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Toward Metal- and Catalyst-free Reactions: Deciphering the substituent and external electric field effects on the Diels-Alder reaction between Ethylene and Nitrosoethylene

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Abstract
The substituents on the diene and/or dienophile can contribute to the decrease or increase of this energy. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis. The existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy. So, the goal of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field, Lewis acid (BH3) as catalysts and the influence of substituents. All calculations were performed with Gaussian09 software, the compounds were fully optimized using the restricted Hartree-Fock method with the basis set 6-31G, single-point energies determined with MP3 method and basis set 6-31G. The effects of EEFs were studied using the ?Field = M ± N? keyword with F values (F=±0,125 au and ±0,080 au) along the preferred axis. The lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.
Keywords
Electric field catalysis, external electric fields, Lewis acid, Diels-Alder reaction, FERMO.

1 Introduction

According to the Lewis definition, acids are molecules or ions capable of coordinating with unshared electron pairs, and bases are molecules or ions with unshared electron pairs available to share with acids [1]?. To be acidic in the Lewis sense, a molecule must be deficient in electrons. This is the most general acid-base concept. All Lowry-Brönsted acids are also Lewis acids, but in addition, the Lewis definition includes many other reagents, such as boron trifluoride, aluminum chloride, among others [2].
Lewis acids catalyze Diels-Alder reactions. Some examples of these acids are: SnCl4, ZnCl2, BH3 or AlCl3 ,, which can accelerate cycloaddition reactions [3, 4]?, as occurs in the reaction catalyzed by AlCl3 of cycloalkenones with 1,3-butadienes [5, 6]. The effect of substituents in the components of the Diels-Alder reaction affect it according to the Frontier Molecular Orbital (FMO) theory, in which the reactivity, regiochemistry and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial phase interaction of the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other [7]?.
The separation between the HOMO-LUMO components controls the reactivity of the Diels-Alder reaction: the smaller the energy difference between these two orbitals, the smaller the difference in activation energy between the transition state and the reaction reactants [8?11]. The substituents on the diene and/or dienophile can contribute to decrease or increase this energy. Electron-withdrawing substituents decrease the energy of LUMO and increase of HOMO, while electron-donor groups increase the energy of LUMO and decrease of HOMO [7]??. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis [12?14].
Chemical reactions can be described by the movement of electrons as well as the movement of nuclei. Thinking about it, we can understand that they can then be influenced by external electric fieldsWhether the reaction is redox or not, some theoretical studies [12, 13, 15, 16]?? the stability of molecules involved in the reaction can be influenced by electrostatic effects: stabilizing or destabilizing resonance contributors separated by charge [13]?. This fact was announced some time ago by Shaik and collaborators for the Diels-Alder reaction [16] and in another work for simple reactions of halogen and hydrogen transfer by Bertrán and collaborators [17, 18]?. Thus, there is a great interest in metal-free catalysis and specifically in catalysis by hydrogen bonding models [19].
In this scenario, the existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy [12, 20?22]?. Meir et al (2010) explored by theoretical means the effect of targeted EEFs on the rate, mechanism and endo/exo selectivity of DA reactions between butadiene and ethylene and cyclopentadiene and maleic anhydride. According to the authors, it is necessary then that the electric field is aligned in order to attenuate or strengthen the dipole along the reaction axis [13, 23].
Theoretical predictions were confirmed experimentally in 2016 by means of intermittent tunneling scanning microscopy (STM) experiments [12]?. In summary, the experiment was carried out as follows: the diene and the dienophile were "attached" to the tip and plate of the STM, respectively, restricting their orientation , providing a means of controlling the stimulus of the electric field and measuring its effect on the reaction rate [23]?. They obtained as results that, in the tested range of field forces, the reaction rate was independent of the positive polarity of the field, but it was catalyzed by increasing the intensity of the field to negative polarization. Parallel quantum-chemical calculations of the same system under experimental conditions, which confirmed that these results were due to the effect of the field on the reaction barriers [23]?. Therefore, external electric fields instead of charged chemical species such as the ?catalyst?, can manipulate a much wider range of reactions, conveniently altering reactivity and selectivity in a tunable way

that can be predicted by theory [13].
As electrostatic catalysis is the least developed form of catalysis in synthetic chemistry [12]?, the aim of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field and a Lewis acid as catalysts, in addition to checking the influence of substituents on the reaction?s diene and dienophile, in order to determine if the electric field is the best catalyst for the reaction studied.

