_p). The z axis intersects R_p and is perpendicular to the plane defined by R_p and the C3 and C4 atoms.

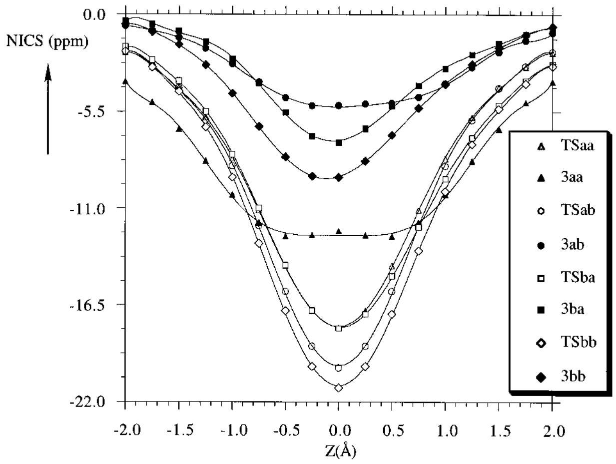

Figure 3. NICS (ppm) vs Z (Å) curves obtained at the GIAO-SCF/6-31+G*// B3LYP/6-31+G* level for cycloadducts **3aa-bb** and saddle points **TSaa-bb**. The z axis is defined in Figure 2.

In order to obtain more information about the hypothetical *in-plane* aromaticity of our transition structures, we decided to compute the NICSs along the z axis, as defined in Figure 2. Since the eigenvector associated with the negative eigenvalue of the (3,+1) ring critical point defines a unique axis along which the electron density exhibits the fastest increase for motion toward the critical point,[27] calculated values of the NICS along various points on this z axis must have a maximum at $z = 0$. Indeed, this was the behavior found for all the transition structures included in our study (see Figure 3). In the case of nonaromatic cycloadducts **3ab**, **3ba**, and **3bb**, on the other hand, the curves show small irregularities induced by the diamagnetic effect of the lone pairs of heteroatoms and/or by the double bonds.

Another interesting feature of Figure 3 is that it shows rapid decays of the NICSs with respect to z. However, the curve corresponding to isoxazole **3aa** shows a *plateau* within *ca.* -0.6 Å $< z < +0.6$ Å, with two small maxima at $z \approx \pm 0.5$ Å, which also correspond to the maximum of the probability of the radial function $4\pi r^2 R^2(r)$ for a 2p atomic orbital of carbon.[28] Therefore, the π-aromaticity

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of isoxazole is characterized by the relative invariance of the diamagnetic shielding above and below the molecular plane within the interval -0.5 Å $\leq z \leq +0.5$ Å. In **3aa** the six electrons are involved in π-aromaticity and are thus dispersed over a larger volume. This makes for a lower maximum value of the NICS at the (3,+1) point.

One might also think that π-aromaticity could play a significant role in the aromatic character of **TSaa**. However, the NICS *vs z* curves for **TSaa** and **TSab** (the latter leading to the nonaromatic isoxazoline **3ab**) are very similar. In order to analyze this problem in a different way, we have computed the π-aromatic stabilization energy (π-ASE) of isoxazole **3aa** as the quantity defined by eq 5:

$$\pi\text{-ASE} = E(\mathbf{3ab}) + E(\mathbf{3ba}) - [E(\mathbf{3aa}) + E(\mathbf{3bb})] \quad (5)$$

The π-ASE value for isoxazole is found to be +22.91 kcal/mol and +19.14 kcal/mol at the MP2(fc)/6-31+G*+ΔZPVE and B3LYP/6-31+G*+ΔZPVE levels, respectively. These values are in line with the ASEs computed by Schleyer for furan or pyrrole.[29] We have also defined an analogous magnitude for the transition structure **TSaa** in the form

$$\pi\text{-ASE}^{\ddagger} = E(\mathbf{TSab}) + E(\mathbf{TSba}) - [E(\mathbf{TSaa}) + E(\mathbf{TSbb})] \quad (6)$$

We have found that at the MP2(fc)/6-31+G*+ΔZPVE and B3LYP/6-31+G*+ΔZPVE levels the calculated π-ASE‡ values are -0.53 and $+2.85$ kcal/mol, respectively. This implies that π-aromaticity does not play any significant stabilizing role in these transition structures, in agreement with the NICS data. This result can be readily interpreted by considering the relatively long interaction distances of the σ-bonds under formation. This leads to a low or negligible overlap between the P_z-AOs perpendicular to the molecular plane, thereby disrupting the π-electron current. Thus, only *in-plane* aromaticity is operating in these transition structures.

Acknowledgment. This work was supported by the Gobierno Vasco/Eusko Jaurlaritza (Project 170.215-EX97/11) and by the Universidad del País Vasco/Euskal Herriko Unibertsitatea (Project UPV 170.215-EA126/96). One of us (I. M.) gratefully acknowledges a predoctoral grant from the Universidad del País Vasco/Euskal Herriko Unibertsitatea. We thank the Plan Nacional de I+D (CICYT) and the CIEMAT for a generous gift of computing time at the CRAY YMP-EL computer. We are also grateful to Prof. J. M. Ugalde (Euskal Herriko Unibertsitatea) for helpful discussions.

Supporting Information Available: Total energies, zero-point vibrational energies, and Cartesian coordinates of all the stationary points mentioned in this work (8 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[28] In addition, the average electron−nucleus distance of the 2p AO of carbon is $\langle r \rangle_{2p(C)} = 0.44$ Å. See, for example: Weissbluth, M. In *Atoms and Molecules*; Academic Press: New York, 1978; p 333.

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