Why do Electron-Deficient Dienes React Rapidly in Diels−Alder Reactions with Electron-Deficient Ethylenes? A Density Functional Theory Analysis

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The Diels–Alder reaction of the electron-deficient (ED) dimethyl 2,3-dimethylenesuccinate with two electron-rich (ER) and two ED ethylenes has been studied at the B3LYP/6-31G* level of theory. The analysis of the geometry and electronic structure of the transition state of the reaction with the ED dimethyl 2-methylenemalonate along with the analysis of the global and local electrophilicity indices of the reagents provide an explanation of the participation of this ED diene as nucleophile against powerful electrophiles in polar Diels–Alder reactions.

Introduction

The Diels−Alder (DA) reaction is arguably one of the most powerful reactions in the arsenal of the synthetic organic chemist.[1] Many different types of carbocyclic structures can be built up by varying the nature of the diene and dienophile. However, not all possibilities take place easily. For instance, the DA reaction between butadiene and ethylene must be forced to take place: after 17 hours at 165 °C and 900 atmospheres it gives a yield of 78%.[2] This cycloaddition has a large activation energy of 27 kcal·mol^{-1}.[3] Density functional theory (DFT) studies of the concerted mechanism have computed a potential energy barrier (PEB) close to the experimental data (24.8 kcal·mol^{-1} at the B3LYP/6-31G* level of theory).[4] However, substitution on the diene or dienophile can modify this unfavourable barrier, although not all possibilities are applicable. Recently, Peeters et al.[5] have studied the influence of the diene substitution on the DA reaction. The PEBs for the DA reactions with ethylene range between 21 and 28 kcal·mol^{-1} (B3LYP/6-31G*) for a wide series of electron-deficient (ED) and electron-rich (ER) 1- and 2-substituted butadienes, with the larger values corresponding to the ER dienes. The low reduction of the barriers can be explained by the poor ability of ethylene to act as either a good electron-donor or electron-acceptor dienophile. These results are consistent with the very low charge transfer (CT) found at the transition structures (TSs) of less than 0.1 electrons.[5] However, the presence of electron-releasing substituents in the diene and electron-withdrawing substituents in the dienophile, or vice versa, can drastically accelerate the process.[6]

Studies on the polarity of the substituents, the role of Lewis acid catalysts, and the solvent effects suggest that the feasibility of the DA reaction can be related to the CT along the bond-formation process, i.e. to the polar character of the cycloaddition.[7] Thus, an increase of the ER character of the diene (the nucleophilicity), together with an increase of the ED character of the ethylene (the electrophilicity), or vice versa, results in an increase of the CT and a decrease of the PEB.[7] It is interesting to note that for polar DA reactions at least the ethylene must possess efficient electron-withdrawing groups; the presence of electron-releasing groups on the diene is not essential. Thus, cyclopentadiene reacts with a series of ED cyanoethylenes in polar DA reactions with PEBs which range from 17.5 (16.7 in benzene) kcal·mol^{-1} for the reaction with cyanoethylene to 11.5 (8.7 in benzene) kcal·mol^{-1} for the reaction with tetracyanoethylene.[8] However, the sole presence of electron-releasing groups does not favour the cycloaddition process sufficiently.

Very recently, Spino et al.[9] have reported an experimental study of the DA reactions of dimethyl 2,3-dimethylenesuccinate (**1**) with a wide variety of ER ethylenes, including 1,1-diethoxyethene (**2a**) and ethyl vinyl ether (**3a**), and ED ethylenes, including methyl acrylate (**4**) and diethyl 2-methylenemalonate (**5a**; see Scheme 1). Some observations can be draw from the kinetic results: i) the faster DA reaction corresponds to the cycloaddition between the ED diene **1** and the ER ethylene **2a**; ii) the rate coefficient k_r for the cycloaddition between the ED diene **1** and the ER ethylene **2a**, 0.77 mL·mol^{-1}·s^{-1}, is only twice as large as that for the reaction between **1** and the ED ethylene **5a** (0.26 mL·mol^{-1}·s^{-1}); and iii) the cycloadditions involving the disubstituted ethylenes **2a** and **5a** are faster than those involving the monosubstituted ones **3a** and **4**.

