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A Molecular Electron Density Theory Study of the [3+2] Cycloaddition Reaction of *Pseudo(mono)radical* Azomethine Ylides with Phenyl Vinyl Sulphone

Mar Ríos-Gutiérrez ^{1,*} , Assem Barakat ²  and Luis R. Domingo ¹ 

¹ Department of Organic Chemistry, University of Valencia, Dr. Moliner 50, Burjassot, 46100 Valencia, Spain; luisrdomingo@gmail.com

² Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia; ambarakat@ksu.edu.sa

* Correspondence: m.mar.rios@uv.es

Abstract: The [3+2] cycloaddition (32CA) reaction of an azomethine ylide (AY), derived from isatin and L-proline, with phenyl vinyl sulphone has been studied within Molecular Electron Density Theory (MEDT) at the ω B97X-D/6-311G(d,p) level. ELF topological analysis of AY classifies it as a *pseudo(mono)radical* species with two monosynaptic basins at the C1 carbon, integrating a total of 0.76 e. While vinyl sulphone has a strong electrophilic character, AY is a supernucleophile, suggesting a high polar character and low activation energy for the reaction. The nucleophilic Parr functions indicate that the *pseudoradical* C1 carbon is the most nucleophilic center. The 32CA reaction presents an activation Gibbs free energy of 13.1 kcal·mol^{−1} and is exergonic by −26.8 kcal·mol^{−1}. This reaction presents high *endo* stereoselectivity and high *meta* regioselectivity. Analysis of the global electron density transfer (GEDT) at the most favorable *meta/endo* TS, 0.31 e, accounts for the high polar character of this 32CA reaction, classified by forward electron density flux (FEDF). A Bonding Evolution Theory (BET) study along the most favorable *meta/endo* reaction path characterizes this 32CA reaction, taking place through a non-concerted *two-stage one-step* mechanism, as a *pseudo(mono)radical-type* 32CA reaction, in agreement with the ELF analysis of the AY.

Keywords: Molecular Electron Density Theory; azomethine ylides; [3+2] cycloaddition reaction; molecular mechanism; selectivity; reactivity



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1. Introduction

[3+2] Cycloaddition (32CA) reactions are one of the most efficient synthetic methods for the construction of five-membered heterocyclic compounds, due to their ability to build organic cyclic motifs regio- and/or stereoselectively [1–4].

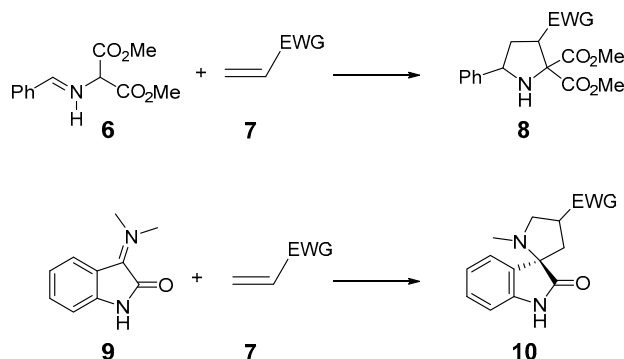
The understanding of the 32CA reactions is a challenge for organic chemists as a consequence of the chameleonic electronic structures of the three-atom-components (TACs) participating in these reactions [5–8]. Unlike the Diels–Alder reactions in which the diene is characterized by a unique Lewis structure, recent Molecular Electron Density Theory (MEDT) [9] studies of 32CA reactions have categorized four different types of TACs participating in this class of cycloaddition reactions [5–8], i.e., *pseudodiradical*, *pseudo(mono)radical*, carbenoid, and zwitterionic TACs (see Scheme 1). These MEDT studies have allowed establishing a very good correlation between the electronic structure of the simplest TACs and their reactivity towards ethylene **5** [10]. Accordingly, 32CA reactions have been classified into *pseudodiradical* (*pdr*)-, *pseudo(mono)radical* (*pmr*)-, carbenoid (*cb*)-, and zwitterionic (*zw*)-type reactions, respectively (see Scheme 1) [10], in such a manner that while *pdr-type* 32CA reactions take place very easily [5], *zw-type* 32CA reactions demand suitable nucleophilic/electrophilic activations of the reagents (see Scheme 1) [7].

Azomethine ylide 1	Azomethine imine 2	Nitron 3	Nitrile ylide 4
Structure			
<i>pseudodiradical</i>	<i>pseudoradical</i>	zwitterionic	carbenoid
Reactivity			
<i>pdr-type</i>	<i>pmr-type</i>	<i>zw-type</i>	<i>cb-type</i>
1.0 kcal/mol	7.7 kcal/mol	13.4 kcal/mol	7.8 kcal/mol

Scheme 1. Electronic structure of simplest TACs and proposed reactivity types in 32CA reactions. MPWB1K/6-311G(d) gas phase activation energies of the non-polar 32CA reactions between the four simplest TACs 1–4 and ethylene 5, relative to the corresponding molecular complexes, are given in kcal·mol^{−1}.

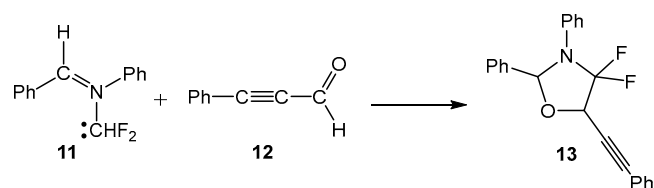
However, simplest TACs do not participate in experimental 32CA reactions. In general, TACs are very reactive intermediates which are usually generated in situ. The adequate substitution that stabilizes TACs can change their electronic structure and, consequently, their reactivity. Therefore, it is desirable to know how substitution modifies their chemical properties.

