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MEDT Study of the Mechanism and Regioselectivity of Diazocompounds and Alkenes in [3+2] Cycloaddition Reaction

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Abstract

The mechanism and regioselectivity of diazomethane with 2-methyl-but-2-ene and (diazomethylene)dibenzene with Methylene-trifluoromethyl-phosphane in [3+2] cycloaddition, have been theoretically studied at the DFT/ B3LYP/6-31(d) computational level. The possible ortho/meta regioselective channels were explored and characterized, the energies analysis associated with the different reaction pathways and the analysis of the density map of the transition indicates that the 1,3-DC reaction of diazomethane with 2-methyl-but-2-ene and (diazomethylene)dibenzene with Methylene-trifluoromethyl-phosphane are highly regioselective, in good agreement with the experimental observations.

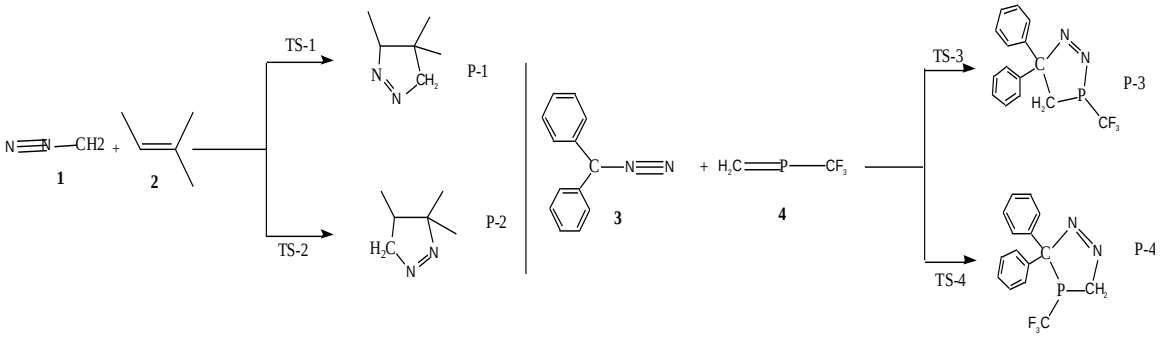
Keywords: Molecular Electron Density Theory, chemoselective, regioselective, [3+2] cycloaddition, the potential electrostatic.

1. Introduction

The reaction of a 1,3-dipole to an double bond is a classic reaction in organic chemistry for the synthesis of five-membered rings. The [2+3] dipolar cycloaddition reactions are used for the preparation of molecules of importance for both biology and industry. These reactions are also used for the synthesis of natural products such as sugar derivatives, l-lactams, amino acids, alkaloids, and pharmacological products such as pyrazolines having several biological activities (anti-inflammatory, analgesic and herbicides) (El Sayed et al., 2012; Khode et al., 2009). Among the products prepared from the cycloaddition reactions are pyrazolines which possess important pharmacological and biological activities such as: antiviral (Rollas, S., Küçükgüzel, Ş. G., 2007), antimicrobial (Sahu et al., 2008; Samshuddin et al., 2012), anticancer (Bansal, Y., Silakari, O., 2012), antitumor (Chauhan et al., 2011) and these products as good derivatives as corrosion inhibitors for mild steel in hydrochloric acid medium (addouri et al., 2009; Cherrak et al., 2017). In 2008 a distortion/interaction (Osuna, Houk 2009; Ess, Houk, 2009) was introduce by Houk (Ess, Houk 2008) to explain the reactivity, this model is analogous of that proposed by Bicklehaupt in 1999 (Bickelhaupt 2014; Fernández, Bickelhaupt 2014). Houk found that the activation enthalpies correlated very nicely with distortion energies. The partition of the total density of the

TS geometry into two separated structure does not any physical sense within density functional DFT (Hohenberg, Kohn, 2014). Consequently, the energy of two Reagents cannot be correlated with the energy of TS because each of them losses the external potential created by the other Reagents. The changes in the electron density and not molecular orbital interaction are responsible for the reactivity in organic molecules (Domingo, 2014). Very recently Domingo proposed a new theory to study the reactivity in organic chemistry named Molecular Electron Density Theory (MEDT) (Domingo et al., 2016; Ríos-Gutiérrez et al., 2015).