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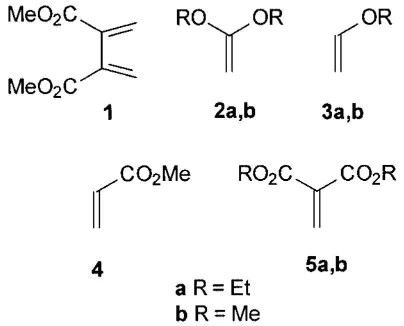


Scheme 1

Frontier molecular orbital (FMO) theory[10] was used to predict the reactivity of these reagents in a DA reaction. Spino et al. concluded that, in the normal DA reaction, FMO theory could predict the relative reactivity, while in the case of the inverse-electron-demand one, it could not.[9] In this work, several questions were raised but they were not resolved: Why do a series of 2-azadienes react with a host of ED ethylenes including methyl acrylate but none react with ER vinyl ether?[11] Why does 2-carbomethoxy-1,3-butadiene dimerize much faster than it reacts with ER reagents?[12] (Note that these cases are similar to the DA reaction between the ED diene **1** and the ED ethylene **5a**, which has a rate of the same order of magnitude as that for the reaction between **1** and the ER ethylene **2a**.)[9] In these cases, the choice of which pair of frontier orbitals to take is sometimes difficult because of the closer HOMO−LUMO gap energies for both ED reagents.

Recently, the use of the global electrophilicity index, ω, proposed by Parr et al.[13] and defined within density functional theory,[14] was reported[15] to classify the dienes and dienophiles currently used in DA reactions on a unique scale of electrophilicity. The difference in electrophilicity for the diene/dienophile pair, $\Delta\omega$, was found to be a measure of the more- or less-polar character of the cycloaddition. Recent studies devoted to [2 + 2],[16] [3 + 2],[17] [4 + 2][18] and [4 + 3][19] cycloaddition reactions have shown the feasibility of these DFT-based indices to analyse these reactions. In addition, we have shown that the analysis based on the local electrophilicity index,[20] ω_k, at the more electrophilic DA reagent, together with analysis of the nucleophilic Fukui functions,[21] f_k^-, at the less-electrophilic one, allows the prediction of the regioselectivity in these cycloadditions.[20] This local analysis has been used recently to explain the loss of effectiveness of symmetrically substituted 1,2-dicyanoethylenes and tetracyanoethylene in a series of DA reactions of these cyanoethylene derivatives with cyclopentadiene.[8]

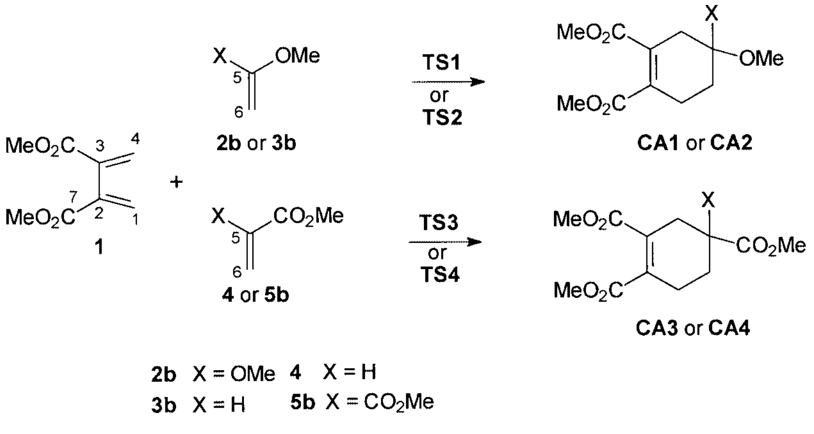
In this paper a DFT analysis of a short series of DA reactions between the ED diene **1** and the ER ethylenes **2b** and **3b** and the ED ethylenes **4** and **5b** is reported (see Scheme 2). Both the characterisation of the electronic structure of the TSs involved in these DA reactions, and the analysis of the global and local reactivity index at the ground state (GS) of the reagents, will be used to explain the participation of the ED diene **1** as the nucleophile in a DA reaction with strong electrophiles. (Note that the DA reactions involving entirely ER reagents are not feasible.)