Pyrrolidines **8** are five-membered heterocyclic units with only one nitrogen and great pharmaceutical importance [11–13], and are easily obtained by 32CA reaction of an azomethine ylide (AY) **6** with a variety of olefins **7** (see Scheme 2). The use of AY **9**, generated from isatin, permits the synthesis of spirooxindoles **10** with significant biological activities [14–18].



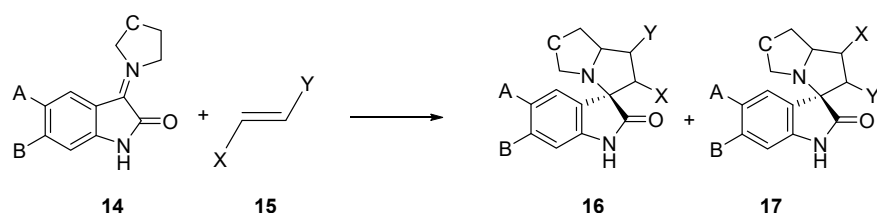
Scheme 2. Synthesis of pyrrolidines and spirooxindoles by 32CA reactions of AYs.

MEDT studies of the 32CA reactions of the simplest AY **1** [5] and the simplest carbonyl ylide CH₂-O-CH₂ [19] have shown that the presence of a *pseudoradical* center at each one of the two methylenes of these TACs causes the *pdr-type* 32CA reactions with non-activated ethylenes to have an unappreciable electronic activation energy (see Scheme 1) [5,19]. However, the presence of an electron-releasing phenyl (Ph) group and electron-withdrawing carboxyl CO₂R or nitrile CN groups at the two methylenes of the simplest AY **1** stabilizes its *pseudodiradical* electronic structure, modifying the experimental reactivity of these substituted AYs to that of a *pseudo(mono)radical* TAC [20] or even a zwitterionic TAC [21]. Very recently, a MEDT study of the 32CA reactions of fluorated AY **11** with ynals has shown that the presence of two fluorine atoms in one of the two methylenes of this AY changes its structure and reactivity to that of a carbenoid TAC (see Scheme 3). Consequently, depending on the substitution on the AYs, these TACs can display one of the four types of electronic structures categorized in Scheme 1, and hence, experience a different reactivity.



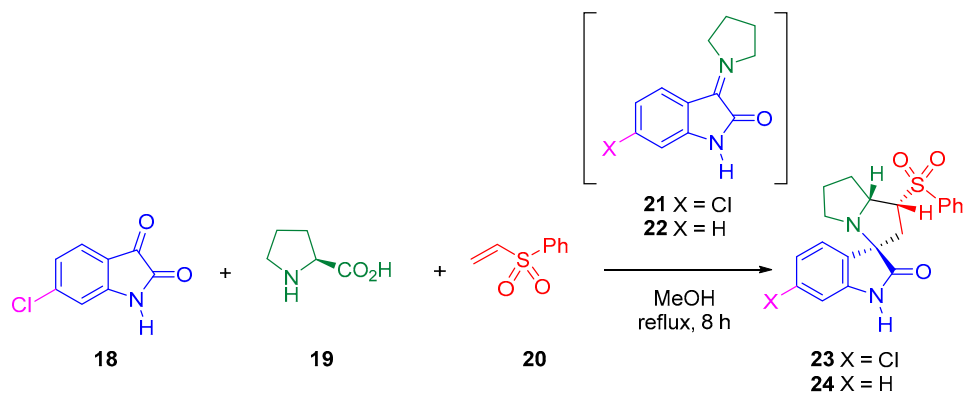
Scheme 3. Cb-type 32CA reactions of fluorinated AY **11**.

Very recently, Barakat et al. have experimentally studied a series of 32CA reactions of AYs **14**, obtained in situ from isatin derivatives and secondary amines, with different ethylene derivatives **15**, in the synthesis of spirooxindoles **16** and **17**, with high regio- and stereoselectivity (see Scheme 4) [22–24]. While these 32CA reactions were *endo* stereoselective, the regioselective formation of spirooxindoles **16** or **17** was found to be dependent on the substitution on the ethylene derivative **15**.



Scheme 4. 32CA reactions of AYs **14** derived from indol-2,3-diones.

Thus, the 32CA reaction of AY **21**, generated in situ from the reaction of 6-chloroisatin **18** and L-proline **19**, with phenyl vinyl sulphone **20** yielded the spirooxindole **23** with total *meta* regio- and *endo* stereo-selectivities (see Scheme 5) [25].



Scheme 5. 32CA reactions of AY **21** with phenyl vinyl sulphone **20** yielding spirooxindole **23** regio- and stereoselectively.

Herein, the 32CA reaction of AY **22** with phenyl vinyl sulphone **20** yielding spirooxindole **24**, as a model of the 32CA reaction studied by Barakat et al., is theoretically studied within MEDT in order to understand the electronic structure of AY **21** and its reactivity in this 32CA reaction (see Scheme 5). The origin of the *meta* regio- and *endo* stereoselectivity will be analyzed.

2. Materials and Methods

The ω B97X-D [26] functional, together with the standard 6-311G(d,p) [27] basis set, which includes d-type polarization for second row elements and p-type polarization functions for hydrogen atoms, was used in this MEDT study. The TSs were characterized by the presence of only one imaginary frequency. The Berny method was used in optimizations [28,29]. The intrinsic reaction coordinate (IRC) paths [30] were obtained to establish the unique connection given between the TSs and the corresponding minima [31,32]. Solvent

effects of methanol were taken into account by full optimization of the gas phase structures at the same computational level using the polarizable continuum model (PCM) [33,34] in the framework of the self-consistent reaction field (SCRF) [35–37]. Values of ω B97X-D/6-311G(d,p) enthalpies, entropies, and Gibbs free energies in methanol were calculated with standard statistical thermodynamics at 337.8 K and 1 atm [27], by PCM frequency calculations at the solvent optimized structures.

