# Understanding the Reactivity of Captodative Ethylenes in Polar Cycloaddition Reactions. A Theoretical Study[†]

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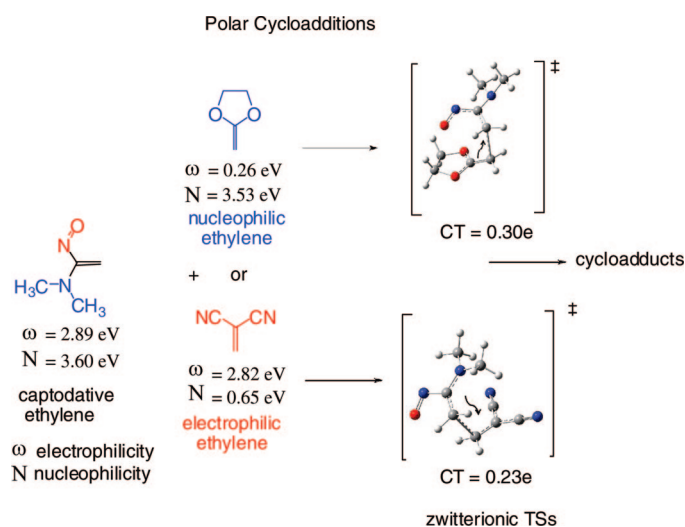
The electrophilic/nucleophilic character of a series of captodative (CD) ethylenes involved in polar cycloaddition reactions has been studied using DFT methods at the B3LYP/6-31G(d) level of theory. The transition state structures for the electrophilic/nucleophilic interactions of two CD ethylenes toward a nucleophilically activated ethylene, 2-methylene-1,3-dioxolane, and an electrophilically activated ethylene, 1,1-dicyanoethyelene, have been studied, and their electronic structures have been characterized using both NBO and ELF methods. Analysis of the reactivity indexes of the CD ethylenes explains the reactivity of these species. While the electrophilicity of the molecules accounts for the reactivity toward nucleophiles, it is shown that a simple index chosen for the nucleophilicity, N, based on the HOMO energy is useful explaining the reactivity of these CD ethylenes toward electrophiles.

Introduction

Cycloaddition reactions are one of the most important processes with both synthetic and mechanistic interest in organic chemistry.[1] In this type of reaction, two new σ bonds are formed at the ends of two interacting π systems along with the formation of a carbocycle system. These reactions have been mechanisti-cally classified in the class of the pericyclic reactions.[2] The feasibility of these processes has been related to the Woodward–Hoffmann rules.[3] For unsaturated hydrocarbon reagents, the activation energies associated with the concerted bond-formation processes show very high values. It is well-known, however, that electron-withdrawing (EW) and (or) electron-releasing (ER) substituents on one or both reagents notably increase the cycloaddition reaction rate. This chemical substitution affords to change the

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SCHEME 1
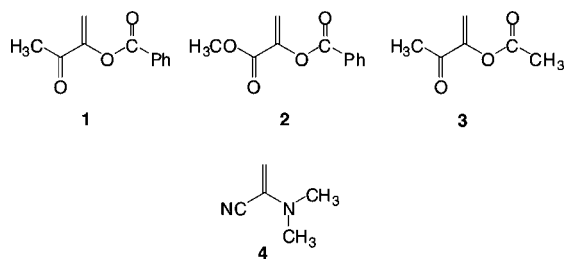
reaction mechanism from a non polar process to a polar one through highly asynchronous transition structures (TSs).[4]

The decrease of the activation energy associated with the cycloaddition has been related with the zwitterionic character of the TSs involved in such process.[5] The characterization of the electrophilic/nucleophilic nature of reagents allows prediction of the polar character of the cycloaddition, and as a consequence, the feasibility of the entire process. [2 + 2], [4 + 2], [3 + 2], and [3 + 4] cycloaddition reaction mechanisms have been shown to obey this rationalization. For instance, it is worth noting the Lewis acid (LA) catalyzed cycloadditions, which take place through TSs with a large zwitterionic character.[6] The cationic cycloadditions of iminium salts named as [4 + 2+] reactions,[7] exhibiting an ionic character, are others remarkable examples. These cycloadditions are characterized by a strong electrophilic/nucleophilic interaction at the first stages of the reaction.[8]

Recently, we have reported the use of the global electrophilicity index, ω, proposed by Parr et al.[9] to classify the global electrophilicity of a series of regents currently present in cycloaddition reactions involving simple EW or ER substitution.[10] For cycloaddition reactions involving a simple substitution, we found *an interesting linear correlation between the difference in electrophilicity for two reagent pairs, $\Delta\omega$, and the polar character of the cycloaddition reaction*.[10] It should be interesting to explore if such an observation could be further generalized for reagents with more complex substitution patterns.

Within this context, and owing to the opposite demands displayed by the geminal substituent functional groups, captodative (CD) ethylenes have attracted particular interest in cycloaddition reactions. For instance, the CD ethylenes 3-oxobut-1-en-2-yl esters **1**, **2**, and **3** (see Scheme 1) have been used as highly reactive,[11] stereoselective,[12] and regioselective[13] reagents in Diels–Alder (DA) and 1,3-dipolar cycloadditions.[14] On the other hand, 2-(dimethylamino)acrylonitrile **4** has shown

to be a useful reagent in domino reactions involving a [2 + 2] cycloaddition.[15]

While the CD ethylenes **1** and **2** have been used in DA reactions with cyclopentadiene (Cp) **5** and electron-rich butadienes,[16] the CD ethylene **4** has been used in polar [2 + 2] cycloadditions toward electron-deficient acetylene as dimethyl acetylendicarboxylate **6** (see Scheme 2).[15] It is worth noting however, those reactions with opposite electronic demand have not been experimentally reported. In addition, the reactions of the CD ethylenes **1** and the aryl derivatives of **2** toward Cp requires the use of LA catalysts in order to carry out the reaction in mild conditions (see Scheme 2).[16]

SCHEME 2
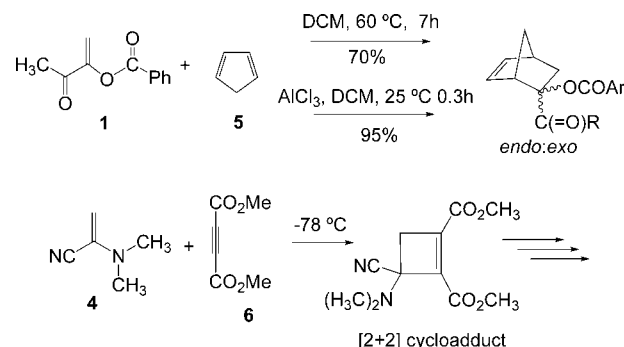
Bernard-Henriet and Chanon[17] reported the DA reaction of the CD α-mehylthioacrilonitrile **7** with 2-phenylcyclopentadiene **8** exhibiting a high regio and stereoselectivity (see Scheme 3).