2 Methodology
Gaussian09 software was used for all calculations [24]. The optimization calculation for all compounds was performed with restricted Hartree-Fock method with the basis set 6-31G(d). No imaginary frequencies were found for the optimized reactants geometries, which were used in all subsequent calculations and had their single-point energies determined with MP3 method and the basis set 6-31G(d). GAMESS software for Linux, version 30 SEPT 2017 (R2) and MOLPROJ software, were used to analyze their MO eigenvectors and overlapping matrices of the reaction between ethylene and nitrosoethylene, both extracted from output files of single-point energy calculations with GAMESS.
The effects of EEFs were studied using the ?Field = M ± N? keyword, which defines in Gaussian09, the axis of the EEFs, its direction along that axis, and its magnitude. For each reaction, we initially evaluated the EEF effects at different Fx,y,z values, using single-point calculations on the critical species with F values (F=±0,125 au and ±0,080 au) along the preferred axis.
In opposition to the conventional definition in Physics, in Gaussian09, the positive direction of the electric field vector is defined from negative to positive charge [14]. Thus, whenever the dipole moment (?) and field vectors (F) are oriented opposite to each other, the EEF?s will stabilize the dipole, as shown in Scheme 1 for an X-EEF. The EEFs were further oriented along the X, Y and Z axes as defined in Scheme 1, where in each case the X axis defines the "reaction axis", which is approximately the direction along which two new C? C bonds are forming [13, 14, 25].

Scheme 1: Definitions of the x, y and z directions.

Figure 1: Reactants (A) nitrosoethylene and ethylene, (B) nitrosoethylene with borane connected to oxygen and ethylene and (C) nitrosoethylene with borane connected to nitrogen and ethylene.
The optimized compounds, as shown in Figure 1, were analyzed using the MOLPROJ software [26, 27]. The eigenvectors of the MOs and the matrices of were extracted from output files of single point energy calculations with GAMESS. The degree of location of each MO (2px-z orbitals of the carbon and oxygen atoms involved in the DA reaction) and their respective energies were calculated and analyzed. [28]. For comparison, degree of localization coefficients were calculated for the molecular orbitals ?HOMO and ?FERMO. We define that the degree of localization ?FERMO is the norm of an MO projected on the expected set of atomic orbitals (that participate in the reaction), as follows in Equation 1, where ?, is the matrix of molecular orbital coefficients and ? is the overlap matrix:

Equation 1: degree of localization ?FERMO
3 Results
3.1 Validation of the theoretical strategy: The Reaction of Ethylene and Nitrosoethylene - Catalysis of a Diels-Alder reaction using a Lewis acid.

The synthetic versatility of cycloaddition reactions was extended by introducing heterodienes, which allowed rapid access to various heterocycles. Nitrosoethylene compounds lead to valuable heterocyclic compounds with an N-O bond in the cycle. However, the reactivity of these compounds strongly depends on their structure and a catalyst. This is because nitrosoethylenes are generally unstable and are generated by base promoted elimination of -haloximes. Jursic and Zdravkovski, in 1995 [29], showed in a study the difference in the activation barrier when BH3 is used as a catalyst. According to literature, the activation barrier decreased by 2.08 kcal.mol-1 when borane is linked to nitrosoethylene nitrogen.
These same authors [29] used the reaction between ethylene and butadiene to compare the reliability of the results obtained computationally from the reaction between ethylene and nitrosoethylene with the experimental values of the first reaction. The activation energy for the ethylene and butadiene reaction was 25.98 kcal.mol-1 using MP3/6-31G(d), a value which is in reasonable agreement with the experimental value (25.4 and 27.5 kcal.mol-1) [30]. As our values were obtained with a difference of approximately 0.03 kcal.mol-1 in the activation barrier values of the base article, we consider that our results are also close to the experimental values, since there are no experimental studies of the reaction between ethylene and nitrosoethylene in literature.
Given the importance and versatility of this cycloaddition reaction, we sought validation (Table 1) of the author's results to compare them when we apply the electric field and use substituents as a catalyst. Figure 2 illustrates the energy profile for the reaction without and with the use of borane (bonded to oxygen and nitrogen atoms) as catalyst.
Table 1: Activation barrier of Lewis acid to trans reaction.

Figure 2: difference in the energy of the activation barrier without catalyst and with the catalyst borane bound to the oxygen atom and to the nitrogen atom.
As can be seen in Table 1, the lowest activation barrier found was for borane bound to nitrosethylene nitrogen. The borane-catalyzed reaction has a lower activation barrier than the uncatalyzed reaction [29]. Boron reagents are often employed as Lewis acids due to their strong electrophilic nature because of a vacant p orbital that can readily accept electrons from donor molecules [31]. So, as BH3 is acting as an electron acceptor, the reaction in question occurs with reverse electron demand. Therefore, borane as a catalyst has a profound influence on the reactivity of the system, decreasing the electron density in the diene and decreasing its LUMO energy.
Note that the values of the calculated activation barriers differ slightly from this current work [29]. This minimal difference in ?E# occurred because the coordinates of the structures were not made available by the researchers. Therefore, the difference in bond lengths in the optimization had a minimal influence on the activation barriers.