The global electron density transfer (GEDT) [38] values were computed by using the equation $\text{GEDT}(f) = \sum q_f$, where q are the natural charges [39,40] of the atoms belonging to one of the two frameworks (f) at the TS geometries. Global and local Conceptual Density Functional Theory (CDFT) indices [41,42] were calculated by using the equations given in reference [42].

The Gaussian 16 suite of programs was used to perform the calculations [43]. Electron Localization Function (ELF) [44] analyses of the ω B97X-D/6-311G(d,p) monodeterminantal wavefunctions were done by using the TopMod [45] package with a cubical grid of step size of 0.1 Bohr. Molecular geometries and ELF basin attractors were visualized by using the GaussView program [46]. The topological analysis of the non-covalent interactions (NCI) [47] was performed with the NCIPLOT program [48].

3. Results and Discussion

3.1. ELF Topological Analysis at the Ground State of AY 22 and Phenyl Vinyl Sulphone 20

The topological analysis of the ELF [44] allows a quantitative and qualitative description of the electronic structure of molecules [49]. Given the structure–reactivity relationship in TACs [10], an ELF topological analysis of AY 22 was first performed in order to characterize its electronic structure and gain some insight about its reactivity. The most significant ELF basin attractor positions and ELF basins of AY 22 and phenyl vinyl sulphone 20 are given in Figure 1, while those for the experimental AY 21 are given in Figure S1 in the Supporting Information.

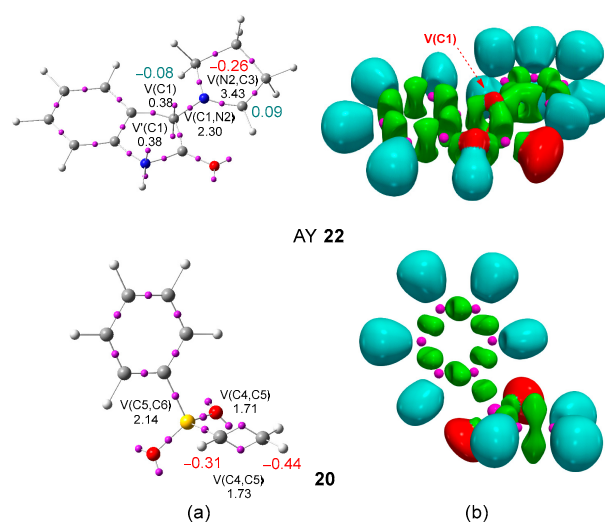


Figure 1. ω B97X-D/6-311G(d,p) (a) ELF basin attractor positions together with the most relevant valence basin populations, and (b) ELF localization domains represented at an isosurface value of ELF = 0.70, of AY 22 and phenyl vinyl sulphone 20. Valence basin populations and natural atomic charges are given in average number of electrons, e. Negative charges are colored in red and negligible charges in green.

The ELF of AY 22 shows the presence of two monosynaptic basins, V(C1) and V'(C1), integrating a total of 0.76 e, one V(C1,N2) disynaptic basin, integrating 2.30 e, and one V(N2,C3) disynaptic basin, integrating 3.43 e. While the V(C1,N2) disynaptic basin is associated to a C1–N2 single bond, the V(N2,C3) disynaptic basin is associated to an underpopulated N2–C3 double bond. The presence of the two monosynaptic basins at the

C1 carbon, which is associated with a *pseudoradical* carbon [19], allows the classification of this AY as a *pseudo(mono)radical* TAC. A comparative analysis of the ELF of the experimental AY **21** given in Figure S1 in Supporting Information and that of AY **22** indicates that the substitution of the chlorine atom by the hydrogen one in the model does not produce any electronic change in the AY core.

On the other hand, ELF of phenyl vinyl sulphone **20** shows the electronic structures of ethylene and benzene separately. The vinyl framework of vinyl sulphone **20** is characterized by the presence of two disynaptic basins, $V(C4,C5)$ and $V'(C4,C5)$, integrating a total of 3.44 e, and a $V(C5,S6)$ disynaptic basin, integrating 2.14 e. The populations of these disynaptic basins indicate some delocalization of the electron density of the C4–C5 double bond at the sulfur S6 atom.

The analysis of the natural atomic charges [39,40] shows that the two carbons of AY **22** are negligibly charged by less than ± 0.1 e. Interestingly, the natural charges indicate that the C4 and C5 carbons of the ethylene framework of vinyl sulphone **20** are negatively charged by -0.44 and -0.31 e, respectively, the methylene CH_2 carbon being the more negatively charged. Thus, according to charges, AY **22** would have no tendency for a supposed nucleophilic attack of the C4 carbon of vinyl sulphone **20**.

3.2. Conceptual DFT Analysis at the Ground State of the Reagents

The reactivity indices defined within Conceptual DFT (CDFT) [41,42] have shown to be powerful tools to understand the reactivity in polar reactions. The global reactivity indices, namely, the electronic chemical potential μ , chemical hardness η , electrophilicity ω and nucleophilicity N , for AYs **21** and **22**, and phenyl vinyl sulphone **20** are gathered in Table 1.

Table 1. B3LYP/6-31G(d) electronic chemical potential μ , chemical hardness η , electrophilicity ω , and nucleophilicity N indices, in eV, of AYs **21** and **22** and phenyl vinyl sulphone **20**.

	μ	η	ω	N
vinyl sulphone 20	-4.39	5.97	1.61	1.75
AY 21	-2.97	3.34	1.32	4.48
AY 22	-2.76	3.36	1.14	4.68

The electronic chemical potentials [50] of AYs **21** and **22**, $\mu = -2.97$ and -2.76 eV, respectively, are higher than that of vinyl sulphone **20**, $\mu = -4.39$ eV, indicating that along a polar 32CA reaction the global electron density transfer (GEDT) [38] will take place from AYs **21** and **22** to the vinyl sulphone **20**, the reaction being classified as of forward electron density flux (FEDF) [51].

