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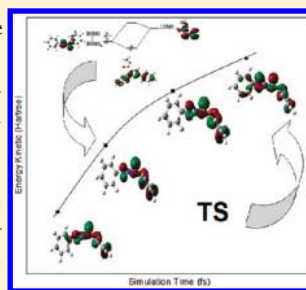
Orbital Signatures as a Descriptor of Regioselectivity and Chemical Reactivity: The Role of the Frontier Orbitals on 1,3-Dipolar Cycloadditions

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S Supporting Information

ABSTRACT: The FERMO concept emerges as a powerful and innovative implement to investigate the role of molecular orbitals applied to the description of breakage and formation of chemical bonds. In this work, Hartree–Fock (HF) theory and density functional (DFT) calculations were performed for a series of four reactions of 1,3-dipolar cycloadditions and were analyzed by molecular orbital (MO) energies, charge transfer, and molecular dynamics (ADMP) techniques for direct dynamics using the DFT method. The regioselectivity for a series of four 1,3-dipolar cycloaddition reactions was studied here using global and local reactivity indexes. We observed that the HOMO energies are insufficient to describe the behavior of these reactions when there is the presence of heteroatoms. By using the frontier effective-for-reaction molecular orbital (FERMO) concept, the reactions that are driven by HOMO, and those that are not, can be better explained, independent of the calculation method used, because both HF and Kohn–Sham methodologies lead to the same FERMO.



1. INTRODUCTION

The cycloaddition reactions can be considered as one of the most important tools for synthetic organic chemistry and mechanistic studies.^{1,2} In a cycloaddition reaction, two different molecules, which contain π bonds, react to form a molecule by cyclic rearrangement of the π electrons, and two new σ bonds. This interaction of two π systems are usually intermolecularly different.¹ The cycloaddition reactions are classified according to the number of π electrons that interact in the reaction, only counting the π electrons that participate in the electronic rearrangement.³

1,3-Dipolar cycloadditions (Figure 1) are among the most important and versatile synthetic methods for the preparation of five membered heterocycles.⁴ This cycloaddition proceeds by a concerted mechanism of the $[3 + 2]$ type, and the interaction between asymmetric reagents can form two isomers depending on the relative position of the substituent.

Molecular orbitals (MOs) and their properties, like energies and symmetries, are very useful for chemists. According to Fukui, the MO properties have used the frontier electron density for predicting the most reactive position in π -electron systems. Hoffmann and Woodward set out orbital symmetry rules to explain several types of reactions in conjugated systems, and the frontier MOs gained importance for the better understanding of chemical reactions. The concept of the frontier orbital, introduced by Fukui around 1952, relates reactivity with the properties of two molecular orbitals: HOMO and LUMO. In fact, one application of the HOMO–LUMO argument is the description of the cycloaddition reactions.^{5–8} It should be kept in mind, however, that the HOMO–LUMO argument has certain limitations

and new efforts are necessary to understand when the HOMO energy works and when it does not; currently, that important topic in chemistry has been the target of several research groups.^{8–14} More recently, the frontier effective-for-reaction molecular orbital (FERMO) concept has emerged as a powerful approach for studying this situation.^{15–21} The localization and the composition of the orbitals can reveal a frontier molecular orbital close to the HOMO with large contribution in atoms present at the active site (APAS). Actually, a large MO contribution in APAS can fit our orbital choice criterion, because they are common to all of the studied compounds and are mainly located where the reaction takes place. Thus, perhaps that orbital could better describe the reactivity than the HOMO. Therefore, this special orbital will be called FERMO. In this concept, the FERMO provides the adequate orbital shape and composition to correlate with reactive indexes.^{15–21}

It is important to mention that, in general, the reactivity indexes involving molecular orbitals are obtained from theoretical static calculation. However, the thermal effects might play an important role on the chemical reactivity. In spite of its great importance, surprisingly little detailed computational work on this subject has appeared. In this scenario, the molecular dynamics (MD) simulation may be employed.

The MD is a technique to study the movements of atomic-molecular systems for which the effects of temperature cannot be neglected. Its key elements are the knowledge of the potential interaction between the particles and the motion equations that

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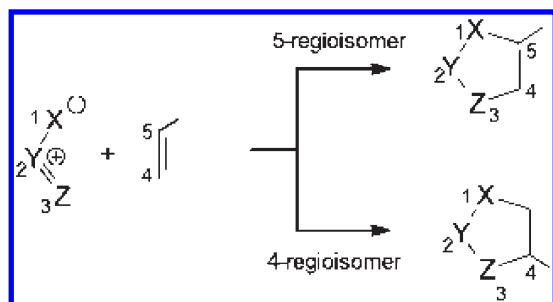


Figure 1. Regioisomeric pathways of 1,3-dipolar cycloaddition.

govern the dynamics of these particles.²² In a wide band around room temperature, approximately between 100 and 800 K, the energy scales involved in the processes and properties of interest are typical of the interactions between atoms, ions, and molecules and the conformations of polyatomic molecules. Nevertheless, for reactive processes involving chemical reactions among different constituents of the system, their inherently quantum nature cannot be treated by conventional classical molecular dynamics techniques.²³

The ADMP direct dynamics method combines classical and quantum information, providing equivalent functionality to the BOMD method with a low computational cost. This method belongs to an extended approach of the Lagrange formalism by extending the molecular dynamics using Gaussian basis functions and a spread of the density matrix.²⁴ The use of *ab initio* direct dynamics methods provides a detailed description of chemical reactions: new pathways and mechanisms, new phenomena, and new effects are being and will be discovered.^{25,26}

The FERMO concept comes from a dose of intuition, together with the criteria for the composition and location to correctly determine the reactant molecular orbital. This concept can be understood as a complement to the HOMO–LUMO argument. Another important feature in FERMO is that both HF and Kohn–Sham orbitals lead to the same conclusions about reactivity.^{15–17} A careful study is still necessary to understand when the use of HOMO energy works or not.