SCHEME 3
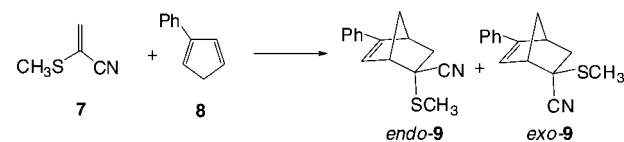
An AM1 frontier molecular orbital[18] (FMO) analysis was performed in order to explain the observed regioselectivity. Since the FMO model did not account for the formation of the *para* cycloadducts **9**, these authors concluded that regio- and stereoselectivity seem to be better rationalized by a concerted reaction process via an unsymmetrical TS with a diradicaloid character.[17] A further ab initio study for the DA reaction of the CD ethylene **7** with the cyclopentadiene derivative **8** carried out at the HF/6-31G* level gave further insights about the role played by the CD ethylene **7** in a polar DA reaction.[19] This DA reaction takes place through an asynchronous TS resulting from the nucleophilic attack of the cyclopentadiene derivative **8** to the β conjugated position of the acrilonitrile derivative **7**. The presence of the phenyl group on C2, acting as an electron-

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releasing substituent (see later), activates the C1 position in support of the consequential *para* regioselectivity. Interestingly, the observed *endo* selectivity was the opposite of that expected in a polar DA reaction because the nitrile group is positioned in an *exo* arrangement to the cyclopentadiene moiety (see *endo*-**9** in Scheme 3). The favorable electronic interactions between the sulfur atom in **7** and the positively charged cyclopentadiene moiety (e.g., +0.25e at the *para endo* TS) are responsible for the preferred *endo* approach mode.[19]

Recently, Jorgensen and co-workers[20] reported the first catalyzed DA reaction of nitrosoalkene **10** acting as a hetero-diene (Scheme 4). These DA reactions involve a highly nucleophilic activated enamine intermediate **11** formed by condensation of the carbonyl compounds with pyrrolidine yielding finally the DA adduct **12**.
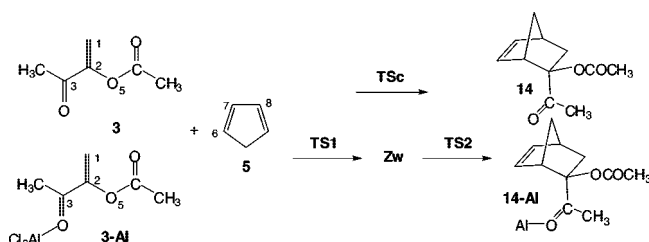
SCHEME 4
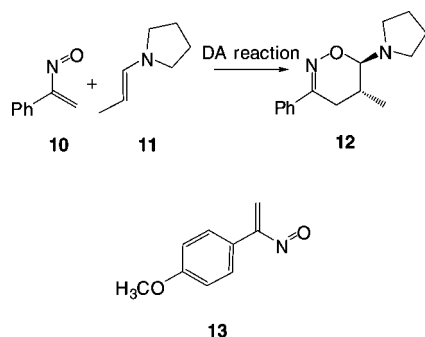
A further density functional theory (DFT) study[21] showed that the larger electrophilic character of nitrosoethylene **10** and the larger nucleophilic character of enamine **11** are responsible for the greater acceleration found in these polar DA reactions. The (1-nitrosovinyl)benzene **10** presents a very large electrophilicity value, $\omega = 3.12$ eV. Inclusion of an ER methoxy group on the *para* position of the aryl group, which decreases the reactivity on these organocatalyzed reactions, slightly decreases the electrophilicity value of the corresponding nitrosoethylene **13**, $\omega = 3.00$ eV.[21] However, it is expected that this new situation may increase the nucleophilicity of the corresponding nitrosoethylene. Due to the geminal condition of nitroso and *p*-MeOPh groups on the ethylene, nitrosoethylenes as **13** could in effect be considered as CD-ethylenes.

In this work, we present a theoretical analysis intended to provide a guide to further understanding the electronic nature and role of CD ethylenes experimentally used in cycloaddition reactions. Furthermore, we postulate new structures of these systems, which may act efficiently in polar cycloadditions exhibiting both types of electron-demanding patterns. Within this aim, a simple model of nucleophilicity is introduced in the next section in order to categorize the nucleophilic character of these reagents. First, an analysis of the CD ethylenes based on the reactivity indices will be presented. In a second part, the TSs involved in the addition of the CD ethylene **3**, in the absence and presence of a LA catalyst, to Cp has been studied in order to explain the experimental results (see Scheme 5). Then, the TSs involved in the nucleophilic/electrophilic additions of the CD ethylene **3** toward 2-methylene,1,3-dioxolane **15**, as a model

SCHEME 5

of strong nucleophilically activated ethylenes, and 1,1-dicyanoethyne **16**, as a model of strong electrophilically activated ethylenes[22] (see Scheme 6), have been studied in order to explain the behaviors of this class of reagents in polar cycloadditions. Finally, the TSs involved in the nucleophilic/electrophilic addition of the CD ethylene **17**, as a benchmark of a high-quality CD ethylene toward **15** and **16**, will be also analyzed as theoretical useful models for these cycloadditions (see Scheme 6). The natural bond orbital (NBO) partitioning and the topological analysis of the electron localization function (ELF) of TSs involved in the attack of the CD ethylene **17** to **15** and **16** will be used in order to rationalize the electronic behavior of these CD species in polar cycloadditions. It is worth noting that the aim of the present study is to analyze not the *captodative effect* defined as the combined action of EW and ER substituents to stabilized a radical center[23] but the ability of the these groups to stabilize neighboring charges generated along a polar DA cycloaddition.

SCHEME 6
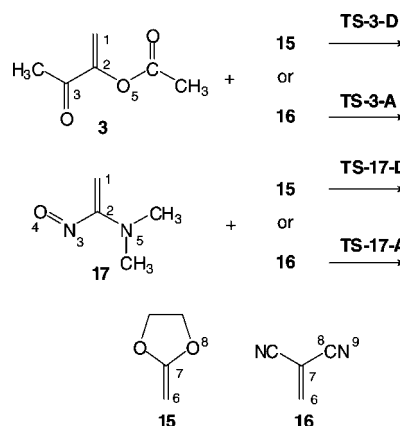
The N Nucleophilicity Descriptor

Global and local reactivity indexes defined within the conceptual DFT[24] have shown to be powerful tools in the study of the polar character of cycloaddition reactions.[10] In this context, the electrophilicity ω index[25] allowed us to properly classify the global electrophilicity of a series of reagents currently employed in cycloaddition reactions. When the electronic activation of the π system is achieved through only one type of EW or ER group, *a linear correlation between the difference in electrophilicity of the reagents pair, $\Delta\omega$, and the polar character of the cycloaddition reaction* is found. In this case, the electrophilicity index ω categorizes the good electrophiles and good nucleophiles (i.e., marginal electrophiles) with

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high and low values, respectively, on a single scale.[10] However, when the molecule bear more than one functional group with opposite electronic demand, the nucleophilic character cannot be straightforwardly associated with the inverse of the electrophilicity. In these cases, $\Delta\omega$ does not account for the polar character of the entire reaction. Thus, the ω index of the CD ethylenes accounts for its electrophilic character but it cannot give any information about its nucleophilic character. In consequence, it could be desirable to choice a different descriptor able to give further information about the nucleophilicity pattern of reactivity.