AYs **21** and **22** present an electrophilicity ω index [52] of 1.32 and 1.14 eV, respectively, classified as strong electrophiles within the electrophilicity scale [42], and a nucleophilicity N index [53] of 4.48 and 4.68 eV, respectively, classified as strong nucleophiles within the nucleophilicity scale [42]. The strong nucleophilic character of AY **21** and **22**, higher than 4.0 eV, allows their classification as supernucleophiles [54]. Substitution of the chlorine atom in the experimental AY **21** by a hydrogen atom in the model AY **22** slightly decreases the electrophilicity and slightly increases the nucleophilicity of the latter.

Vinyl sulphone **20** presents an electrophilicity ω index of 1.61 eV, classified as a strong electrophile within the electrophilicity scale. On the other hand, it presents a nucleophilicity N index of 1.75 eV, classified as marginal nucleophile within the nucleophilicity scale.

The supernucleophilic character of AY **21** and **22** together with the electrophilic character of vinyl sulphone **20** indicate that the corresponding 32CA reactions will have a high polar character, classified as FEDF [51].

Along a polar reaction involving non-symmetric species, the most favorable reaction path involves the two-center interaction between the most electrophilic and the most nucleophilic centers [55]. Many studies have shown that the analysis of the electrophilic

P_k^+ and nucleophilic P_k^- Parr functions [56], resulting from the excess of spin electron density gathered via the GEDT [38] is one of the most accurate tools for the analysis of the local reactivity in polar and ionic processes. Hence, according to the characteristics of the reagents, the nucleophilic P_k^- Parr functions of AYs **21** and **22**, and the electrophilic P_k^+ Parr functions of vinyl sulphone **20** were analyzed (see Figure 2).

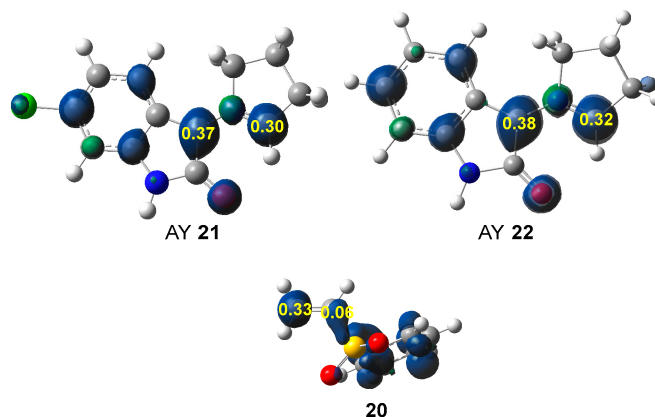


Figure 2. B3LYP/6-31G(d) nucleophilic P_k^- Parr functions of AYs **21** and **22**, and electrophilic P_k^+ Parr functions of vinyl sulphone **20**.

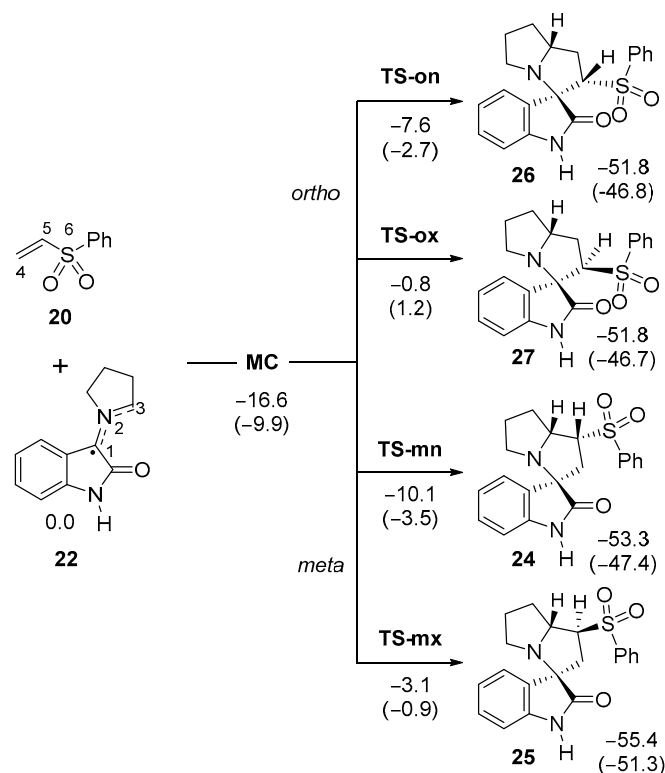
The two C1 and C3 carbons of AYs **21** and **21** are nucleophilically activated by $P_k^- = 0.37$ and 0.38 (C1), and 0.30 and 0.32 (C3), respectively, the exocyclic C1 carbon being slightly more activated. Note that the nitrogen atom is deactivated. Both AYs show a similar nucleophilic activation. On the other hand, the conjugated C4 carbon of vinyl sulphone **20** is the most electrophilically activated center, $P_k^+ = 0.33$. Consequently, the most favorable two-center interaction along the corresponding polar 32CA reaction will take place between the C1 carbon of AYs **21** and **22** and the conjugated C4 carbon of vinyl sulphone **20**. Note that the most electrophilic C4 carbon of vinyl sulphone **20** is negatively charged by -0.44 e (see Figure 1). This finding supports Domingo's proposal made in 2012 that the local electrophilic/nucleophilic behaviors of organic molecules are not simply caused by charges [57]. The most electrophilic center of a molecule is the one that accepts the highest amount of electron density resulting from the nucleophilic/electrophilic interactions taking place along the approach of the two reagents [57]. Interestingly, in some cases, such as in vinyl sulphone **20**, the most electrophilic C4 carbon is negatively charged [57].