Herein, in order to understand the molecular mechanism and the regioselectivity of the [2+3] dipolar cycloaddition reaction between diazomethane and alkenes 1-2 (scheme 1), a theoretical characterization of the molecular mechanism of these [2+3] dipolar cycloaddition reactions is carried out within the MEDT using DFT methods at the B3LYP/6-31G(d) computational level.



Scheme 1. Competitive regio-isomeric pathways associated with [2+3] cycloaddition reactions of the diazomethane (1) with 2-methyl-but-2-ene (2) and (diazomethylene)dibenzene (3) with Methylene-trifluoromethyl-phosphane (4).

2. Computational methods

DFT computations were carried out using the B3LYP functional (Yanai et al., 2004), together with the standard 6-31(d) basis set (Yanai et al., 1982). The optimizations have been realized using the Berny analytical gradient optimization method. All computations have been shown with the Gaussian 09 suite of programs (Frisch et al., 2009). The global electrophilicity index (Parr et al., 2009) ω, was given by the following expression $\omega = \frac{\mu^2}{2\eta}$, in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities could be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L as $\mu = \frac{\varepsilon_H + \varepsilon_L}{2}$ and $\eta = \varepsilon_H - \varepsilon_L$, respectively. The empirical nucleophilicity index N (Domingo et al., 2008; Domingo, Pérez, 2011), based on the HOMO energies obtained within the Kohn-Sham (Kohn, Sham, 1965), and defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. the nucleophilicity was referred to tetracyanoethylene (TCE). This choise allowed us to handle conveniently a nucleophilicity scale of positive values. Electrophylic P_k^+ and nucleophilic P_k^- Par functions were obtained through analysis of the Mulliken atomic spin density (ASD) of the radical anion and radical cation of the reagents. The local electrophilicity and the local nucleophilicity indices were evaluated using the following expressions $\omega_k = \omega P_k^+$ and $N_k = NP_k^-$ (Zeroual et al., 2015; El Idrissi et al., 2016; Zeroual et al., 2015; Ourhriss et al., 2017; Zoubir et al., 2017; Zeroual et al., 2015). The stationary points were characterized by frequency computations in order to verify that TSs have one and only one imaginary frequency. Intrinsic reaction coordinate (IRC) (Fukui, 1970) pathways were traced to verify the connectivity between minima and associated TSs. Solvent effets of dichloromethane were taken into account through single point energy calculation using the polarizable continuum model (PCM) developed by Tomasi's group in the framework of the self-consistent reaction field (Tomasi, Persico, 1994).

3. Results and discussion

This theoretical study has been divided into three parts: (1) first, an analysis of the DFT reactivity indices of the reagents involved in these cycloaddition reactions; (2) then, a PES study of the reactions involved in these cycloaddition reactions are discussed and characterized; (3) finally, an analysis of the transition state structures are analyzed.

3.1. DFT analysis based on the global and local reactivity indexes

In order to understand the mechanism of the cycloaddition reactions studied, we used DFT B3LYP/6-31G (d) to calculate the global indices shown in Table 1 the electronic chemical potential μ, chemical hardness η, global electrophilicity ω and nucleophilicity N of the diazomethane (1), 2-methyl-but-2-ene (2), (diazomethylene)dibenzene (3) and Methylene-trifluoromethyl-phosphane (4).

Table 1. Electronic chemical potential μ, chemical hardness η, electrophilicity ω and nucleophilicity N calculated using DFT B3LYP/6-31G (d) (eV)

System	μ	η	w	N
1	-3.64	4.72	1.40	3.52
2	-2.55	7.17	0.43	3.39
3	-3.35	3.70	1.52	4.32
4	-5.00	5.72	2.18	1.66

The electronic chemical potential of 2-methyl-but-2-ene 2, μ = −2.55 eV, is higher than that of diazomethane 1, μ = −3.64 eV, thereby indicating that along a polar reaction the global electron density transfer (GEDT) will go from 2-methyl-but-2-ene 2 towards diazomethane 1. In the reaction 2 the electronic chemical potential of the (diazomethylene)dibenzene (3), μ = −3.35 eV, is higher than that of methylene-trifluoromethyl-phosphane (4), μ = −5.00 eV, thereby indicating that along a polar reaction the GEDT will go from (diazomethylene)dibenzene (3) to methylene-trifluoromethyl-phosphane (4).