Since the introduction of the nucleophile and electrophile concepts in the 1930s,[27] many efforts have been made to construct nucleophilicity/electrophilicity scales. Swain, Scott, and Edwards proposed the first nucleophilicity scales through a linear free energy relationship based on rate constants for S_N2 reactions.[28–30] Mayr and Patz have proposed on the other hand nucleophilicity/electrophilicity scales based on the rate constants for wide nucleophile/electrophile combination reactions.[31–33] Note that the availability of empirical scales of electrophilicity and nucleophilicity have been very useful to rationalize the chemical reactivity in terms of selectivity, reaction mechanisms, solvent, substituent effects, etc.[31–33] For instance, several studies have shown relationships between the nucleophilicity with pK_a values,[29] polarizability,[30] the HSAB principle,[34] and the low frequency hydrogen bond stretching modes measured for several B−HX dimers (B is a Lewis base; HX with X = F and Cl).[35] Additionally, the minimum values of the molecular electrostatic potential (MEP)[36] at the electrophilic site of HX in interaction with a nucleophile, V_H, have been also proposed as the basis for a nucleophilicity scale.[37–39] Roy et al.[40] have stressed the usefulness of a local relative nucleophilicity index to categorize the intramolecular nature of this reactivity. In the same context, Chattaraj et al.[41] proposed a generalized philicity concept to identify the most electrophilic and nucleophilic sites in regioselectivity studies. Recently, an empirical nucleophilicity index for soft−soft interactions has been introduced by considering the electronic properties of the electrophilic partner.[37,42,43] Recent attempts in the establishment of relative nucleophilicity

values have been performed on the basis of solution-phase ionization potentials (IPs).[44]

In the present work, we decided to investigate the simplest approach relating the nucleophilicity with the negative value of the gas-phase (intrinsic) IPs, $N = -IP$,[44] (e.g., high (low) nucleophilicities are associated with low (high) ionization potentials). This is partially justified on the basis that most of the reagents used on cycloaddition reactions are neutral and the solvents have low dielectric constants. In order to handle a simple descriptor for the nucleophilicity, we use the highest occupied molecular orbital (HOMO) energy obtained within the Kohn−Sham scheme.[45] Hence, we introduce the nucleophilicity (N) index as:

$$N_{(Nu)} = E_{HOMO(Nu)} \text{ (eV)} - E_{HOMO(TCE)} \text{ (eV)} \qquad (1)$$

Note that this scale of nucleophilicity is referred to tetracyanoethylene (TCE) taken as a reference because it presents the lowest HOMO energy in a large series of molecules already considered. That is, the N scale is simply the negative of the ionization potential calculated by Koopmans' theorem with an arbitrary shifting of the origin. This choice allows us conveniently to handle a nucleophilicity scale of positive values. The feasibility of such an N index describing the nucleophilic behavior of an organic molecule is tested in the Results and Discussion in the context of the analysis of the nucleophilic nature of the CD ethylenes.

Computational and Theoretical Methods

DFT calculations were carried out at the B3LYP/6-31G(d) level of theory.[46,47] The optimizations were carried out using the Berny analytical gradient method.[48] All stationary points were characterized by frequency calculations in order to verify that the TSs have one and only one imaginary frequency. The intrinsic reaction coordinate (IRC)[49] path was traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism by using the second order González-Schlegel integration method.[50] All

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calculations were carried out using the Gaussian03 suite of programs.[51] Biradical mechanisms were discarded by the stability analysis of the wave function at the UB3LYP/6−31G(d) by using the Stable = opt keyword. The electronic structures of stationary points were analyzed by the NBO method,[52] and the topological analysis of the electron localization function (ELF), $\eta(\mathbf{r})$.[53,54]

As the details of the ELF technique of analysis are widely known, we only recall very briefly in the Appendix 1 of Supporting Information the basic issues in the interest of the current application.[54–57] The ELF study was performed with the TopMod program[58] using the corresponding monodeterminantal wave functions of transition state structures.

Results and Discussion

Analysis of the Global Reactivity Indexes at the Ground State of the CD Ethylenes. The ω and N values for a short series of organic molecules used in cycloaddition reactions most of them having a known electrophilic/nucleophilic character are displayed in Table 1. The molecules are given in decreasing order of the ω value. At the top of this table appears nitrosoethylene 19, which is classified as a strong electrophile (ω = 3.30 eV), while at the end is *N,N*-dimethylvinylamine 25 (ω = 0.21 eV), a marginal electrophile classified as good nucleophile.[10] Note that coordination of a LA, AlCl$_3$, to the carbonyl oxygen atom of methyl vinyl ketone (21, ω = 1.66 eV) noticably increases the electrophilicity of the corresponding complex 18 (ω = 4.18 eV).

By examining the nucleophilicity descriptor N (third column in Table 1) for these molecules, we found that 1,1-dicyanoethylene 16 (N = 0.65 eV) is one of the poorest nucleophiles of

TABLE 1. Electrophilicity (ω, eV) and Nucleophilicity (N, eV) Values of Some Regents Involved in Cycloaddition Reactions

	ω	N
CH$_2$=CHCO(AlCl$_3$)Me (18)	4.18	1.33
CH$_2$=CHNO (19)	3.30	2.99
CH$_2$=C(CN)$_2$ (16)	2.82	0.65
CH$_2$=CHCN (20)	1.74	1.25
CH$_2$=CHCOMe (21)	1.66	2.38
CH$_2$=CHOAc (22)	1.12	2.42
2−PhCp (8)	1.06	3.56
Cp (5)	0.83	3.37
CH$_2$=CH$_2$ (23)	0.73	1.86
CH$_2$=CHOMe (24)	0.42	3.20
CH$_2$=C(OCH$_2$)$_2$⊃ (15)	0.26	3.53
CH$_2$=CHNMe$_2$ (25)	0.21	4.28

TABLE 2. Electrophilicity (ω, eV) and Nucleophilicity (N, eV) Values of Some Captodative Ethylenes

CD	A	D	ω	N
3-Al	CO(AlCl$_3$)Me	OAc	4.01	1.29
10	NO	Ph	3.12	3.00
13	NO	MeOPh	3.00	3.26
17	NO	NMe$_2$	2.89	3.60
1	COMe	Obz	1.85	2.12
2	COOMe	Obz	1.73	2.15
3	COMe	OAc	1.70	2.13
7	CN	SMe	1.67	2.51
4	CN	NMe$_2$	0.98	3.46

this series, while *N,N*-dimethylvinylamine 25 (N = 4.28 eV) represents the best nucleophile. These results are consistent with the expected reactivity pattern. On the other hand, for this series of simple functionalized molecules in general there is a clear inverse relationship between the electrophilic ω and the nucleophilic N powers. It is worth noting that the ω and N values for the 2-phenylcyclopentadiene 8, ω = 1.06 eV and N = 3.56 eV, are slightly higher than those for Cp, ω = 0.83 eV and N = 3.37 eV. Therefore, the presence of the phenyl group in 8 is able to activate both electrophilically and nucleophilically the diene system of Cp (see later).