3.3. Study of the Reaction Paths Associated with the 32CA Reaction of AY **22** with Phenyl Vinyl Sulphone **20**

Due to the non-symmetry of both reagents, two pairs of *endo* and *exo* stereoisomeric, as well as *ortho* and *meta* regioisomeric, reaction paths are feasible. The words *ortho* and *meta* account for the relative position of the sulphone group with respect to the spiro C1 carbon at spirooxindoles **24–27**. The four competitive reaction paths were studied (see Scheme 6). Analysis of the stationary points found in these reaction paths indicates that this 32CA reaction takes place through a one-step mechanism. The ω B97X-D/6-311G(d,p) relative energies in gas phase and in methanol are given in Scheme 6.

A series of molecular complexes (MCs) in which the two reagents are already linked by weak intermolecular interactions were found. Only the most stable of them, **MC**, was selected as the energy reference. The distance between the two frameworks at this MC is ca. 3.26 Å (the geometry of **MC** is given in Figure S1 in the Supporting Information); in the gas phase, **MC** is found 16.6 kcal·mol^{−1} below the separated reagents (see Scheme 2). The most favorable **TS-mn** is found 10.1 kcal·mol^{−1} below the separated reagents, the corresponding reaction path being strongly exothermic by 53.3 kcal·mol^{−1}. Some appealing conclusions can be obtained from the relative energies given in Scheme 6: (i) the most favorable **TS-mn** is found energetically below the separated reagents, but if the formation of **MC** is considered, the activation energy becomes positive by 6.5 kcal·mol^{−1}; (ii) in gas

phase, this 32CA reaction is highly *meta* regioselective as **TS-on** is found 2.5 kcal·mol^{−1} above **TS-mn**; (iii) this 32CA reaction is totally *endo* stereoselective as **TS-mx** is found 7.0 kcal·mol^{−1} above **TS-mn**; and (iv) the high exothermic character of the formation of spirooxindole **24**, −53.3 kcal·mol^{−1}, makes this 32CA reaction irreversible. Consequently, spirooxindole **24** is formed by kinetic control.



Scheme 6. 32CA reaction of AY **22** with phenyl vinyl sulphone **20**. Relative energies, with respect to the separated reagents, are given in kcal·mol^{−1}. ω B97X-D/6-311G(d,p) relative energies in methanol are given in parentheses.

Inclusion of the solvent effects of methanol decreases the relative energies of the stationary points involved in the 32CA reaction of AY **22** with vinyl sulphone **20** by between 2.2 and 6.7 kcal mol^{−1} as a consequence of a better solvation of the reagents than the other species (see Scheme 6) [58]. In methanol, the regioselectivity strongly decreases to 0.8 kcal·mol^{−1}, as a consequence of a stronger solvation of **TS-on** than **TS-mn**.

The thermodynamic data of the 32CA reaction of AY **22** with vinyl sulphone **20** were subsequently analyzed. The relative enthalpies, entropies, and Gibbs free energies, computed at 65 °C, are given in Table 2. Addition of the thermal corrections to the electronic energies in methanol increases the relative enthalpies by between 1.6 and 4.4 kcal·mol^{−1}. Those of the TSs are only increased by less than 1.6 kcal·mol^{−1}. Inclusion of entropies to enthalpies increases the relative Gibbs free energies by between 11.1 and 17.3 kcal·mol^{−1} due to the unfavorable activation entropies associated with this bimolecular reaction, which are found in the range −32.8 and −51.2 cal·mol^{−1}·K^{−1}. The activation Gibbs free energy associated with this 32CA reaction via **TS-mn** rises to 13.1 kcal·mol^{−1}, while formation of **24** remains exergonic by −26.8 kcal·mol^{−1}. Consequently, spirooxindole **24** is formed by kinetic control.

Considering the activation Gibbs free energies of the four TSs and the Eyring–Polanyi equation [59], a reaction mixture of 87.9 (**24**), 3.4 (**25**), 8.2 (**26**), and 0.1 (**27**) is expected, in reasonable agreement with the experimental results in which only spirooxindole **24** was isolated [25].

Table 2. ω B97X-D/6-311G(d,p) relative enthalpies (ΔH , kcal·mol^{−1}), entropies (ΔS , cal·mol^{−1}·K^{−1}) and Gibbs free energies (ΔG , kcal·mol^{−1}) of the stationary points, computed at 65 °C in methanol, involved in the 32CA reaction of AY 22 with phenyl vinyl sulphone 20.

	ΔH	ΔS	ΔG
MC	−7.6	−32.8	3.4
TS-on	−1.1	−46.7	14.7
TS-ox	2.8	−44.0	17.6
TS-mn	−1.9	−44.4	13.1
TS-mx	0.7	−43.0	15.2
26	−42.4	−51.2	−25.1
27	−42.7	−50.6	−25.6
24	−43.3	−48.7	−26.8
25	−47.2	−48.5	−30.8

The geometries of the four TSs are given in Figure 3. The C–C distances between the four interacting carbons at the four TSs indicates that they correspond with high asynchronous C–C single bond formation processes, in which the shorter C–C distance corresponds to that involving the most electrophilic β -conjugated carbon of the vinyl sulphone 20. At the most favorable TS-mn, the C–C distances between the two pairs of interacting carbons, 2.104 and 2.635 Å, indicate that this TS is associated with a highly asynchronous C–C single bond formation process, in which the shorter C–C distance also involves the *pseudoradical* C1 carbon of AY 22. Considering that C–C single bond formation takes place in the short range of 2.0–1.9 Å [38], the C–C distances at the four TSs indicate that they correspond to early processes in which the formation of the new C–C single bond has not yet begun (see later). The inclusion of the solvent effects of methanol does not substantially modify the optimized geometries (see Figure 3); in methanol, the TSs are only slightly more asynchronous.