For this reason and because of its great importance in organic synthesis, our work is devoted to investigating which MO is the best for describing the 1,3-dipolar cycloaddition reactions, for a collection of compounds evaluating the thermal effects in light of the FERMO concept.

2. COMPUTATIONAL METHODS

In recent years, theoretical methods based on the density functional theory (DFT) have emerged as an alternative to traditional *ab initio* methods in the study of structure and reactivity of chemical systems.^{27,28} All calculations were carried out with the Gaussian 98 package.²⁹ For each structure studied, calculations were made for optimization, using the DFT with the B3LYP functional^{30,31} employing the 6-31G(d,p) basis set. No symmetry constraint was imposed during the optimization process. Those optimized geometries were used in all subsequent calculations. This theoretical level was also used for the frequency calculations. Furthermore, *ab initio* HF energy calculations were computed using the 6-31G(d,p) basis set. The MO figures were prepared using the Gauss View 2.1 package²⁹ with a contour value of 0.020. All structure calculations in this work were performed in gas phase, and the solvent effect was not considered.

The charges were obtained using the ChelpG method (charge electrostatic potential grid), due to their low computational cost. These calculations were conducted using the MP2 method with basis functions 6-31 g(d, p), and provide a satisfactory description of the electrostatic potential.³²

Moreover, the 1,3-dipolar cycloaddition reactions were also studied with the first-principle ADMP molecular dynamics technique at 400 K with the DFT method at level B3LYP with the basis set 6-31 g (d, p).^{33,34}

3. RESULTS AND DISCUSSION

3.1. Chemical Reactivity. Initially the optimizations were made to obtain the minimum energy of the studied systems (A, B, C, and D); these calculations were performed for totally relaxed molecules and in the gas phase. Figure 2 reports the reactants and products for the studied reactions. The substituents H, CH₃, CF₃, and Ph were chosen, in order to address the influence of small and large groups as well as electron withdrawing and donating in the reactants.

Molecular interactions are difficult to study experimentally, as they often occur in complex systems where secondary interactions and the effect of the solvent can complicate the interpretation of results.^{35–37} Refined theoretical calculations, however, in gas phase, have enabled important information about the molecular interactions. Thanks to the remarkable development of computational chemistry, the calculations in the gas phase can have good accuracy when compared to experimental data.³⁸ Moreover, some previous studies have shown that the calculations in the gas phase have the same reliability as the liquid phase in the study of molecular orbitals, when based on the FERMO concept.^{19,20} Therefore, in this work, the solvent effect was not taken into account.

The transition state structures as well as the bond lengths involved in the studied reactions were characterized in the infrared theory and are shown in Figure 3. For reaction A, the bond lengths involved in the transition state structures were 2.341 and 2.921 Å and 2.529 and 2.436 Å for the formation of the 4-regioisomer and 5-regioisomer, respectively. On the other hand, for reaction D, we have obtained the bond lengths 2.267 and 2.461 Å and 2.661 and 2.275 Å for the formation of the 4-regioisomer and 5-regioisomer, respectively (see Figure 3). The analysis indicates that 1,3-dipolar cycloadditions occur along a concerted asymmetry. Table 1 presents the values from the thermodynamic and kinetic studies. First, from the kinetics parameters (ΔG^\ddagger), the transition state energy values for the formation of the 4-regioisomer were 13.83, 15.45, 5.18, and 19.06 kcal mol^{−1}. Turning to formation of the 5-regioisomer, the ΔG^\ddagger values were 17.06, 15.67, 4.40, and 18.63 kcal mol^{−1}. Now, a deeper analysis of the thermodynamics parameters (ΔG) of the studied reactions reveals that the lowest ΔG values were obtained for reaction D, which is in good agreement with the experimental data (Table 1).

By analyzing the values from Table 1, we show the kinetic and thermodynamic parameters in the chemical reactions (A, B) and (C, D) from the 4-regioisomers and 5-regioisomers, respectively. In fact, these products are kinetically more favorable; for instance, we can notice a ΔG^\ddagger value of just 4.40 kcal mol^{−1} for product 5-II in reaction C. It should be kept in mind, however, that the products formed at the first moment will not necessarily be the most thermodynamically stable at the end of the chemical reaction. Thus, the major products are those that present the lower Gibbs free energy value (ΔG), such as compound 4-I (83.50 kcal mol^{−1}) in the reaction D. Assessing these properties, we can theoretically predict the subproduct proportion and the kinetics with which