The diazomethane (1) presents an electrophilicy ω index of 1.40 eV and a nucleophilicity N index of 3.52 eV, being classified as strong electrophile than ω index of the 2-methyl-but-2-ene (2), 0.43 eV and a nucleophilicity N index of 3.39 eV. Consequently, the diazomethane 1 is classified as a strong electrophile, while the -methyl-but-2-ene (2) a strong nucleophile. On the other hand, the electrophilicity ω and nucleophilicity N indices of the (diazomethylene)dibenzene (3) are 1.52 and 4.32 eV, being classified on the borderline of marginal electrophiles and as a strong nucleophile. Inclusion of one florine atom of the carbon atom of (diazomethylene)dibenzene (3) notably increases both the electrophilicity ω and nucleophilicity N index of trifluoromethyl-phosphane (4) to 2.18 and 1.66 eV, being classified as a moderate nucleophile and a strong electrophile. Consequently, the trifluoromethyl-phosphane (4) will participate as electrophile and the (diazomethylene)dibenzene (3) will participate as nucleophile.

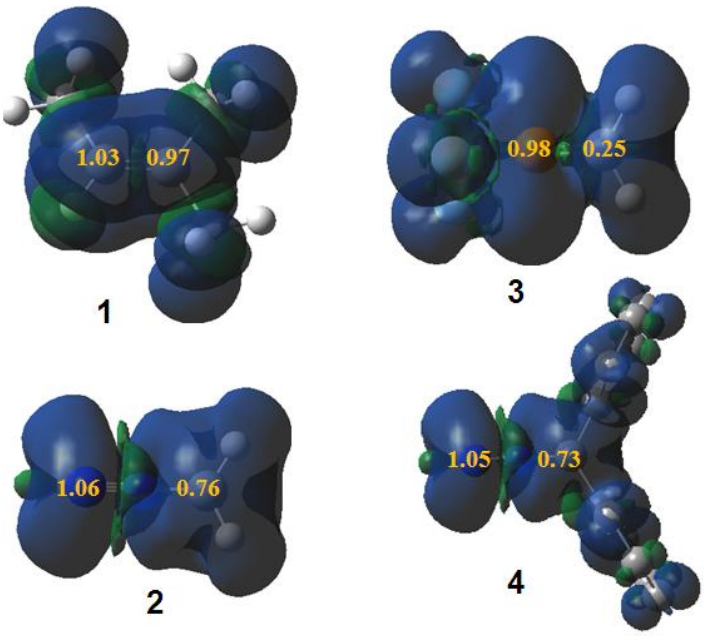


Fig. 1. Map of the ASD of the neutral radical Po of the diazomethane (1), 2-methyl-but-2-ene (2), (diazomethylene)dibenzene (3) and Methylene-trifluoromethyl-phosphane (4).

The deference between an electrophilicy of the reagents is smaller than one indicating that these reactions are not polar reactions the fact that we use atomic spin density of the neutral radical P0, from Figure 2 we can observed that P0 of the carbon atom C3 is 1.03 and C2 is 0.97, for the diazomethane P0 of the nitrogen atom strong is 1.06 and for the carbon atom is 0.76, this result indicating that the best interaction will be between C3 and N1 and C2 with carbon of diazomethane in good agreement with experimental observations.

3.2 Energies study

Due to the non-symmetry of both reagents, [2+3] cycloaddition reactions of the diazomethane (1) with 2-methyl-but-2-ene (2) and (diazomethylene)dibenzene (3) with Methylene-trifluoromethyl-phosphane (4) can take place through two competitive reactive channels namely meta and ortho (scheme 1) and to interpret the regioselectivity experimentally observed in these reactions, the energies and relative energies were calculated and summarized in table 2, PES of the reaction was calculated by B3LYP/6-31G(d) method. Intrinsic Reaction Coordinate (IRC) calculations were performed to characterize the transition states on the PES (Figure 2).