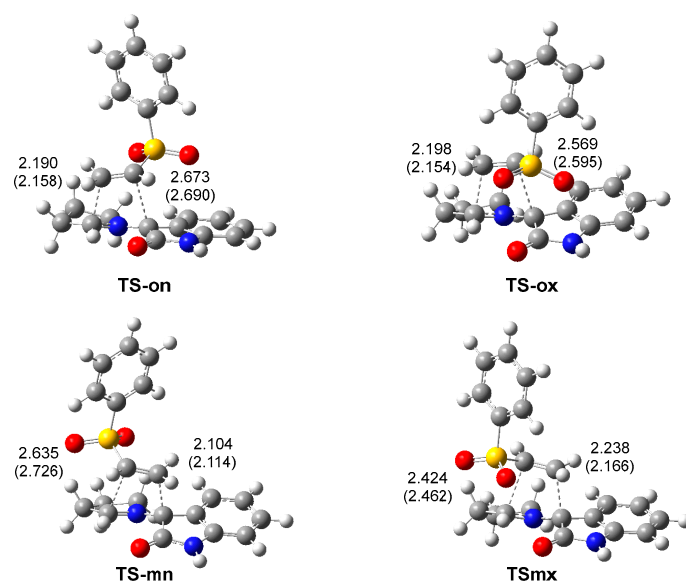


Figure 3. ω B97X-D/6-311G(d,p) geometries of the TSs involved in the 32CA reaction of AY 22 with phenyl vinyl sulphone 20. Distances are given in angstroms, Å. Distances in methanol are given in parentheses.

Finally, the analysis of GEDT [38] at the TSs permits the assessment of the polar character of these 32CA reactions. GEDT values lower than 0.05 e correspond with non-polar processes, while values higher than 0.20 e correspond with polar processes. The GEDT value at the TSs are 0.22 e (TS-on), 0.20 e (TS-ox), 0.31 e (TS-mn), and 0.24 e (TS-mx). The high value found at the most favorable TS-mn, which is a consequence of the

supernucleophilic character of AY 22 and the strong nucleophilic character of phenyl vinyl sulphone 20, indicates that this 32CA reaction has a high polar character and accounts for its low activation energy, $6.5 \text{ kcal}\cdot\text{mol}^{-1}$. The flux of the electron density, which flows from AY 22 to vinyl sulphone 20, classifies this 32CA reaction as FEDF [51], in clear agreement with the analysis of the CDFT indices.

3.4. BET Analysis along the Most Favorable Meta/Endo Reaction Path. Characterization of the Pmr-Type Mechanism

In order to characterize the C–C bond formation along the 32CA reaction between AY 22 with vinyl sulphone 20, and thus to characterize the type of 32CA reaction, a Bonding Evolution Theory (BET) [60] study along the most favorable *meta/endo* reaction path was performed. BET allows for a full description of the bonding changes along a reaction path by analyzing the changes in the topology of the ELF at all the structures of the corresponding IRC [30] path and selecting those chemically meaningful. As ELF valence basins and their populations can be related to the Lewis bonding model [49], a molecular mechanism can be elegantly represented by rigorous Lewis-like structures based on the quantum chemical topology framework. Complete BET data for the *meta/endo* reaction path of 32CA reaction between AY 22 with vinyl sulphone 20 are given in Table S3, while the representation of the molecular mechanism of this *pmr-type* 32CA reaction by Lewis-like structures based on the topological analysis of the ELF along the reaction path is given in Scheme S1 in Supporting Information. ELF basin attractor positions are represented in Figure 4.

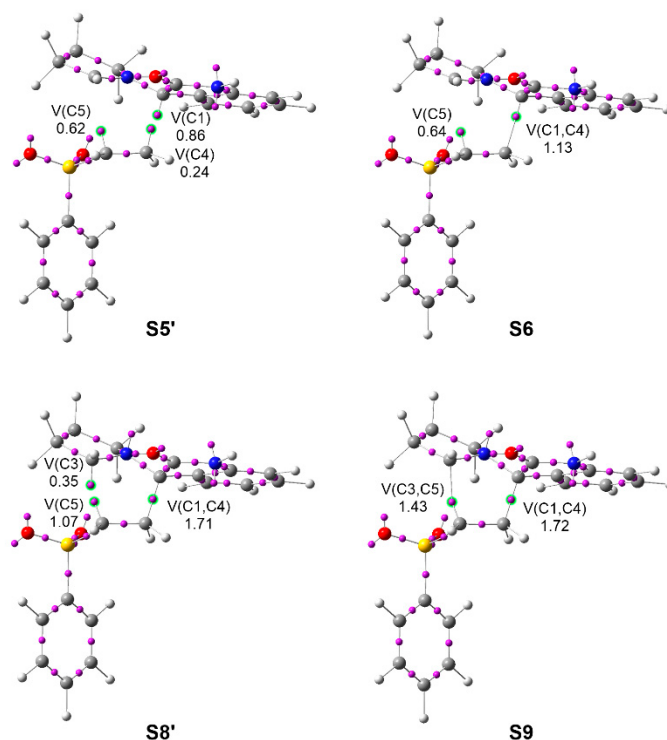


Figure 4. ELF attractor positions and populations of the ELF valence basins involved in the C1–C4 and C3–C5 bond formation at S6 and S9, respectively, and the structures immediately before, along the *meta/endo* path of the *pmr-type* 32CA reaction between AY 22 with vinyl sulphone 20. Populations are given in average number of electrons, e.