Results and Discussions

Firstly, in part (a) the activation energies and the geometrical parameters of TSs for the four DA reactions will be analysed. The electronic structure of the TSs will be studied in terms of bond orders and natural population analysis. In part (b) an analysis based on the global and local reactivity indices of the reagents will be performed.

a) Analysis of Activation Energies, Geometries, Bond Orders, and Charge Transfer at the Transition State Geometries

An analysis of the results indicates that these DA reactions are asynchronous concerted processes. Therefore, only one TS (**TSX**) connecting the reagents with cycloadduct (**CAX**) was located and characterised for each cycloaddition. For the DA reactions involving the asymmetric monosubstituted ethylenes **3b** and **4**, two reactive channels are feasible: the *endo* and the *exo*. Both channels were stud-



Scheme 2

ied, but only the results for the more favourable one in each case will be presented: the *endo* for the DA reaction with the ER ethylene **3b** and the *exo* for the reaction with the ED ethylene **4**.[22] The stationary points corresponding to these DA reactions are presented in Scheme 2 together with the atom-numbering scheme. The total and relative enthalpies are compiled in Table 1, while the geometries of the TSs are presented in Figure 1.

Table 1. Total (H, in au) and relative (ΔH, in kcal·mol^{-1}) enthalpies computed at 383.78 K for the stationary points involved in the DA reactions of the diene **1** with the ER ethylenes **2b** and **3b** and with the ED ethylenes **4** and **5b**

	H	ΔH[a]		H	ΔH[a]
1	−611.550588				
2b	−307.513781		**4**	−306.364314	
TS1	−919.040006	15.3	**TS3**	−917.885218	18.6
CA1	−919.111967	−29.9	**CA3**	−917.973723	−36.9
3b	−193.019918		**5b**	−534.185478	
TS2	−804.544791	16.1	**TS4**	−1145.710129	16.3
CA2	−804.625017	−34.2	**CA4**	−1145.793197	−35.9

[a] Relative to **1** + **2b**, **3b**, **4**, or **5b**.

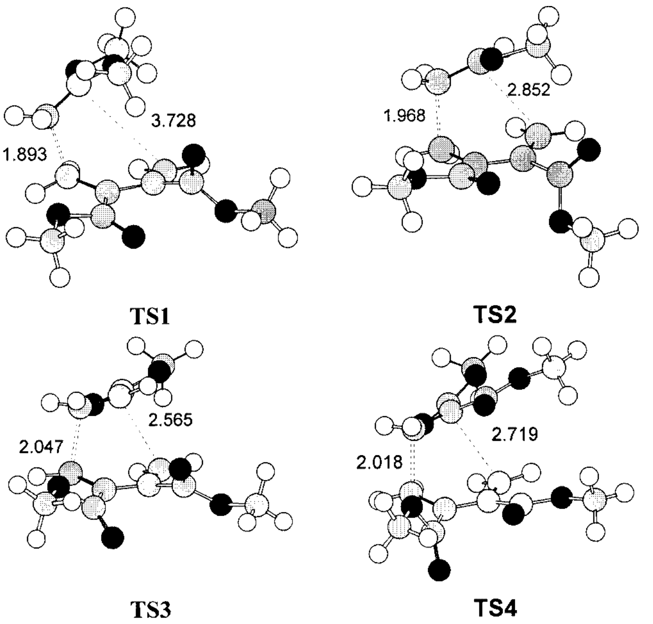


Figure 1. Optimized geometries of the transition structures for the DA reactions of the diene **1** with the ER ethylenes **2b** and **3b** (**TS1** and **TS2**, respectively) and with the ED ethylenes **4** and **5b** (**TS3** and **TS4**, respectively); the distances directly involved in the bond-forming processes are given in angstroms