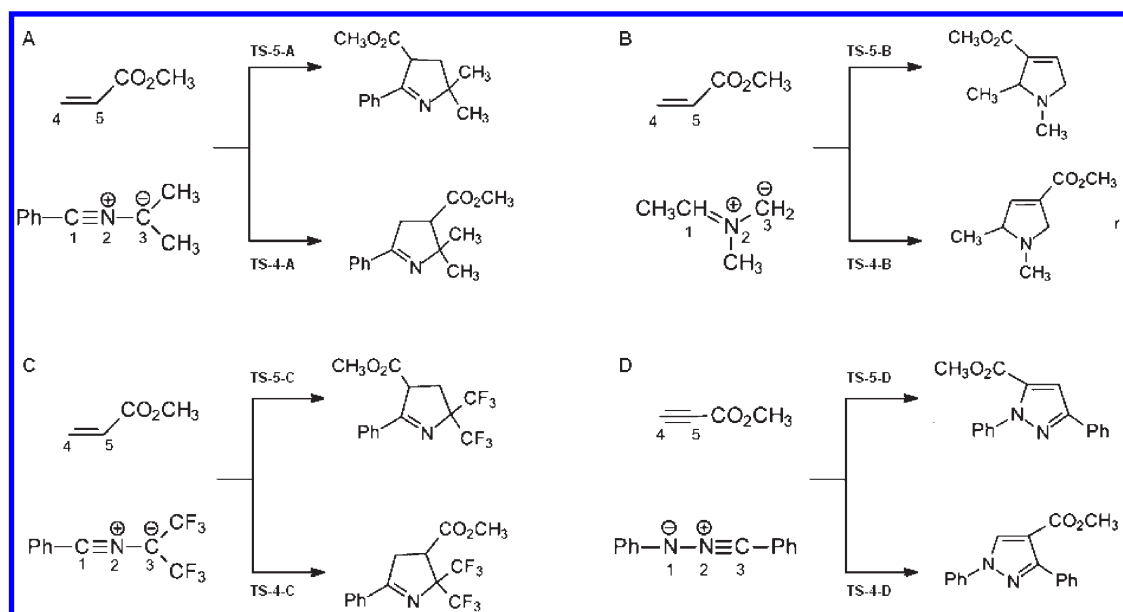


Figure 2. Reactions of 1,3-dipolar cycloaddition investigated.

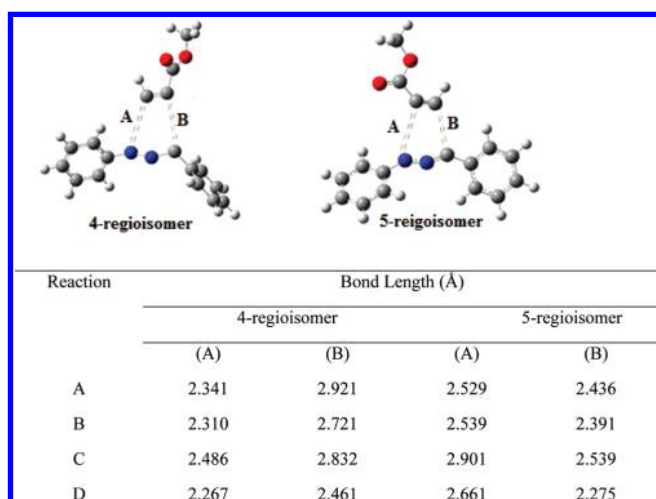


Figure 3. Bond lengths involved in the reaction (values in angstroms) of regioisomers studied and the structures of the transition state.

they are formed. Our ΔG results are in agreement with the experimental values.^{1,38–42}

The chemical reactivity can be described in terms of long-range forces by electrostatic potential. During the discussion of our results, we observed an intense variation in distance and electronic density of molecules. Due to the charge transfer phenomenon, the electron density in the molecules must be an important factor that justifies the changes observed during the reaction.^{43,44} In this line, it is quite important to investigate the charge transfer process from an orbital point of view.

3.2. Charge Transfer. In this study, we determined the charge transfer (ΔQ) involved in the studied reactions according to eq 1 and Scheme 1. In general, the charge transfer occurs through the interaction between ligand and antiligand orbitals.

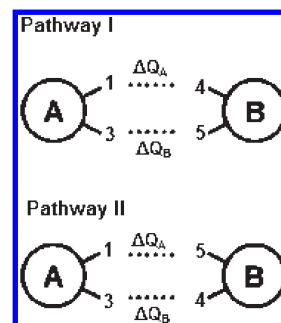
$$\Delta Q = \Sigma \Delta Q_{AB(C \dots AB)} - \Sigma \Delta Q_C \quad (1)$$

Here, the charge transfer from atom “c” to species AB occurs, and $\Delta Q_{AB(C \dots AB)}$ is the sum of electrostatic charges of the

Table 1. Free Energy (ΔG) Values and the Transition State (ΔG^\ddagger) Results in kcal mol^{−1}

reaction	ΔG^\ddagger	ΔG	product
A, 4-I	13.83	−43.62	majority
A, 5-II	17.06	−42.33	minority
B, 4-I	15.45	−44.29	minority
B, 5-II	15.67	−45.40	majority
C, 4-I	5.18	−74.00	minority
C, 5-II	4.40	−73.58	majority
D, 4-I	19.06	−83.50	majority
D, 5-II	18.63	−82.20	minority

Scheme 1. Charge Transfer System Studied



atoms A and B, which represent the active site of the isolated molecule AB, ΔQ_C .⁴⁴

It is important to note that there are several methods that describe the molecular electronic distribution in terms of atomic charges, which may be applied to the phenomenon of charge transfer study, such as the Mulliken population analysis, the dipole GAPT model, and the ChelpG scheme.^{45–47} Thus, the ChelpG formalism may be qualified as an appropriate methodology in this study, because the electrostatic contribution is a

Table 2. Charge Transfer (ΔQ) Values, Δ_{FERMO} Values, and CT Results

reaction	CT ¹		ΔQ^{CHELPG}		Δ_{FERMO}	
	4-regioisomer	5-regioisomer	4-regioisomer	5-regioisomer	4-regioisomer	5-regioisomer
A (i) ^a	0.23	0.18	0.178	0.125	0.03	0.04
A (ii)			0.211	0.166		
B (i)	0.12	0.11	0.106	0.142	0.13	0.02
B (ii)			0.238	0.165		
C (i)	0.21	0.21	0.022	0.008	0.11	0.17
C (ii)			0.128	0.176		
D (i)	0.10	0.10	0.473	0.509	0.28	0.40
D (ii)			0.190	0.110		

^a (i) ΔQ_{A} ; (ii) ΔQ_{B} .

predominant factor in determining the intermolecular stabilization energy.