The most relevant mechanistic aspects obtained from the BET analysis can be summarized as follows: (i) the *pseudoradical* C1 carbon present at AY 22, which characterizes this TAC as *pseudo(mono)radical* (see Figure 4), is initially delocalized into the indolinone C1–CO region due to the presence of vinyl sulphone 20, reappearing at a very early stage of the reaction with an unappreciable energy cost of only $0.4 \text{ kcal}\cdot\text{mol}^{-1}$; (ii) the other three *pseudoradical* carbons participating in the formation of the two new C–C single

bonds [38] are created by the depopulation of the double bond regions along the reaction path; (iii) given the insignificant energy cost demanded for the reappearance of the delocalized *pseudoradical* C1 carbon, the low activation energy associated with **TS-mn**, $5.8 \text{ kcal}\cdot\text{mol}^{-1}$ from the first structure of the IRC, can mainly be associated with the depopulation of the C4–C5 double bond of vinyl sulphone **20**; (v) formation of the C1–C4 single bond at the **S6** structure, and that of the C3–C5 single bond at the **S9** structure, takes place at C–C distances of 2.02 and 2.16 Å, with initial populations of 1.13 and 1.43 e, respectively, through the C-to-C coupling of the two C1 and C4, and C3 and C5 pairs of *pseudoradical* centers present at the structures **S5'** and **S8'** (see Figure 4) [38]; (vi) while the *pseudoradical* C1 carbon present at **AY 22** contributes 78% to the formation of the first C1–C4 single bond, the ethylene *pseudoradical* C5 carbon contributes 75% to the formation of the second C3–C5 single bond. Consequently, formation of both single bonds can be considered to take place mainly by donation of the electron density of one of the two *pseudoradical* centers to the other one; (vii) the participation of the *pseudoradical* C1 carbon present at the *pseudo(mono)radical* **AY 22** in the formation of the first C3–C5 single bond makes it possible to characterize this 32CA reaction as a *pmr-type* reaction; and finally, (viii) formation of the second C3–C5 bond takes place when the first C1–C4 bond has reached 91% of its population at spirooxindole **24**, and with a synchronicity value of 0.12. Consequently, the *pmr-type* 32CA reaction between **AY 22** with vinyl sulphone **20** takes place through a non-concerted *two-stage one-step* mechanism [61].

3.5. Analysis of the Origin of the Meta Regio- and Endo Stereo-Selectivities

Both analysis of the TS geometry and BET study of the *meta/endo* reaction path indicate that the highly asynchronous **TS-mn** is associated with the most favorable two-center interaction taking place between the *pseudoradical* C1 carbon of **AY 22**, which corresponds to the most nucleophilic center of this TAC, and the β -conjugated C4 carbon of vinyl sulphone **20**, which corresponds to the most electrophilic center of this ethylene derivative (see the values of the Parr functions in Figure 2). These favorable electronic interactions account for the fact that the *ortho* **TS-on** will be located $2.5 \text{ kcal}\cdot\text{mol}^{-1}$ above **TS-mn**, and consequently, these favorable electronic interactions are responsible for the *meta* regioselectivity found in this *pmr-type* 32CA reaction [10]. Note that at the *ortho* TSs, the *pseudoradical* C1 carbon present at **AY 22** does not participate in the initial C3–C4 single bond formation.

Endo stereoselectivity in cycloaddition reactions has been explained within the outdated Frontier Molecular Orbital (FMO) theory [62] by “secondary orbital interactions” (SOI) present at the *endo* TSs, a concept introduced in 1983 by Gleiter and Bohm to explain the regio- and stereoselectivity in Diels–Alder reactions [63]. Today, SOI continues being used to explain *endo* stereoselectivity in cycloaddition reactions [64]. However, molecular orbitals, which are only mathematical artefacts without any physical reality used in the approximation to the molecular wave function, cannot control anything [9]. In 2000, Salvatella et al. proposed that a combination of well-known mechanisms, such as solvent effects, steric interactions, hydrogen bonds (HBs), electrostatic forces, and others, can be invoked instead of SOI in the *endo/exo* selectivity of Diels–Alder reactions [65].

Analysis of the geometry of the most favorable **TS-mn** shows that the two oxygen atoms of the sulfonyl group of the vinyl sulphone **20** are located at 2.27 and 2.35 Å from two methylene hydrogens of the proline residue (see Figure 5). These short distances suggest the presence of two HBs at *endo* **TS-mn**, which are not at the *exo* **TS-mx**. These HBs, which are already present at the most favorable **MC**, can be responsible for the high stabilization in gas phase of **MC** with respect to the separated reagents; ca. $16 \text{ kcal}\cdot\text{mol}^{-1}$ (see Scheme 5).

In order to characterize the presence of the two HBs at the most favorable **TS-mn**, a topological analysis of the non-covalent interactions (NCI) [47] taking place at this TS was performed. The NCI surfaces are shown in Figure 6. The topological analysis of the NCI at **TS-mn** shows the presence of two green surfaces at the interatomic separation between the two oxygen atoms of the sulfonyl group and the two methylene hydrogens of the proline residue. In order to characterize the rather attractive nature of these surfaces, the NCI

interactions at **TS-mn** were decomposed into their attractive ($\text{sign}(\lambda_2)\rho(r) < 0$) counterpart (see Figure 6b). As can be observed, after removing the repulsive interactions, two green surfaces at the two HBs regions are observed. Consequently, formation of two HBs at **MC** and **TS-on** along the *meta/endo* reaction path may be responsible for the high stabilization of **MC** with respect to the separated reagents, and hence for the *endo* stereoselectivity found in this *pmr*-type 32CA reaction.

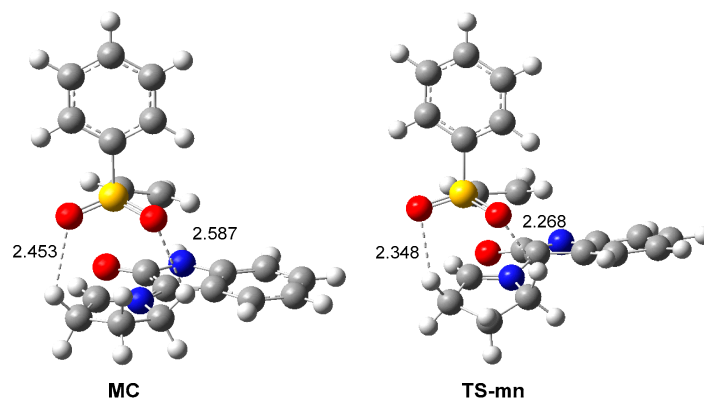


Figure 5. ω B97X-D/6-311G(d,p) geometries of **MC** and **TS-mn** showing the distances of the two O-H HBs. Distances are given in angstroms, Å.