The activation enthalpies for these cycloadditions range between 15.3 and 18.6 kcal·mol^{-1}. The faster DA reaction corresponds to the cycloaddition between the ED diene **1** and the ER ethylene **2b** (15.3 kcal·mol^{-1}). This activation enthalpy is about 9 kcal·mol^{-1} lower than that for the butadiene plus ethylene reaction, showing that the opposite substitution on both reagents produces a large acceleration. However, the activation enthalpy associated with the DA reaction between the ED diene **1** and the ED ethylene **5b** is only 1 kcal·mol^{-1} higher in energy than that for the reaction with the ER ethylene **2**. These energetic results are in reasonable agreement with the kinetic data reported by Spino et al.[9] These cycloadditions are exothermic in the range of −30 to −37 kcal·mol^{-1}.

The length of the forming C1−C6 bond at the TSs is 1.893 Å (**TS1**), 1.968 Å (**TS2**), 2.047 Å (**TS3**) and 2.018 Å (**TS4**), while the distance between the C4 and C5 atoms is 3.728 Å (**TS1**), 2.852 Å (**TS2**), 2.565 Å (**TS3**) and 2.719 Å (**TS4**). The bond order (BO) values[23] of the forming C1−C6 and C4−C5 bonds are 0.58 and 0.04 at **TS1**, 0.53 and 0.04 at **TS2**, 0.45 and 0.23 at **TS3** and 0.46 and 0.16 at **TS4**, respectively. Therefore, these TSs correspond to asynchronous bond-formation processes. The cycloadditions involving the ER ethylenes **2b** and **3b** are more advanced and more asynchronous than those involving the ED ethylenes **4** and **5b**. In spite of the high asynchronicity of **TS1**, the intrinsic reaction coordinate (IRC) analysis supports the one-step nature of this cycloaddition. The BO between the C2 carbon and the carbonyl C7 carbon is 1.14 at **TS1** and 0.96 at **TS4**.

The arrangement of the substituents on the diene and ethylene moieties at the TS geometries should be noted (see Figure 2). The two electron-releasing OMe groups on the ER ethylene **2b** and the two electron-withdrawing COOMe groups on the ED ethylene **5b** are planar relative to the C5−C6 double bond (see a and b in Figure 2). This planar arrangement, which allows a maximum overlap between the p_z oxygen lone-pair of OMe and the π* C=O bond of COOMe with the C5=C6 π-bond, is responsible for the nucleophilic and electrophilic character of the ethylenes **2b** and **5b**,

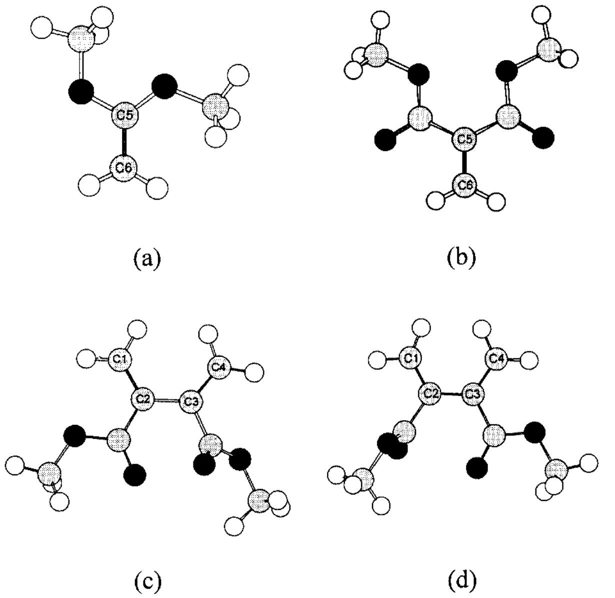


Figure 2. Planar arrangement of the two OMe groups of the ER ethylene **2b** at **TS1** (a) and of the two COOMe groups of the ED ethylene **5b** at **TS4** (b) relative to ethylene systems; planar (c) and twisted (d) arrangements of the COOMe group are present at the C2 position of the diene **1** at **TS1** and **TS4**, respectively

respectively (see below). The same arrangement is found at the monosubstituted ethylenes **3b** and **4**.