In Table 2, we present the ω and N values for a short series of CD ethylenes, CH$_2$=CD(A), including those used experimentally, 1−4 and 7, the Lewis acid coordinated complex 3-Al, and the 1,1-disubstituted ethylene 17 proposed as a high-quality CD ethylene. This series is given in decreasing order of ω values. Most of these CD ethylenes present high values of electrophilicity (ω > 1.7 eV), being classified as strong electrophiles. The increase of electrophilicity for these CD ethylenes follows the same order as that found for the corresponding electron-deficient ethylenes: CH$_2$=CH−COR ≈ CH$_2$=CH−CN < CH$_2$=CH−NO. Note that the relative position for the carbonyl derivatives, which is in the range 1.70 < ω < 1.85, depends of the ER group on the ethylene. In all cases, the presence of the ER group does not modify substantially the expected electrophilicity of these CD ethylenes. Only the CD ethylene 4 shows a low electrophilicity value, ω = 0.98 eV, as a consequence of the strong ER character of the amine group.

It is worth noting the increase of electrophilicity power that experiments the CD ethylene 3 (ω = 1.70 eV) with the coordination to the LA AlCl$_3$ (3-Al, ω = 4.01 eV) (see Table 2). This increase of ω that is closer to that found at the methyl vinyl ketone 21 (see Table 1) allows to explain the large

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acceleration found at the DA reaction between the CD ethylene **1** and Cp in presence of AlCl₃ (see Scheme 2):[16] the enhance of the electrophilicity of the acceptor reagent decreases the activation energy of the cycloaddition through a more polar process (see later).[10]

An analysis of the N values points out also a relationship between the nucleophilicity of these CD ethylenes and the nature of the ER substituent, which appear also to be not dependent on the nature of the EW substituent. Thus, we can distinguish three subgroups clearly differentiated: those derived from amines with N > 3.4 eV, those derived from aryl derivatives with 3.0 < N < 3.3 eV, and those derived from esters with N < 2.2 eV.

On the other hand, an analysis of the ω and N indices of the experimental CD ethylenes **1**−**3** and **7** allows explaining the experimental observed reactivity.[16] Thus, the CD ethylenes **1**−**3** present low ω values, between 1.70 and 1.85 eV. Therefore, it will be expected that at the DA reactions of these reagents toward nucleophiles as Cp, the reaction will has a low polar character. In consequence, these DA reactions will require hard reaction conditions as large temperatures and long times of reaction (see Scheme 2). However, their electrophilic activation by coordination to a LA favors the DA reaction in clear agreement with the experiment outcomes.[16] On the other hand, these CD ethylenes present also low N values, between 2.12 and 2.15 eV. In fact, it is expected that these CD ethylenes will not react toward electron-deficient reagents.

The CD ethylene **4** presents the large value of N, 3.46 eV, of the series of reagents given in Table 2. This fact allows to explain the large reactivity of this CD ethylene toward DMAD ($\omega = 2.27$ eV). The domino reaction between **4** and DMAD in the presence of acrylonitrile **17**, which takes place at −78 °C,[15] is initialized by a polar [2 + 2] cycloaddition between **4** and DMAD (see Scheme 2).[59] However, the very low ω value of **4** ($\omega = 0.98$ eV) indicates that this CD ethylene will not react toward electron-rich reagents.

The ω and N values for the CD α-mehylthioacrilonitrile **7**, 1.67 and 2.51 eV, respectively, are closer to those found at the CD ethylenes **1**−**3**. As a consequence, it is expected that the CD ethylene **7** will have a reactivity similar to that of these CD ethylenes **1**−**3**. An analysis of ω and N for **7** and the cyclopentadiene derivative **8** explains the reactivity of the CD ethylene **7** in a polar DA reaction (see Scheme 3). Within the electrophilicity scale, the CD ethylene **7** is located above the cyclopentadiene derivative **8**. Thus, along a polar DA reaction, the CD ethylenes **7** will act as electrophile and the diene **8** as nucleophile, in clear agreement with the flux of the charge transfer (CT) at the TSs.[19] In addition, although the CD ethylene **7** is slightly less electrophilic than acrylonitrile **20**, the cyclopentadiene derivative **8** has a more nucleophilic activation than Cp (see Tables 2 and 3). As a consequence, the DA reaction between **8**/**7** will have a more polar character that the DA reaction between Cp and **20**. This analysis is in complete agreement with the lower activation energy computed for the more favorable *para/endo* reactive channel for the DA reaction between **8**/**7**, 14.7 kcal/mol, than for the DA reaction between Cp and acrylonitrile, 16.5 kcal/mol, and with the lager CT found at the former, 0.22 e, than at the later, 0.15 e.

The nitrosoethylenes **10** and **13** have been used as efficient reagents in organocatalyzed DA reactions toward enamines[20] (see Scheme 4), in clear agreement with the large ω values of

TABLE 3. Total (*E*, au) and Relative (Δ*E*, kcal/mol) Energies of the Stationary Points Involved in the Addition Reactions to the CD Ethylenes **3** and **17**

|	*E*	Δ*E*
3	−459.112094	
3-Al	−2082.396506	
17	−341.845112	
5	−194.101064	
15	−306.441320	
16	−263.062684	
TSc	−653.188977	15.2
14	−653.243296	−18.9
TS1	−2276.497129	0.3
Zw	−2276.506294	−5.5
TS2	−2276.506160	−5.4
14-Al	−2276.533787	−22.7
TS-3-D	−765.534918	11.6
TS-3-A	−722.151247	14.8
TS-17-D	−648.279906	4.1
TS-17-A	−604.908245	−0.3

these reagents, 3.12 and 3.00 eV, respectively.[21] Moreover, they also present large N values, 3.00 and 3.26 eV, respectively. Therefore, it will be expected that these nitrosoethylenes could be considered as CD ethylenes able to react also toward electron-deficient reagents.