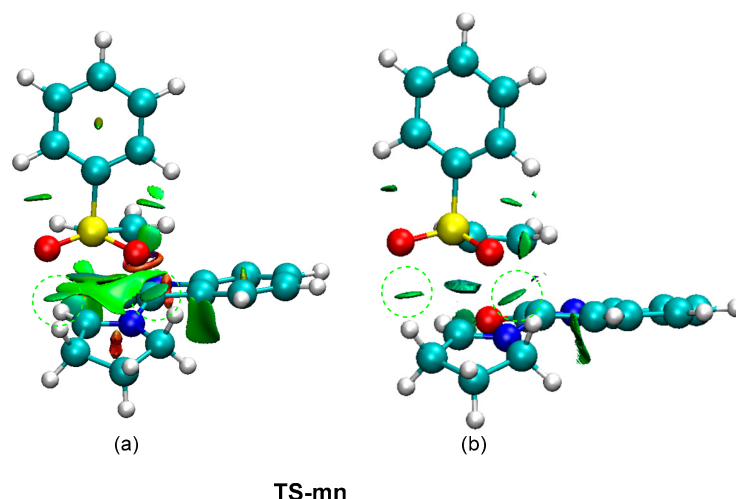


Figure 6. (a) NCI isosurfaces associated with the density overlap at **TS-mn** from $-0.08 < \text{sign}(\lambda_2)\rho(r) < 0.08$ a.u., and (b) attractive contribution from $-0.08 < \text{sign}(\lambda_2)\rho(r) < 0.00$ a.u. The attractive NCI surfaces associated with the two HBs are highlighted by a line-dashed green circle.

4. Conclusions

The *pmr*-type 32CA reaction of AY **22**, derived from isatin and L-proline, with phenyl vinyl sulphone **20** has been studied within MEDT at the ω B97X-D/6-311G(d,p) computational level.

Analysis of the ELF topology of AY **22** indicates that this TAC has a *pseudo(mono)radical* structure characterized by the presence of two monosynaptic basins, integrating a total of 0.76 e, at the C1 carbon. Analysis of the CDFT reactivity indices indicates while vinyl sulphone **20** has a strong electrophilic character, AY **22** is a supernucleophile, suggesting that the corresponding 32CA reaction will have high polar character. Analysis of the nucleophilic P_k^- Parr functions indicates that the *pseudoradical* C1 carbon of AY **22** is the most nucleophilic center of this TAC, while analysis of the electrophilic P_k^+ Parr functions of vinyl sulphone **20** indicates that the β -conjugated C4 carbon is the most electrophilic center.

The most favorable reaction path via the *meta/endo* **TS-mn** presents an activation Gibbs-free energy of $13.1 \text{ kcal}\cdot\text{mol}^{-1}$, the 32CA reaction being exergonic by $-26.8 \text{ kcal}\cdot\text{mol}^{-1}$. This

reaction presents high *endo* stereoselectivity and high *meta* regioselectivity. While the *meta* regioselectivity is determined by the most favorable two-center interaction between the most nucleophilic center of AY 22, the *pseudoradical* C1 carbon, and the most electrophilic center of vinyl sulphone 20, the β -conjugated C4 carbon, the *endo* stereoselectivity is determined by the formation of two intramolecular HBs between the two oxygens of sulphone 20 and two methylene hydrogens of the proline residue. Analysis of the GEDT at the most favorable TS-mn, 0.31 e, accounts for the high polar character of this 32CA reaction, classified as FEDF, in complete agreement with the analysis of the CDFT indices at the ground state of the reagents.

A BET analysis along the most favorable *meta/endo* reaction path characterized this 32CA reaction, which takes place through a non-concerted *two-stage one-step* mechanism, as a *pmr-type* 32CA reaction, in agreement with the *pseudo(mono)radical* structure of AY 22.

The present MEDT study shows that substitution on the simplest AY 1 can modify its *pseudodiradical* structure and reactivity to that of a *pseudo(mono)radical*, carbenoid, or zwitterionic TAC, but in any case, substituted AYs are found in one of the four types of TACs, characterizing their chemical reactivity.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/org3020010/s1>, Figure S1: ELF basin attractor positions of AY 21; Figure S2: geometries of MC; Table S1: ω B97X-D/6-311G(d,p) total electronic energies of the stationary points involved in the 32CA reaction of AY 22 with phenyl vinyl sulphone 20 in gas phase and in methanol; Table S2: ω B97X-D/6-311G(d,p) total enthalpies, entropies, and Gibbs-free energies of the stationary points involved in the 32CA reaction of AY 22 with phenyl vinyl sulphone 20; Table S3: most relevant ELF valence basins and their total populations, C–C bond formation distances, IRC values, and relative energies, for the structures of the IRC in which there is a relevant chemical change along the *meta/endo* path of the *pmr-type* 32CA reaction between AY 22 with phenyl vinyl sulphone 20; Scheme S1: representation of the molecular mechanism of the *pmr-type* 32CA reaction between AY 22 with phenyl vinyl sulphone 20 by Lewis-like structures based on the topological analysis of the ELF along the *meta/endo* reaction path; ω B97X-D/6-311G(d,p) gas phase Cartesian coordinates of the stationary points involved in the 32CA reaction between AY 22 with phenyl vinyl sulphone 20.

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