At the TS associated with the DA reaction with the ER ethylene **2b** (**TS1**), the COOMe group present at the C2 position of **1** is coplanar with the diene system, while the COOMe group present at the C3 position is twisted due to the hindrance between the oxygen atoms of the two carboxylate groups in the planar conformation (see c in Figure 2). This fact, which allows a maximum delocalisation of the negative charge that is being transferred to the substituted diene during the nucleophilic attack at the C1 position, accounts for the electrophilic behaviour of **1** towards the ER ethylene **2b**. Note that the C1 carbon corresponds to the β-position of a Michael acceptor (C1=C2−COOMe). However, a different behaviour is found at the TS associated with the DA reaction with the ED ethylene **5b** (**TS4**), where the COOMe group present at the C2 position is now twisted by −61° (see d in Figure 2). This twist, together with C2−C7 BO value (0.96), suggests the non-conjugation of the COOMe group with C1−C2 double-bond, and explains the participation of the C1−C2 π-bond in a nucleophilic attack. A similar participation would be expected for the C3−C4 π-bond of 2-azadienes[11] and 2-carbomethoxy-1,3-butadiene[12] towards strong electrophiles. Note that the COOMe group present at the C3 position is now planar to the diene system, but it is not in a conjugated position relative to the C1−C2 π-bond.

A natural population analysis allows the evaluation of the CT along these cycloadditions. The B3LYP/6-31G* natural atomic charges at the TSs have been partitioned between the diene **1** and the substituted ethylene frameworks. A different behaviour is found at these DA reactions. While for the reactions between the ED diene **1** and the ER ethylenes **2b** and **3b** the CT flows from these ethylenes to the diene **1**, by 0.41 electrons at **TS1** and 0.26 electrons at **TS2**, for the reactions between **1** and the ED ethylenes **4** and **5b** the CT flows from the diene **1** to these ethylene derivatives: 0.04 electrons at **TS3** and 0.15 electrons at **TS4**. These results point to a different comportment of the diene **1** towards these substituted ethylenes. Thus, while diene **1** acts as a strong electrophile towards ER ethylenes, such as **2b**, with a $\mathrm{LUMO_{diene}}$ participation, towards stronger ED ethylenes, such as **5b**, the diene **1** appears to act as a nucleophile, with a $\mathrm{HOMO_{diene}}$ participation.

b) Analysis Based on the Global and Local Electrophilicity at the Ground State of the Reagents

These DA reactions were analysed using the global and local indexes defined in the context of density functional theory.[24] The electronic chemical potential, μ, chemical hardness, η, and the global electrophilicity, ω, are displayed in Table 2. Also included in Table 2 are the values of the electrophilic, f_k^+, and nucleophilic, f_k^-, Fukui functions, and the local electrophilicity, ω_k, for the diene **1**, the ER ethylenes **2b** and **3b**, and the ED ethylenes **4** and **5b**.

Table 2. Global and local properties at the k sites of the ED diene **1**, the ER ethylenes **2b** and **3b**, and the ED ethylenes **4** and **5b**

	Global properties			Local properties			
	μ (au)	η (au)	ω (eV)	k	f^+	f^-	ωk (eV)
5b	−0.1683	0.2135	1.80	5	0.1780	0.0306	0.32
				6	0.4590	0.0737	0.83
1	−0.1560	0.2100	1.58	1	0.2636	0.2527	0.42
				2	0.1019	0.1543	0.16
				3	0.1017	0.1544	0.16
				4	0.2631	0.2529	0.42
4	−0.1586	0.2268	1.51	5	0.1969	0.0713	0.30
				6	0.4153	0.0048	0.63
3b	−0.0894	0.2564	0.42	5	0.4627	0.2045	0.19
				6	0.4365	0.4682	0.18
2b	−0.0724	0.2674	0.27	5	0.4438	0.1627	0.12
				6	0.3804	0.5549	0.10