Furthermore, in this paper, we propose a new reactivity index (Δ_{FERMO}) based on the charge transfer in the system, as described in eq 2. This reactivity index might allow for obtaining appropriate information about the thermodynamic properties of these reactions. For instance, it is possible to verify a good correlation between the Gibbs free energy values and the Δ_{FERMO} data (Tables 1 and 2). Actually, the higher ΔG values reveal lower Δ_{FERMO} results; i.e., there is more effective charge transfer as higher orbital interaction occurs.

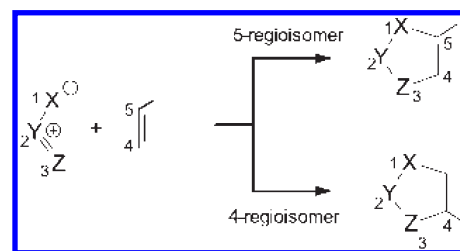
$$\Delta_{\text{FERMO}} = \Sigma |\Delta Q_{\text{A}} - \Delta Q_{\text{B}}| \quad (2)$$

However, to calculate this parameter the interpretation of electrostatic charges is frequently used. An explanation about the appropriate atomic charge density in the donors can be demonstrated for the charge transfer and the Δ_{FERMO} results could, in principle, rationalize the regioselectivity of these reactions (Table 2). The Δ_{FERMO} values found for the studied reactions vary from 0.02 to 0.40.

On the basis of the chemical intuition and through a qualitative analysis of the charges, we can note that there is a concerted process. For instance, analyzing the transition state structure of the reaction that forms the 4-regioisomers and comparing with the atomic charge values (Table 3) in the reactants, we can rationalize the process involved. Ongoing from atom 1 to 4, a decrease is observed in the electrostatic charge at 1, increasing the charge simultaneously on the atoms 4 and 5. The charge excess is transferred to the empty orbital on atom 2. The same tendency is observed for formation of the 5-regioisomers.

As described above, several studies in the literature have related the chemical reactivity to the frontier orbitals HOMO and LUMO. However, it is important to note that not only the HOMO and LUMO are responsible for the reactions. Furthermore, when comparing HF and KS orbitals, the first thing that can be noticed, for some molecules, is that the shape of the HOMO orbitals given by the HF method can be different from those obtained by the DFT method, as shown in cases of chemical reactivity for phenols, aromatic amines, and aliphatic alcohols.^{15,17,18} In this way, we could obtain a different panorama of reactivity for the same system, with the use of different theoretical methodologies. On the other hand, it is important to mention that, in some cases, the MOs obtained by both HF and DFT methods might show roughly the same shape, but with different energy orders. The DFT orbitals, named Kohn–Sham (KS) orbitals, and the MOs are sometimes

Table 3. Electrostatic Charges on the Reactants, Transition States, and Products



atom	reactants	TS-4	TS-5	4-regioisomer	5-regioisomer
A					
1	0.162	0.178	0.125	0.297	0.318
2	−0.433	−0.442	−0.416	−0.535	−0.518
3	0.247	0.329	0.385	0.126	0.114
4	−0.236	−0.218	−0.252	−0.246	−0.237
5	−0.208	−0.276	−0.260	−0.249	−0.279
B					
1	0.362	−0.106	−0.142	0.371	0.370
2	−0.432	−0.415	−0.415	−0.551	−0.534
3	−0.297	0.425	0.441	−0.156	−0.168
4	−0.236	−0.161	−0.222	−0.265	−0.265
5	−0.208	−0.334	−0.281	−0.254	−0.275
C					
1	−0.047	−0.022	0.008	0.090	0.132
2	−0.354	−0.549	−0.553	−0.640	−0.637
3	−0.141	0.184	0.163	0.055	0.014
4	−0.362	−0.144	−0.216	−0.111	−0.131
5	0.099	−0.259	−0.206	−0.159	−0.145
D					
1	−0.531	−0.473	−0.509	−0.560	−0.587
2	−0.172	−0.119	−0.137	0.371	−0.341
3	0.329	0.247	0.294	0.342	0.271
4	−0.362	−0.071	0.012	0.268	−0.241
5	0.099	−0.155	−0.242	−0.366	0.253

treated as different quantum descriptors.⁸ Another reason for that difference arises from the poor results given by the eigenvalues of the