Table 2. B3LYP/6-31G (d) energies E (in a.u.) and relative energies (ΔE, in kcal/mol) of the reagents, transition states and products.

System	E	ΔE
1+2	-345.28284	-------
TS1	-345.24892	21.28
TS 2	-345.24605	23.08
P 1	-345.33060	-29.97
P 2	-345.32837	-28.57
3+4	-1329.10559	---------
TS3	-1329.05759	30.12
TS 4	-1329.05579	31.25
P 3	-1329.14676	-25.83
P4	-1329.14086	-22.13

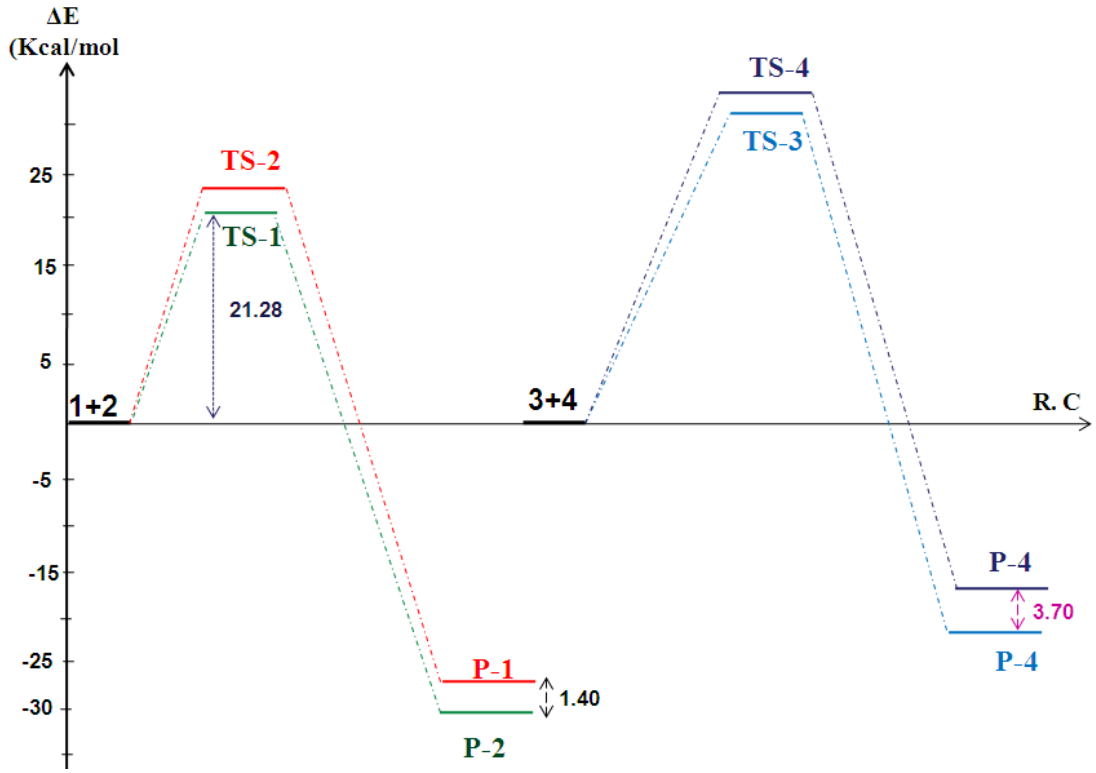


Fig. 2. Pathways for [2+3] cycloaddition reactions of the diazomethane (1) with 2-methyl-but-2-ene (2) and (diazomethylene)dibenzene (3) with methylene-trifluoromethyl-phosphane (4)

The activation energies of reactions of the diazomethane (1) with 2-methyl-but-2-ene (2) and (diazomethylene)dibenzene (3) with methylene-trifluoromethyl-phosphane (4) associated with the two competitive reactive channels are 21.28 (TS-1m), 23.08 (TS-1o), 30.12 (TS-2m) and 31.25 (TS-2o) kcal mol−1 these value indicate that the most favorable channel is meta. In these 32CA reaction, the formation of the products 1-m and 2-m are strongly exothermic by 29.97 and 25.83 kcal mol−1 respectively, the formation of the products 1-o and 2-o are exothermic by 28.57 and 22.13 respectively. Analysis of these relative energies leads to some appealing conclusions: (1) this 32CA reaction the formation of the 1-m and 2-m are kinetically favored (2) the strong exothermic character of this 32CA reaction makes the formation of the products 1m, 1o, 2m and 2o are irreversible Consequently, formation of the product 1m and 2-m are under kinetic and thermodynamic control, These results are in agreement with the meta regioselectivity experimentally observed.