The electronic chemical potential, μ, of diene **1** (−0.1560 au) is lower than those of the ER ethylenes **2b** (−0.0724 au) and **3b** (−0.0894 au), indicating that along the cycloaddition the CT will take place from these ER ethylenes to the diene **1**. On the other hand, the electronic chemical potentials of the two ED ethylenes **4** (−0.1586 au) and **5b** (−0.1683 au) are lower than that of the diene **1**. Thus, for the DA reaction between the diene **1** and the ethylene **5b** there is a clear reversal in the flow of the CT on going from the diene **1** to the ED ethylene **5b**, which possesses the lowest chemical potential value of this series.

The electrophilicity of the diene **1** is 1.58 eV, a value that falls into the range of strong electrophiles within the ω scale.[15] The two ER ethylenes have very low electrophilicity values — 0.27 eV (**2b**) and 0.42 eV (**3b**) — and are therefore classified as marginal electrophiles (good nucleophiles).[15] The difference of electrophilicity, $\Delta\omega$, between the diene **1** and these ethylenes — 1.31 (**2b**) eV and 1.16 eV (**3b**) — indicates that these DA reactions will have a polar character.[15] The cycloaddition between the diene **1** and the ER ethylene **2b** presents the largest $\Delta\omega$ and corresponds to the more-polar and the faster cycloaddition of the series of DA reactions of diene **1** reported by Spino et al.[9]

The local functions are summarised in Table 2. For the symmetrically disubstituted diene **1**, the C1 and C4 carbons present the larger local electrophilicity values (0.42 eV). Therefore, the C1 and the C4 carbons will be the preferred positions for a nucleophile attack. For the ER ethylenes **2b** and **3b** the C6 carbon presents the largest f_k^- value (see Table 2). In consequence, during the nucleophilic attack of the ethylenes **2b** or **3b** on diene **1**, the most favourable two-centre interaction will take place between the C6 carbon of **2b** or **3b** and the C1 carbon of the diene **1**. This local analysis is in complete agreement with the asynchronicity found during the bond-formation at **TS1** and **TS2**.

*What occurs for the DA reaction between diene **1** and the ED ethylene **5b**?* The electrophilicity of the ED ethylene **5b**, 1.80 eV, is larger than that of diene **1**, and the electronic chemical potential of **5b** is lower than that of **1**. Therefore, both reactivity indexes indicate that during the cycloaddition the CT will take place from **1** to **5b**. This analysis is in clear agreement with the CT found at the TS associated with the DA reaction between **1** and **5b** (**TS4**).

For the ED ethylenes **4** and **5b**, the C6 carbon, which corresponds to the β-position of a Michael acceptor,[25] is the more electrophilic site of these molecules; the ω_k value at C6 is 0.63 eV (**4**) and 0.83 eV (**5b**). Note also that the global electrophilicity of the ED ethylene **5b** is 0.22 eV larger than that for the ED diene **1**, while the ω_k at the C6 carbon of the asymmetrically disubstituted ethylene **5b** is 0.41 eV larger than that at the C1 carbon of the symmetrically substituted diene **1**. In addition, the disubstituted diene **1** has a global electrophilicity value that is 0.07 eV larger than that for the monosubstituted ED ethylene **4**, while the local electrophilicity value at the C6 carbon of **4** is 0.21 eV larger than that at the C1 carbon of the diene **1**. Therefore, the local analysis indicates that the ED ethylene **4** will be a more efficient electrophile than the diene **1**. This result may explain the loss of effectiveness of diene **1** as a potential strong electrophile in the sense that, despite its high global electrophilicity, it becomes at the same time less regioselective. This result is reminiscent of that obtained in the analysis of the cyanoethylene series.[8]