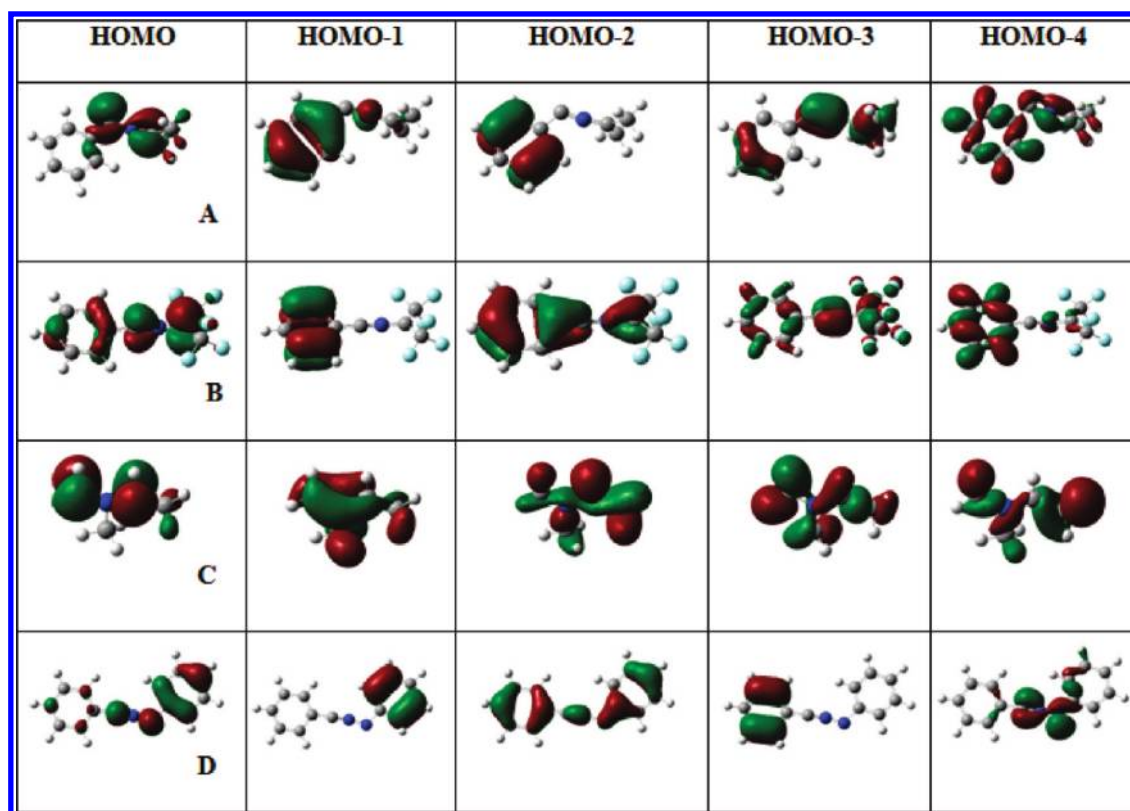


Figure 4. Frontier molecular orbital representation of the cycloaddition reactions.

KS orbitals in the description of the ionization potentials (IPs) of molecules (the Koopmans' theorem) and other electronic parameters when compared to HF orbitals. In view of this, a more general concept that allows unifying HF and DFT calculations for the same MO interpretation could be very useful.

Thus, on the basis of the FERMO idea, we expanded the correlations to other frontier orbitals, namely HOMO - 1, HOMO - 2, and HOMO - 3 (Figure 4). Furthermore, using the FERMO concept, MO composition and shape are taken into account to identify the MO which will actually be involved in a given reaction.

In order to get more accurate values for the orbital energy and to evaluate the limitations in the MO calculations of those orbitals, we have calculated the ionization potential (IP) according to Cederbaum's outer valence Green function (OVGF) method, which is state-of-the art for ionization calculations.¹⁸ Those calculations showed a good correlation ($r^2 = 0.97$) between IP values and the orbital energy calculated by the present approach. So, those results reinforce that the current methodology employed for the HOMO - 1, HOMO - 2, and HOMO - 3 calculations is appropriate.¹⁹

On the basis of the orbital composition and localization, it is possible to get a deeper insight into the orbital that governs the chemical reaction. The orbital composition is an important indicator for discovering the adequate orbital.^{15,16} The MO shape and the atomic composition are very important parameters for analyzing FERMO.¹⁷⁻²¹ Upon analyzing orbital localization and composition more deeply (Table 4), we can observe that there is an MO with energy quite close to the HOMO energy value and with a large contribution of the atoms present at the active site (APAS: 1, 2, 3, 4 and 5, see Figure 1). For the reactions A, B, C, and D the APAS contributions (%) were 78.58, 69.77, 91.10, and 77.34,

Table 4. APAS Contribution (%) and Orbital Energy for the Chemical Reaction Studied

reaction	APAS contribution %	FERMO (Hartree)
A	78.58	-0.276
B	69.77	-0.296
C	91.10	-0.211
D	77.34	-0.393

respectively. Thus, it is supposed that that orbital could describe the behavior of a 1,3-dipolar cycloaddition reaction better than HOMO.

3.3. FERMO and Chemical Intuition. A molecule can have as many FERMOs as it has reaction sites, and it could be the HOMO or any other frontier MO.¹⁶ Reactions involving electron donation and acceptance are related to MO energies, since electrons are occupying and will occupy an MO and a frontier orbital, as stated by Fukui.⁵⁻⁷ A criterion has been established in this study to determine the frontier effective-for-reaction molecular orbital, abbreviated as FERMO. In this concept, FERMO provides the adequate orbital shape and composition to correlate with reactive indexes.

Through simple calculations and chemistry intuition, it was possible to identify the molecular orbital effective for the reaction. On the basis of the composition and location of the molecular orbitals, the FERMO is the HOMO for reactions A, B, and C, while in reaction D, FERMO is a different orbital (Figure 5). On the basis of the results, we can notice that the HOMO is not necessarily the molecular orbital to describe the 1,3-dipolar cycloaddition reaction, but other possible combinations of orbitals may take place.

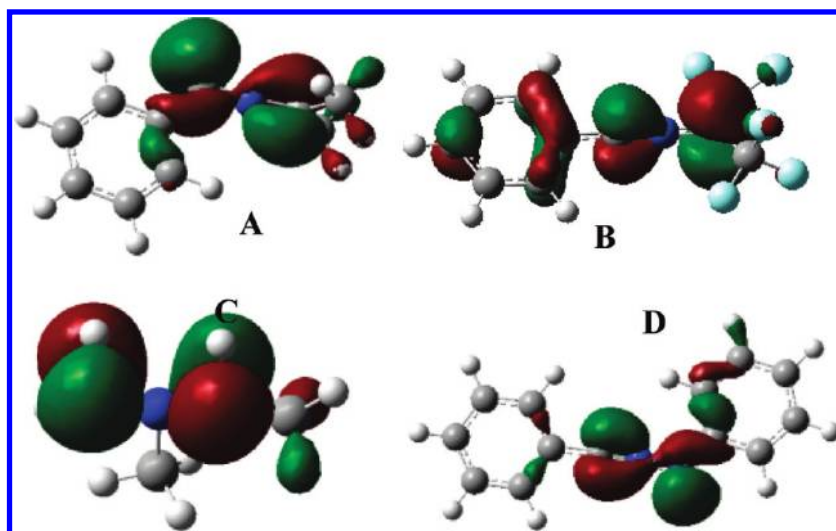


Figure 5. Surfaces plots of FERMO for the reactions studied.