Finally, on the basis of this analysis, a CD ethylene able to react toward electron-rich and electron-deficient reagents is proposed. The CD ethylene model **17**, which includes a strong EW nitroso group and strong ER amino group, presents large values of ω and N descriptors, 2.89 and 3.60 eV, respectively. Therefore, it is expected that this CD ethylene will react easily toward reagents of both electronic demand (see later).

On the basis of the precedent analysis, it can be nicely observed that the N *descriptor introduced in eq 1* seems to be a suitable quantity providing valuable information about the nucleophilic character of these CD ethylenes in the context of polar DA cycloadditions, yet despite the very basic assumptions behind a such model based only on intrinsic IPs[44] and without the explicit incorporation of solvent effects.

Diels−Alder Reaction Study of the CD Ethylene Model 3 toward Cyclopentadiene 5 in the Absence and the Presence of the Lewis Acid AlCl₃. First, the DA reactions of the CD ethylene **3** toward Cp in the absence and the presence of the Lewis acid AlCl₃ were studied as reaction models of those experimentally reported (see the DA reaction of **1** with Cp in Scheme 2).[16] Note that the substitution of the phenyl group present in **1** by a methyl group in **3** only affects the ER group included in these CD ethylenes. For these DA reactions, two stereoisomeric reaction channels are feasible: the *endo* and the *exo*. The two reaction channels for the reaction of **3** and **3-Al** were studied. A low *endo:exo* selectivity was observed. In addition, when the LA is coordinated to CD ethylene **3**, a change of the selectivity was observed.[16] Understanding that our main interest is the characterization of the electronic behavior of these DA reactions, only the *endo* approach mode of Cp to the EW carbonyl group of the CD ethylene **3** will be discussed. An exhaustive analysis of the stationary points found on the DA reaction between **3** and Cp indicated a concerted bond-formation process for this reaction. Therefore, one TS, **TSc**, and the corresponding cycloadduct **14** were located and characterized (see Scheme 5) Coordination of the LA AlCl₃ to the carbonyl oxygen atom of the CD ethylene **3** does not only reduce drastically the activation energy but also changes the mechanism of the DA reaction to a stepwise one. Therefore, two TSs, **TS1**

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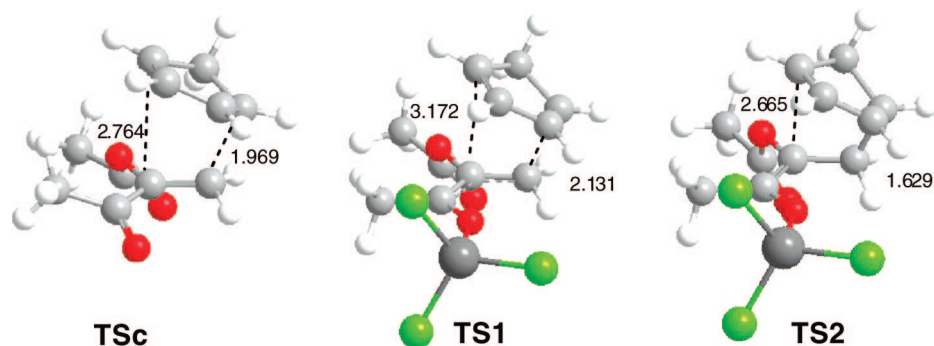
FIGURE 1. Transition structures involved in the polar Diels−Alder reaction of cyclopentadiene with the CD ethylenes **3** and **3-Al**. The distances are given in angstroms.

and **TS2**, the intermediate **Zw**, and the cycloadduct **14-Al** were located and characterized for the LA-catalyzed process (see Scheme 5).

The activation energy associated with the DA reaction of the CD ethylene **3** with Cp is 15.2 kcal/mol (see Table 3). This large value, which is closer to that computed for the DA reaction between methyl vinyl ketone and Cp, 16.3 kcal/mol,[60] is in agreement with the low reactivity of the CD ethylene **3** toward Cp as well as the low electrophilicity power of **3** ($\omega = 1.70$ eV, see Table 2). Coordination of the $AlCl_3$ to **3** provides a drastic acceleration of the LA-catalyzed DA reaction. Now, only 0.3 kcal/mol is the activation energy for the **TS1** (see Table 3). A reduction of ca. 15 kcal/mol is observed when the LA $AlCl_3$ is coordinated to the carbonyl oxygen atom of the EW ketone group of **3**. The intermediate **Zw** is located at 5.5 kcal/mol below the reagents. This species is very unstable, and with an unappreciable barrier, 0.1 kcal/mol, it is transformed into the cycloadduct **14-Al** via **TS2**. Both noncatalyzed and catalyzed DA reactions are exothermic in −18.9 and −22.7 kcal/mol, respectively.

The relative energies given in Table 3 are in clear agreement with the larger acceleration found at the LA-catalyzed DA reaction of **1** with Cp[16] and with the larger electrophilicity of the LA-coordinated CD ethylene **3-Al** ($\omega = 4.01$ eV) compared with that for the CD ethylene **3** ($\omega = 1.70$ eV) (see Table 2).

At the stepwise mechanism, the nucleophilic attack of Cp to the LA coordinated CD ethylene **3-Al** is the rate-limiting step of the cycloaddition. Consequently, the effects of the substitution on the reaction rate must be analyzed at the TS associated with the nucleophilic/electrophilic interaction. Generally, from a kinetic point of view, the formation of a feasible intermediate as well as the TS associated with the ring-closure step has not any relevance. This fact allows us to focus on the study of the electronic behaviors of the CD ethylenes **3** and **17** through the analysis of the energies and structures of the TSs associated with the two-center interactions (see later).

The geometries of the TSs involved in the concerted and stepwise mechanisms are given in Figure 1. The lengths of the C1−C6 and C2−C7 forming bonds at the TSs and intermediate **Zw** are: 1.969 and 2.764 Å at **TSc**, 2.131 and 3.172 Å at **TS1**, 1.628 and 3.123 Å at **Zw**, and 1.629 and 2.665 Å at **TS2**, respectively. The lengths at **TSc** indicate that this TS corresponds to asynchronous bond-formation process in which the C1−C6 bond-formation at the conjugated position of the CD ethylenes is more advanced. The larger distance between the C2 and C7 carbons at **TS1** indicates that this TS is associated

with a two-center interaction between the end of the conjugated system of the diene Cp and the more electrophilic center of the LA coordinated CD ethylene **3-Al**. At **Zw**, the C1−C6 length indicates that this bond is already formed, whereas the C2−C7 distance remains very large.