On the other hand, the C1 and C4 carbons of the diene **1** also present a nucleophilic activation — the f_k^- value at C1 and C4 is 0.2527. Therefore, the analysis of the electrophilic and nucleophilic Fukui functions of the diene **1** indicates that the C1 and C4 carbon atoms are at the same time the most electrophilic and nucleophilic centres of the molecule. These results can be understanding by considering that, for a nucleophilic attack of **2b** or **3b**, the β-positions of the $CH_2{=}CR\text{-}COOMe$ frameworks are the most electrophilic sites of the molecule,[25] while for an electrophile attack by **4** or **5b**, the ends of the $CH_2{=}CX{-}CX{=}CH_2$ diene framework are the most nucleophilic sites. In consequence, along the DA reaction between **1** and the ER ethylene **5b**, the most favourable two-centre interaction will take place between the electrophilically activated C6 position of **5b** and the nucleophilically activated C1 position of the diene **1**. This local analysis is also in agreement with the asynchronicity found at the corresponding **TS4**. All this can be summarised as follows: *a molecule will behave as an electrophile against any molecule situated below it in the electrophilicity scale. However, the same molecule will behave as a nucleophile towards molecules located above it in the aforementioned scale.* Note that symmetric substitution, as is the case in diene **1**, produces a loss of effectiveness of the molecule as a potential electrophile (or nucleophile).[26]

Conclusions

The analysis of the geometry and electronic structure of the TSs of DA reactions involving ED reagents provides an explanation of the participation of an ED diene as a nucleophile towards powerful electrophiles. This fact, which requires the non-participation of the electron-withdrawing substituents during the nucleophilic attack of the C=C π-bond of the diene, can be anticipated by the relative position of the diene/dienophile pair in the electrophilicity scale. A strong electrophile positioned at the top of the scale determines the nucleophilic character of the other reagent located below it. This analysis allows the characterisation of the $\mathrm{HOMO_{Nu}}^{-}{-}\mathrm{LUMO_E}^{+}$ interactions along a polar DA reaction. Finally, analysis of the local indices allows the characterisation of the more-favourable, two-centre interaction along asynchronous bond-formation processes.

Experimental Section

Computational Details: DFT calculations were carried out using the B3LYP,[27] exchange-correlation functionals, together with the standard 6-31G* basis set.[28] The optimisations were performed using the Berny analytical gradient optimisation method.[29] The stationary points were characterised by frequency calculations in order to verify that the TSs had one, and only one, imaginary frequency. The IRC[30] 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.[31] The electronic structures of TSs were analysed by the natural bond orbital (NBO) method.[32] Thermal corrections to enthalpy values were evaluated at 383.15 K, which is the temperature of these cycloadditions. The computed values of enthalpies energies were estimated by means of the B3LYP/6-31G* PEBs, along with the gas-phase harmonic frequencies.[28] All calculations were carried out using the Gaussian 98 suite of programs.[33]

The global electrophilicity, ω,[13] which is a measure of the stabilisation in energy when the system acquires an additional electronic charge, ΔN, from the environment, has been given the following simple expression,[13] $\omega = (\mu^2/2\eta)$, where μ is the electronic chemical potential and η the chemical hardness. Both quantities may be approached in terms of the one-electron energies of the HOMO and LUMO molecular orbitals, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively.[14] The local electrophilicity index, ω_k,[20] can be expressed as $\omega_k = \omega f_k^+$, where f_k^+ is the Fukui function for a nucleophilic attack. This expression shows that the maximum electrophilicity power in a molecule will be developed at the site where the Fukui function for a nucleophilic attack displays its maximum value, i.e. at the active site of the electrophile. Electrophilic and nucleophilic Fukui functions[21] condensed to atoms have been evaluated from single-point calculations performed at the GS of molecules at the same level of theory, using a method described elsewhere.[34] This method evaluates the Fukui functions from the coefficients of the frontier molecular orbitals involved in the reaction and the overlap matrix.

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