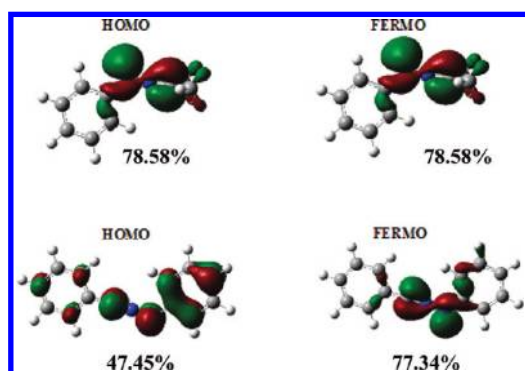


Figure 6. Shape of the HOMO (left) and FERMO (right) for studied reactions A and D and their respective APAS contributions.

In Figure 6, the shape of the HOMO and FERMO for the reaction A and D is shown, and their respective APAS contributions. Thus, it is assumed that this orbital describes better the 1,3-dipolar cycloaddition reactions. Moreover, the results obtained by both HF and DFT methodologies are similar when the FERMO concept was applied; i.e., the HF as well as the KS orbitals lead to the same conclusions on the reactivity when the FERMO idea is applied.^{16,48,49} It is well-known that the Kohn–Sham DFT is a leading method for electronic structure calculations in chemistry mainly due to its high efficiency and relatively low computational cost.^{50,51} It is important to mention that the orbital concept at the DFT level is questionable theoretically.^{8–11} In fact, some authors have analyzed the behavior of HF and KS orbital energies in many molecules and compared the results with the experimental IP,⁴⁸ showing that KS orbital energies differ significantly from experimental IP, while HF energies are in good agreement with them.⁴⁸ On the other hand, our previous findings¹⁵ pointed out that KS orbitals are suitable for being used in qualitative MO theory in combination with the FERMO concept. It should also be kept in mind, however, that, despite the recent improvements in DFT, there are still difficulties in using DFT to properly describe intermolecular interactions, especially van der Waals forces (dispersion) and charge transfer excitations, in part, due to lack of exact Hartree–Fock exchange in some functionals.^{52–54}

Currently, the development of methods designed to overcome this problem, by alterations to the functional or by the inclusion of additive terms, is a very important research topic in DFT. It is also well-known that the hybrid functionals, such as the B3LYP functional used in this work, yield unsatisfactory atomization energies mainly for metals, whose the error can vary between 25% and 40%.^{52–54}

On the other hand, for large gap systems with well-localized electrons, the agreement with experimental and conventional functionals is quite reasonable.^{55,56} In this way, our results using B3LYP combined with the FERMO concept could then be justified, because the respective errors for the constituents of the reaction cancel each other, as electrons are localized for all reactants and the product.^{15–20} This conclusion is in line with previous work of other groups.^{57,58}

Thus, we may notice that the FERMO idea is to use the MO calculations with a valence bond (VB) theory interpretation. In MO theory, the electrons in a molecule occupy delocalized orbitals made from linear combination of AOs. However, it should be kept in mind that the VB approaches are quite useful in analyzing enzymatic reactivity,^{59,60} photochemistry,^{60,61} chemical dynamics,⁶¹ and conductivity theories, where the localized representation seemed indispensable.

In fact, it is well-known that the VB methods allow generating new ideas on chemical bonding. Recently, there has been an intense surge of concepts related to localized representation, for example, multiple bonding between transition metals^{5,62,63} and the development of natural resonance theory.⁶⁴

3.4. Frontier Orbital and Direct Molecular Dynamics ADMP. A direct molecular dynamics started from the transition state structure. The behavior of the reactant molecules was accomplished by analysis of the trajectories generated corresponding to a temperature of 400 K. There were no dynamics trajectories to leave the area of products for times around 100 fs. The results of the dynamics in turn provide detailed explanations at the molecular level of the phenomena observed experimentally. It is noteworthy that all these trajectories involve a concerted reaction path (Figure 7).

Furthermore, the shape of FERMO was accompanied by the conformations obtained during the MD simulation, and the results put in evidence that the reaction mechanism occurs *via*