The electronic structure of the TSs and intermediate of these DA reactions was analyzed by using the Wiberg bond order[61] (BO) and the natural charges obtained by a NBO analysis. The BO values at the C1−C6 and C2−C7 forming bonds at the TSs and intermediate are: 0.51 and 0.17 at **TSc**, 0.39 and 0.05 at **TS1**, 0.86 and 0.09 at **Zw**, and 0.86 and 0.19 at **TS2**, respectively. These values indicate that the more unfavorable **TSc** is more advanced and less asynchronous than **TS1**. On the other hand, the C2−C7 BO values at **TS1** and at **Zw** indicate that there are many appreciable covalent interactions between these atoms, while the C1−C6 BO values at **Zw** and at **TS2** indicate that this σ bond is practically formed.

The natural population analysis (NPA) allows the evaluation of the CT and its direction at the polar DA reactions of these CD ethylenes. The natural atomic charges at the TSs and intermediate were distributed between the CD ethylenes and the Cp fragments. The net charge at the CD ethylene fragments is 0.18e at **TSc**, 0.32e at **TS1**, 0.52e at **Zw**, and 0.46e at **TS2**. These values indicate that some zwitterionic character is presented. The CT at the more favorable **TS1** is ca. twice that at **TSc** in spite of the earlier character of the former. At the stepwise mechanisms, the CT increases along the nucleophilic attack of Cp to **3-Al**, until formation of the zwitterionic intermediate **Zw**. After formation of this intermediate, the net CT decreases as a consequence of the retrodonation that takes place along the ring-closure process. The drastic rate acceleration found at the LA-catalyzed DA reaction can be associated with the increase of the polar character of the reaction, which is anticipated with the enhancement of the electrophilicity of the coordinated **3-Al** complex.

Study of the Nucleophilic/Electrophilic Additions of the Ethylene Derivatives 15 and 16 to the CD Ethylenes 3 and 17. The electronic behaviors of the CD ethylenes **3** and **17** have been evaluated as the response to the nucleophilic and electrophilic attacks of the ethylene derivatives **15** and **16**, respectively. These activated ethylenes have been recently used as strong nucleophilic and electrophilic reagents in the study of the electrophilic/nucleophilic behaviors of electron-deficient 2-substituted and 2,3-disubstituted 1,3-butadienes in polar DA reactions.[22] Because these CD ethylenes can participate in different kinds of cycloaddition reactions, [2 + 2], [2 + 4], [2

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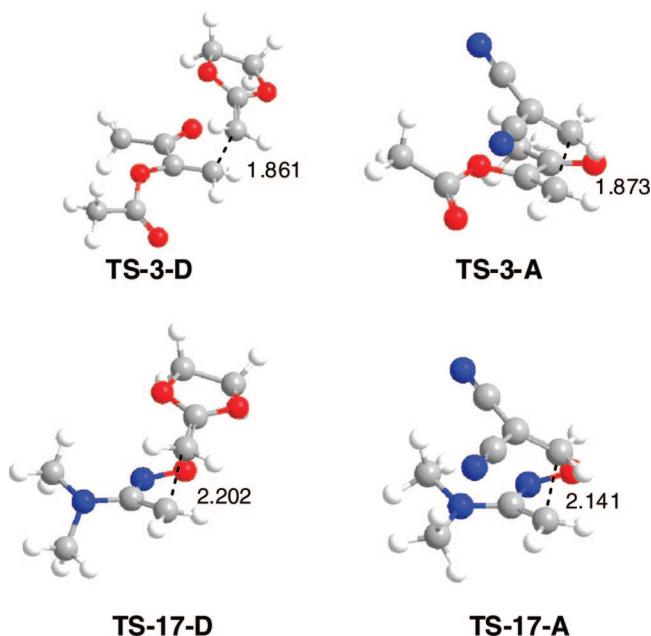
FIGURE 2. Transition structures involved in the polar Diels−Alder reactions of the CD ethylenes **3** and **17** with the electron-rich ethylene **15** and the electron-deficient ethylene **16**. The distances are given in angstroms.

+ 3] ..., we have selected the four TS structures involved in the two-center interactions that take place at the first stage of these polar processes (see Scheme 6). We will analyze the activation energies and the geometrical and the electronic structures of these TS structures. After these TSs, the ring closure, which may take place through a concerted or stepwise bond-formation process, affords the final cycloadduct.

The activation energies associated with the four TSs are summarized in Table 3. These activation energies vary in a wide range that goes from 14.8 kcal/mol for the addition of the electron-deficient ethylene **16** to the experimental CD ethylene **3** to −0.3 kcal/mol for the addition of **16** to the CD ethylene model **17**. It is worth noting that the more unfavorable **TS-3-A** required UB3LYP calculations for its localization. Some interesting conclusions can be drawn from these activation energies: (i) the reactivity of these CD ethylenes toward the electron-rich ethylene **15**, **17** ≫ **3**, is in complete agreement with the larger electrophilicity power of **17** ($\omega = 2.89$ eV) than **3** ($\omega = 1.70$ eV) (see Table 2); (ii) the reactivity of these CD ethylenes toward the electron-deficient ethylene **16**, **17** ≫ **3**, is also in complete agreement with the larger nucleophilicity of **17** (N = 3.60 eV) than **3** (N = 2.13 eV). Therefore, the experimentally explored CD ethylene **3** shows certainly a poor reactivity as compared to the proposed CD ethylene **17**. Both the EW carbonyl group and the ER ester group present in **3** are poor activating groups. Finally, (iii) the CD ethylene model **17** appears to produce a better response toward both type of electron-demanding reagent. It is worth noting that these responses can be anticipated by an analysis of the ω and N indices at the corresponding CD ethylenes.

The geometries of the TSs involved at the nucleophilic/electrophilic additions of the ethylene derivatives **15** and **16** to the CD ethylenes **3** and **17** are given in Figure 2. The lengths the C1−C6 forming bonds at the TSs range from 1.861 Å at **TS-3-D** to 2.202 Å at **TS-17-D**. The shortening of the C2−X(C,N)3 or C2−Y(O,N)5 lengths at the TSs shows the

participation of the EW and ER groups present on the CD ethylenes at these polar reactions. Thus, at the TSs associated with the reactions of the CD ethylene model **17**, the lengths C2−N3 and C2−N5 bonds are 1.375 and 1.417 Å at **TS-17-D** and 1.446 and 1.352 Å at **TS-17-A**. These lengths at the CD ethylene **17** are 1.462 and 1.376 Å, respectively, Thus, while toward the electron-rich ethylene **15** the participation of the EW−N=O group is shown by the shortening of the C2−N3 bond, in the case of the addition of the electron-deficient ethylene **16**, the C2−N5 bond is shortened. These shortening are due to the increase of the π character of the C2−X3 or C2−Y5 σ bonds as a consequence of the electron-delocalization on the geminal-attached groups along the polar process.