3.3. Geometries study

The geometries of the TSs involved in the two competitive reaction channels are given in Fig. 3. At the meta TSs, the lengths of the N1–C3 and C2–C forming bonds are 1.978 and 2.401 Å (TS-1) and , the lengths of the P–N1 and C–C forming bonds are 2.260 and 2.133 Å (TS-3), while at the ortho TSs, the lengths of the C3–C and C2–N1 forming bonds are 2.231 and 2.113Å (TS-2), the lengths of the P–C and N1–C forming bonds are 2.826 and 2.517 Å (TS-4). Some appealing conclusions can be drawn from these geometrical parameters: (1) the TSs associated with the meta channels are more asynchronous than those associated with the ortho one. On other hand the density map of the transition of the transition state indicating that the formation of the products 2-o and 2-o not favored, because the density map are separate, in contrary in TS-1o and TS-2o the density map not separate which indicates that formation of the products 1-m and 2-m are favored.

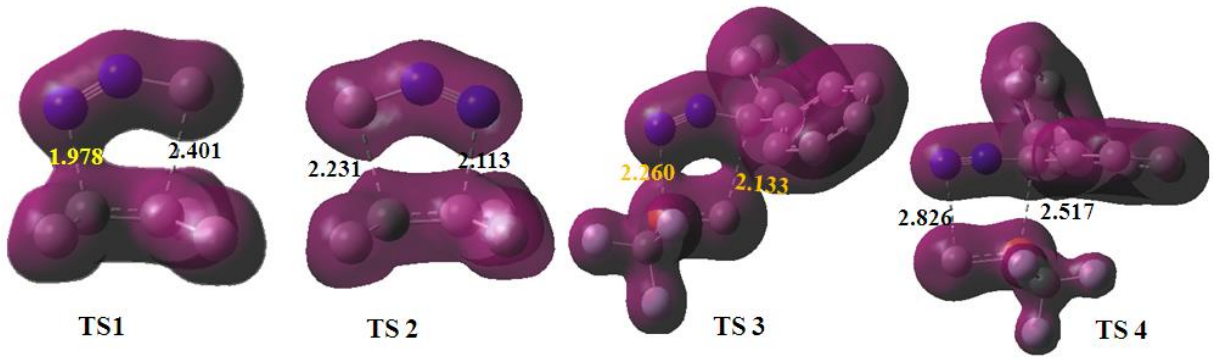


Fig. 3. DFT/6-31G(d) optimized density map and structures of the TSs of the [2+3] cycloaddition reactions of the diazomethane (1) with 2-methyl-but-2-ene (2) and (diazomethylene)dibenzene (3) with methylene-trifluoromethyl-phosphane (4). Lengths are given in Angstroms.

4. Conclusion

The mechanism and the regioselectivity of the [2+3] cycloaddition reactions of the diazomethane (1) with 2-methyl-but-2-ene (2) and (diazomethylene)dibenzene (3) with methylene-trifluoromethyl-phosphane (4) were studied using DFT B3LYP/6-31G (d).

The theoretical results obtained enabled us to conclude that:

the formation of the products 2-o and 2-o not favored, because the density map are separate, in contrary in TS-1o and TS-2o the density map not separate which indicates that formation of the products 1-m and 2-m are favored.

The formation of the product 1m and 2-m are under kinetic and thermodynamic control, in agreement with the meta regioselectivity experimentally observed.

Map of the ASD of the neutral radical P0 of the reagents, indicating that the best interaction will be between C3 and N1 and C2 with carbon of diazomethane in good agreement with experimental observations.

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