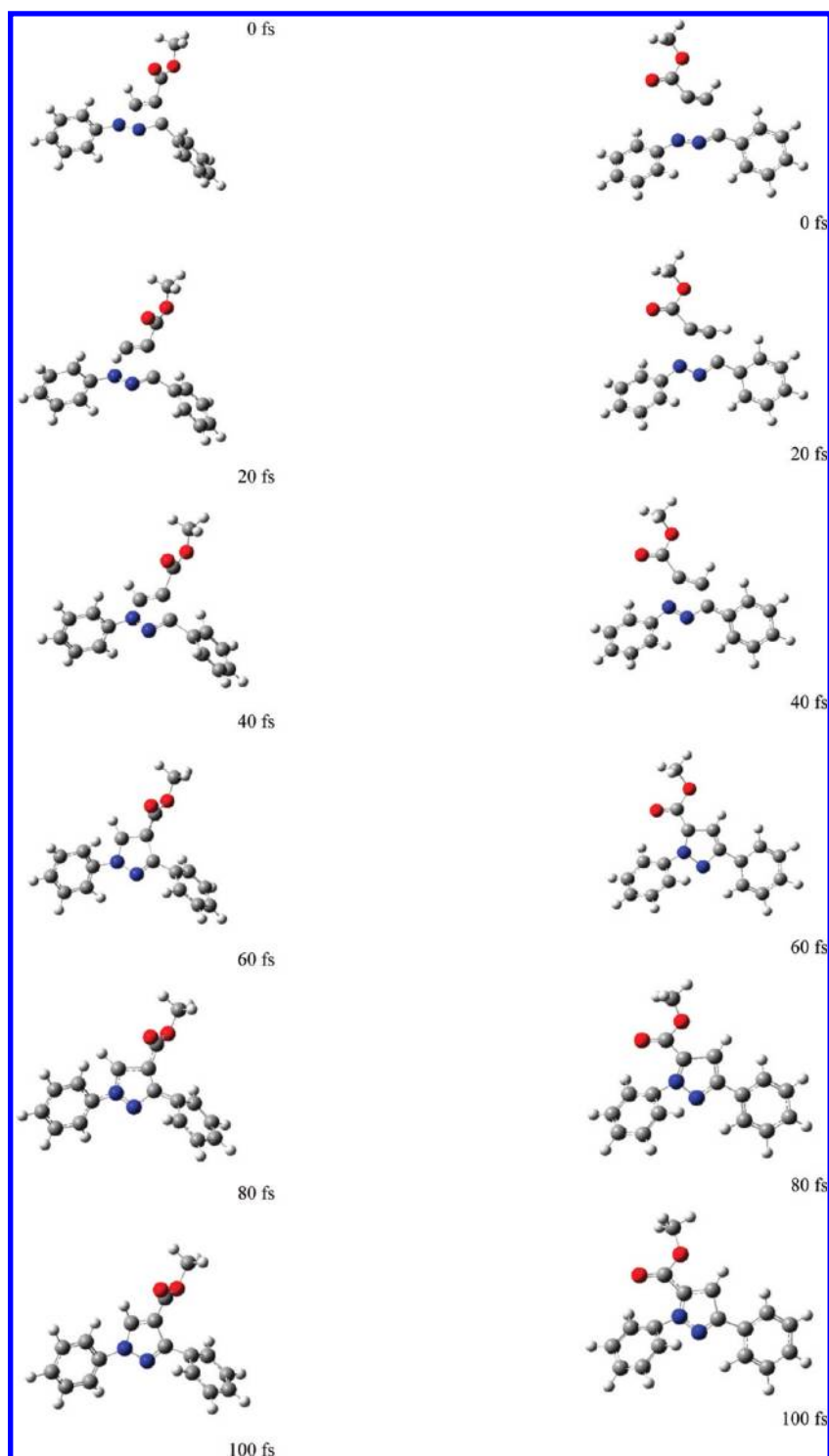


Figure 7. Selected structures from MD trajectories for the (left) 4-regioisomer and (right) 5-regioisomer.

a concerted process (Figure 8), as expected. Table 5 reports the APAS molecular orbital contribution of the frontier orbitals along the reaction pathway, in the case of the FERMO, we have obtained the values 55.28, 60.41, 55.05, and 63.23 for the formation of the 5-regioisomer. The APAS contributions (%) for the FERMO along the MD simulation in reaction D were 55.28, 60.41, 55.05, and 63.23 for the 5-regioisomer.

Interestingly, from the direct MD simulation results, it is possible to notice that the FERMO for reaction D becomes

the HOMO along the reaction pathway. It should be kept in mind that the FERMO is one of the main MOs responsible for the formed chemical bonds.^{15–20} In this line, the chemical bond can be studied through virial theorem involving both kinetic and potential energies. It is well-known that the electron density in the bond region leads to an increase in the electrostatic interactions, thus opposing bond formation. A bond is formed due to a very high decrease in the kinetic energy in the bond region.⁶⁴ In other words, the potential energy increases in that bond region.