The BO values at the C1−C6 forming bonds at the TSs are 0.60 at **TS-3-D** and 0.58 at **TS-3-A**, 0.35 at **TS-17-D**, and 0.38 at **TS-17-A**. The more unfavorable **TS-3-D** and **TS-3-A** are more advanced than the TSs associated with the CD model **17** cycloadditions. At the CD ethylene fragments, the BO values of the C2−X(C,N)3 or C2−Y(O,N)5 bonds are 1.30 and 0.87 at **TS-3-D**, 1.05 and 1.02 at **TS-3-A**, 1.30 and 1.02 at **TS-17-D**, and 1.08 and 1.24 at **TS-17-A**, respectively. At the TSs associated with the additions to **17**, these BO values point out the increase of the π character of the C2−N5 bond at **TS-17-A** and the increase of the π character of the C2−N3 bond at **TS-17-D**. Note that at the more unfavorable **TS-3-A**, these values are near 1.0, in agreement with the birradical character of the process.

The CT at these additions was evaluated sharing the natural charges at the TSs between the CD ethylene fragment and the ethylene fragments. The charges at the CD ethylene fragment are −0.43e at **TS-3-D**, +0.12e at **TS-3-A**, −0.29e at **TS-17-D**, and +0.25e at **TS-17-A**. Some relevant conclusions can be drawn from these values: (i) first, some zwitterionic nature can be redrawn from CT at these TSs as correspond to polar processes; (ii) The change of the direction of the electron density transfer at these TSs is related to the donor or acceptor character of the ethylenes **15** and **16**. Thus, while in the reaction in front of the electron-rich ethylene **15** the CT flows from this reagent toward the CD ethylenes, there is a change on the direction in the reaction toward the electron-deficient ethylene **16**. The CT now goes from the CD ethylenes toward the strong electrophilically activated ethylene **16**; (iii) The CT at **TS-3-D** is larger than that at **TS-17-D** as a consequence of the more advanced character of the former. In a polar cycloaddition, the CT increases along the reaction pathway until formation of the first σ bond. With the formation of the second σ bond there is a retrodonation, decreasing the CT of the process (see CT at the stepwise mechanism of the front part). However, *the geometries of the TSs do not correspond in general with the maximum in the CT of the polar processes.*[62] Early TSs associated with processes with a very polar character can present low CT that increases along the reaction pathway. (iv) The large CTs found at **TS-17-D** and **TS-17-A**, which can be related to the lower relative energies of the TSs, account for the good CD behavior of the disubstituted ethylene **17**. (v) The lower CT is found at the more energetic **TS-3-A**, which has some birradical character $<S^2> = 0.24$. At this TS, the larger Mulliken atomic spin densities are located at the C2 (−0.32) and C7 (+0.32) carbon atoms, which correspond to the end carbons of the two reacting ethylenes.

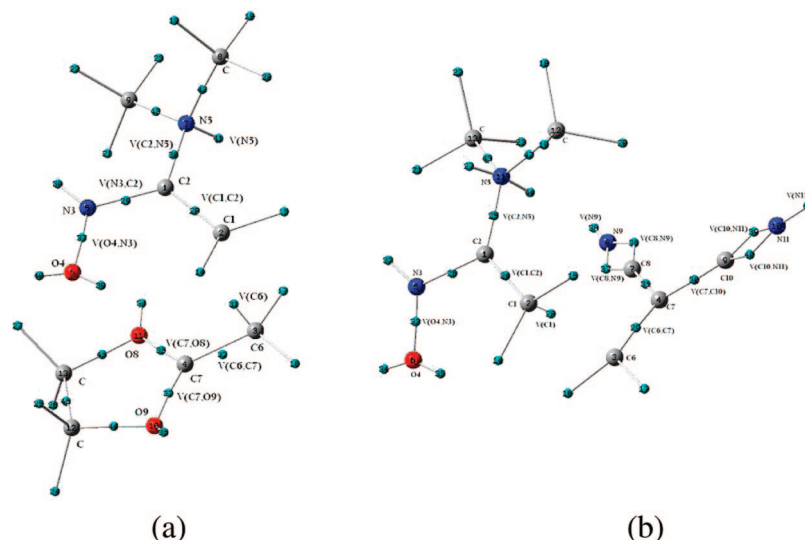(62) Domingo, L. R.; Picher, M. T.; Arroyo, P.; Saez, J. A. *J. Org. Chem.* **2006**, *71*, 9319.

FIGURE 3. Schematic representation of ELF attractors for (a) **TS-17-D** and (b) **TS-17-D**.

Analysis of the ELF at the TSs Involved at the Nucleophilic/Electrophilic Additions of the Ethylene Derivatives 15 and 16 to the CD Ethylene 17. The analysis of the gradient field of ELF for **TS-17-D** and **TS-17-A** reveals in both cases that there are not disynaptic basins associated with the region of C1−C6 forming bonds. Instead, only monosynaptic basins associated with one of the interacting carbon centers are present in each case. At **TS-17-D**, this monosynaptic basin has an average population of 0.45e, and it is associated with the C6 center (attractor no. 31, Figure 3a). At **TS-17-A**, such basin belongs to the C1 center (associated with the attractor no. 28, Figure 3b), and localizes an average population of 0.39e. The two reacting fragments (**17** + **15**) and (**17** + **16**) can be visualized as separated electron localization regions within the topological picture emerging for **TS-17-D** and **TS-17-A**, respectively. This is a consequence of the early nature of TSs with long C−C bond-forming distances. Indeed, at the transition position, the formation of the new C−C bond can be visualized as evolving as a dative bond formation. The CD fragment **17** acts as the donor source in **TS-17-A**, while this role is accomplished by the electron-rich ethylene **15** in **TS-17-D**. Given the absence of polysynaptic basins associated with the two fragments, a straightforward estimation of charge polarization is possible. The assignment of charges is obtained from Tables SI.I and SI.II (see the Supporting Information) as a balance between the electron densities integrated in the basins of each fragment (e.g., basin populations) and the corresponding positive background from nuclei. The charges at the CD ethylene fragment become −0.30 at **TS-17-D** and +0.22e at **TS-17-A** (see Figure 4). Further, the reduction of the localization domains in the region associated with the C1−C6 bond forming for **TS-17-A** (e.g., $\eta^* = 0.571$) as compared to **TS-17-D** (e.g., $\eta^* = 0.508$) (see Figure 5) indicates that such charge polarization in the region of the TSs is higher when the CD fragment behaves effectively as an electron donor fragment along the polar process. This fact is also consistent with the observation of a slightly shorter C1−C6 interatomic distance at **TS-17-A** (e.g., 2.141 Å) in comparison to **TS-17-D** (e.g., 2.202 Å). Thus, the picture of bonding from the ELF analysis is reliably associated with the zwitterionic nature of these structures as they are understood as polar processes.

In order to gain deeper insights about the electron charge reorganization at the TS position, the nature of attractors and
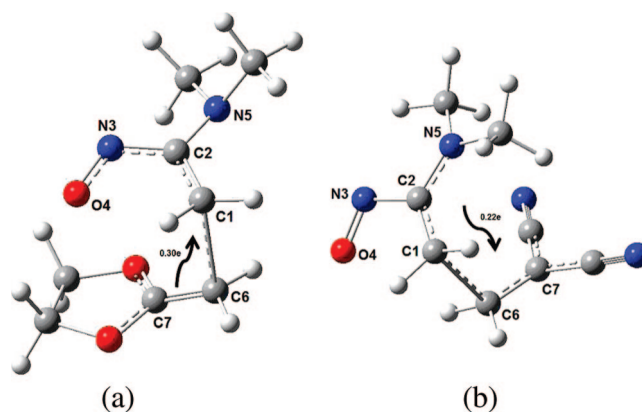

FIGURE 4. Charge-transfer picture for (a) **TS-17-D** and (b) **TS-17-A**. This prediction is supported both from NBO and ELF results. See the text for details.
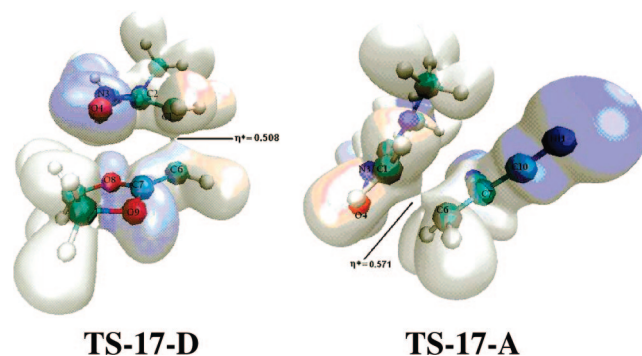

TS-17-D   **TS-17-A**

FIGURE 5. ELF isosurface at the critical value $\eta = 0.508$ (**TS-17-D**) and $\eta = 0.571$ (**TS-17-A**) corresponding to the reduction of the localization domains in the region associated with the C1−C6 bond forming for the TSs. See the text for details. The η^* is a measure of the fluctuation between the two regions.

basin populations in both fragments can be further examined. The results for **TS-17-D** (see Table SI.I, Supporting Information) allow us to realize that in the acceptor CD fragment **17**, the electron density is further delocalized as expected only by a −N=O group. Thus, note for instance that the C1−C2, C2−N5, and N3−O5 populations are 3.26e, 2.50e, and 1.41e, respectively. This polarization is indeed reflected by the nonbonding population on the O4, which is 5.76e. This picture of bonding

is consistent with the above-discussed NBO evidence, and it is in agreement with an enhanced π character of the C2−N3 bond. In this case, it is found that the N(CH$_3$)$_2$ group does not actively participate, as expected, in such a charge stabilization. The nonbonding region on the N3 atom is 2.03e exhibiting a nonplanar hybridization. An examination of the donor fragment (e.g., electron-rich ethylene **15**) reveals also the high polarization of density toward the monosynaptic regions associated with the oxygen centers (e.g., 4.46e) and the C6 atom (i.e., 0.45e, no. 31 basin). This monosynaptic region can be seen as emerging from the delocalization domain associated with the C7−C6 bond region as revealed by the high fluctuation values between them as reported in Table SI.I (Supporting Information). On the other hand, the analysis of **TS-17-A** shows that the electron charge is symmetrically delocalized over the two cyano groups. Note, for instance (see Table SI.II, Supporting Information), that the C6−C7, C7−C8, and C8−N9 basins have average populations of 3.38e, 2.36e, and 4.37e and that the nonbonding region associated with the N9 center localize 3.30e. In the CD ethylene fragment **17**, on the other hand, the electron density is delocalized over the C1, O4, and N5 centers. Indeed, the N(CH$_3$)$_2$ group adopts a planar configuration, enhancing the electron delocalization flow toward the C1−C2 bond region. This picture of electron delocalization is consistent with the above-discussed NBO results and the fact that the π character of the N5−C2 bond at **TS-17-A** becomes increased. In the same context, note for instance that the C1−C2 region is depleted to a population of 2.92e, while the monosynaptic basin associated with C1 (attractor no. 28, Figure 3b) localizes only 0.39e as above-mentioned. This monosynaptic basin population can be considered emerging from the delocalization of the C1−C2 region. Complementing the picture of electron delocalization of the donor fragment **17** at **TS-17-A**, note also that 5.37e and 1.82e are associated with the nonbonding localization basins at O4 and N5, respectively. Henceforth, the topological analysis of the ELF gives us a further support for a picture of bonding where the CD ethylenes behave as an electron acceptor species against the strong nucleophilically activated alkene **15** through the **TS-17-D**. This electronic behavior is reversed when the CD ethylene **17** reacts against the strong electron-deficient ethylene **16** via the **TS-17-A**. The picture of charge separation arising from the ELF analysis at the two TSs is highly consistent with the NBO results previously discussed.

Conclusions

The electrophilic/nucleophilic character of a series of CD ethylenes involved in polar cycloaddition reactions has been studied. Analysis of the reactivity indexes at the ground-state of the CD ethylenes explains the reactivity of these species in polar cycloaddition reactions. While the electrophilicity ω of the molecules accounts for the reactivity toward nucleophiles, a simple nucleophilicity index N based on the HOMO energy has been introduced in order to explain the reactivity of these CD ethylenes toward electrophiles. The analysis of the ω and N indices indicates that, in general, the electronic character of the CD ethylenes can be seen as a cooperative effect of the EW and ER character of the separated groups on the ethylene. In general, the presence of both geminal groups on the ethylene produces a minor alteration on the electronic properties of the separated groups.

The NBO (e.g., a partition orbital-based approach) and ELF (e.g., a relative local measure of the Pauli principle) analyses of the electronic structure of the TSs involved in the electrophilic/nucleophilic interactions of two CD ethylenes toward a nucleophilically activated ethylene and an electrophilically activated ethylene allows explaining the participation of the two groups present on the CD ethylene species in polar cycloaddition reactions. These analyses allow asserting the details of electron-charge delocalization proclivities within the global conclusions obtained from the reactivity indices obtained at the ground state of the CD ethylenes.

Finally, a comparative analysis of the nucleophilic character of the CD ethylenes, measured by the N index, the energetic and topological analysis, as well as the experimentally observed reactivity allow us to assert the feasibility of the nucleophilic index N to analyze the nucleophilic character of neutral organic molecules.

Supporting Information Available: Topological analysis of the electron localization function (ELF). Tables containing basin populations, variance, relative fluctuation, and main contributions from other basins to the variance for **TS-17-D** and **TS-17-A**. B3LYP/6-31G(d) computed total energies, unique frequency imaginary, and Cartesian coordinates of the TSs. This material is available free of charge via the Internet at http://pubs.acs.org.

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