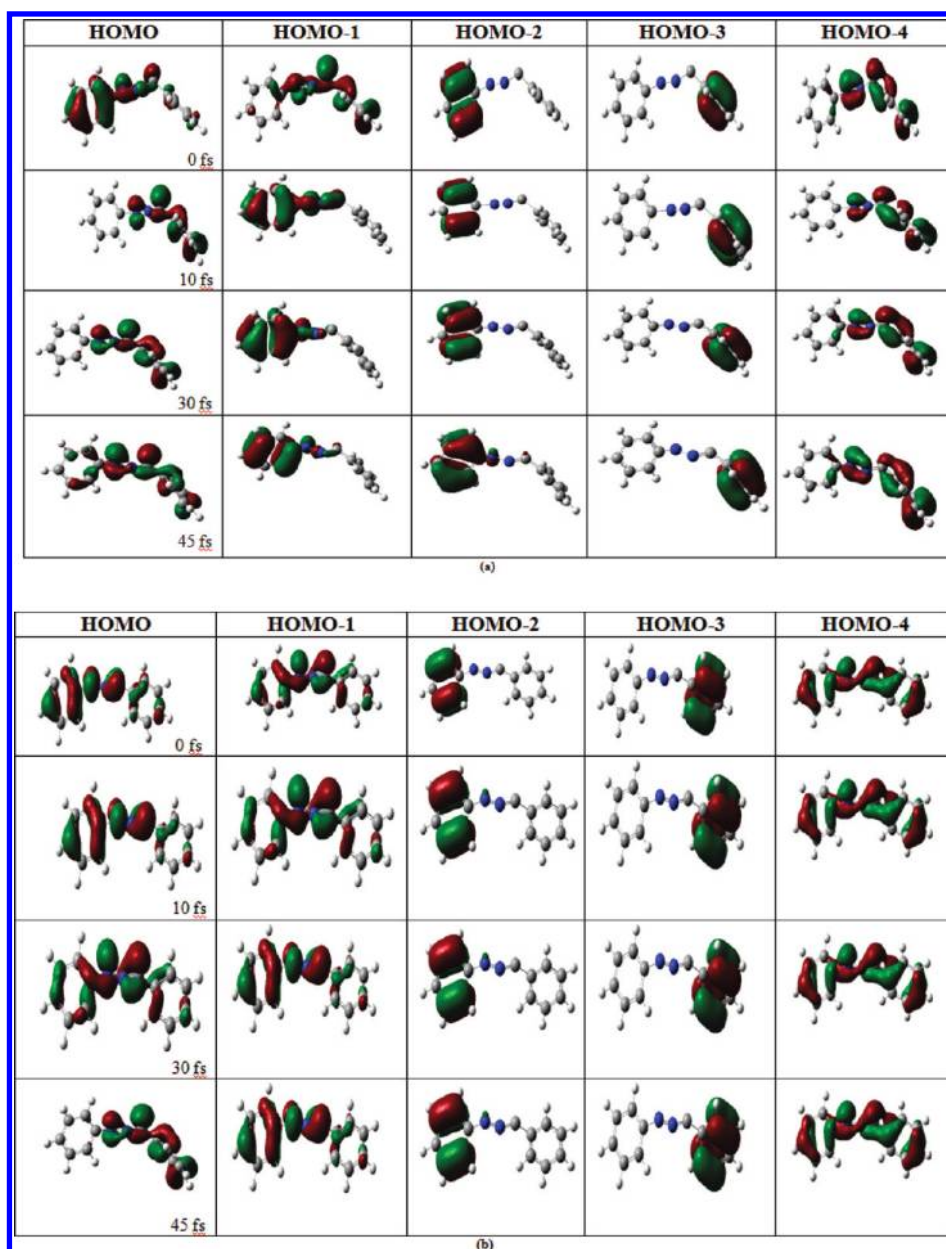


Figure 8. Frontier molecular orbital representations along the reaction pathway considered in the formation of the (a) 4-regioisomer and (b) 5-regioisomer studied for reaction D.

In a chemical bond, one of the most affected MOs is the FERMO.^{15–20} Therefore, its energy will drastically change along the reaction pathway. Table 5 and Figure 7 are in good agreement with this expectation; for instance, for the formation of the 4-regioisomer in reaction D, the APAS contributions (%) for the HOMO – 1 (FERMO for the reactants) is ongoing from 55.28 to 19.93 and the those for the HOMO vary from 40.13 to 63.23. Thus, the FERMO for that reaction becomes the HOMO along the reaction pathway, increasing its initial energy in the proximity of the transition state structures.

Figure 9 shows an energy diagram and the shape of the frontier molecular orbital based on the FERMO concept for the reaction D.

An interesting factor that we observe is that the same FERMO shape is maintained throughout the reaction. This evidence helps to reinforce the idea that the FERMO allows us to obtain insights

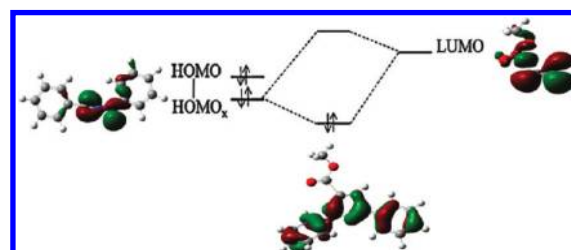


Figure 9. Orbital energy diagram and orbital shape for reaction D.

into the orbital responsible for describing the reaction. So, the FERMO concept might remove the limitations of the HOMO–LUMO argument, employing a small dose of chemical intuition. For instance, the principle of hardness and enervation of Pearson

Table 5. (%) MO Contribution of the Typical Trajectories for Reaction D

molecular orbital	% APAS contribution							
	4-regioisomer				5-regioisomer			
	0 fs	10 fs	30 fs	45 fs	0 fs	10 fs	30 fs	45 fs
HOMO	40.13	60.41	55.05	63.23	57.22	58.16	59.17	73.84
HOMO − 1	55.28	47.23	24.61	19.93	63.82	67.11	35.70	0.18
HOMO − 2	0.02	0.25	0.26	9.18	0.15	3.55	0.40	14.79
HOMO − 3	0.14	0.26	0.44	0.95	0.02	0.06	0.90	0.73
HOMO − 4	51.58	39.84	46.94	32.21	41.23	34.95	55.07	26.35

may also invoke the FERMO concept. The hardness of a molecule is defined as the difference in energy between HOMO and LUMO; thus, according to that definition, only a single value of hardness would exist for a given molecule. Our results clearly reveal the fundamental relationships between the nature of chemical bonding and the thermodynamic parameters for the 1,3-dipolar cycloadditions.

4. CONCLUSIONS

Overall, the FERMO concept has been successfully applied to describe the reactions via 1,3-dipolar cycloaddition. Thus, the composition of a molecular orbital is an important indicator to find the orbital suitable for all reactions. The idea of FERMO is an innovative concept and was recently identified as promising in the study of the importance of molecular orbitals for chemistry. The FERMO concept is intuitive and is based on simple calculations, emerging as a tool that attempts to describe the breaking or forming of chemical bonds. Thus, this concept can be understood as a complement to the HOMO–LUMO argument.

The molecular dynamics directly reinforces the idea of the FERMO concept, and leads us to new perspectives on the role of frontier orbitals. Our data suggest that the main MO responsible for the chemical bond formation might increase its energy along the reaction pathway.

Many molecules have several reactive sites, and the HOMO–LUMO energy difference is not enough to describe the chemical reactivity or regioselectivity. Our results clearly reveal the fundamental relationships between the nature of chemical bonding and the specific contributions of an MO named FERMO. Nevertheless, further and still more accurate theoretical calculations in order to confirm this hypothesis for other systems are now in progress.

■ ASSOCIATED CONTENT

S Supporting Information. Cartesian coordinates, MO energies, and MO energy orders for all of the compounds used in this work at all calculation levels used. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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