3.2 Effect of the substituents to check if the reaction rate becomes even lower when they are related to some type of catalyst
According to Frontier Molecular Orbital (FMO) theory, the reactivity, regiochemistry, and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial in-phase interaction of the HOMO molecular orbital of one component and the LUMO orbital of the other [7]. When the HOMO of the diene controls the reaction, the reaction can be accelerated by electron-donating substituents on the diene and by electron-withdrawing substituents on the dienophile, thus being a normal electron-demand Diels-Alder reaction. On the other hand, the Diels-Alder reactions controlled by the LUMO of the diene are influenced by the

electronic effects of the substituents in the opposite way, that is, it is a Diels-Alder reaction with inverse electron demand.
The influence were studied by considering the following substituents: CH3, Cl and F. Considering the reaction as a normal demand for electrons, the interactions occur from the HOMO/FERMO of the dienophile to the LUMO of the diene, as can be seen in Figure 3A. Table 2 shows the activation barrier values when we replace a diene hydrogen with X = methyl and a dienophile hydrogen with a halogen (Y = Cl and F).

Figure 3: reaction scheme for the Diels-Alder reaction between ethylene and substituted nitrosoehtylene. (A) structures of reactants (left), transition state (middle) and products (right); (B) molecular orbitals involved in the reaction; (C) numbering of the atoms involved in Diels-Alder reaction.
Table 2: activation barrier values when we replace a diene hydrogen with methyl and a dienophile hydrogen with a halogen (Cl and F).

As it can be seen, the substituents did not accelerate the reaction. According to Jursic and Zdravkovski [29], the reaction between ethylene and nitrosoethylene is an inverse demand reaction. Therefore, as we are treating it as a normal electron demand reaction, it is to be expected that the activation barrier will increase in value. This increase was approximately 3.02 kcalmol-1 in relation to the reaction without any type of catalyst (20.3624 kcal.mol-1).

3.3 Effect of the electric field in the reaction between ethylene and nitrosoethylene
Table 3 shows the EEF effects on the barriers for fields oriented along the x-, y- and z-axes in positive and negative directions. It is seen that Fy and Fz do not change the barrier, which remains constant at ~18.3(±2 .8) kcalmol-1. This is because the y,z-oriented EEFs stabilize both the reactant (R?) and the transition state (TS) to the same extent. However, when the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst.

Table 3: values of activation barrier (?E#) with electric field applied in x-, y- and z-axes for two magnitude values of electric field.

As the field becomes more negative, the dipole moment becomes more positive. This change in dipole moment is accompanied by transferring charge between the reactants in the TS. As the value of Fx increases, the direction of charge transfer is reversed. Thus, the EEF not only reduces the energy of the TS , but also polarizes the TS and affects its electronic structure. In addition, the field also induces a charge transfer in its own direction, from nitrosoethylene to ethylene. In conclusion, it is apparent that when the electric field is oriented along the ?reaction axis?, which is the axis along which the two new C-C bonds are formed, it causes the reaction rate to accelerate by preferentially decreasing the transition state.
An EEF oriented in the direction of the ?reaction axis?, along which electronic reorganization takes place, can affect the reaction rate by orders of magnitude, becoming faster or slower, depending on the change in direction of the field. At the same time, the endo/exo stereoselectivity of the Diels-Alder reaction can be manipulated at will with EEFs oriented perpendicular to the reaction axis [13]. EEF changes distribution of

the electron density. Figure 4 show the molecular orbitals involved in the reaction with/without EEFs. Application of EEFs induce the polarizability of electrons, atoms and dipoles, resulting in an eventual reorientation of the molecules along the applied electric field of the molecules and the electron density redistribution at particular atoms [32]. As a general rule, one can module that two orbitals or states, which cannot mix by symmetry in the absence of a field, will do so when an EEF is applied along the axis that possesses the same symmetry as the direct product of the two orbitals/states [33].
We used the FERMO concept [26] to understand how the electric field acted on the molecular orbitals of the studied reaction. This concept is based on simultaneous analysis of composition and shapes of frontier molecular orbitals to determine the real molecular orbital governing a reaction. According to this approach, a frontier molecular orbital may even correspond to the FERMO for a given reaction and not for another. The HOMO itself would only be the orbital that rules a reaction if it fulfills the requirements to be the FERMO [34].
A strategy to quantify the location of the FERMO was developed, leading to the construction of the MOLPROJ software, based on the use of projection operators to build the molecular orbitals (MOs) by linear combination of atomic orbitals (AOs; the LCAO approach). Thus, the location of the FERMO would indicate the orbital in which the reaction occurs and, consequently, would point to the most favorable location for protonation [26, 28].
The values in Table 4 to four atoms involved in the Diels-Alder reaction (carbons: C2, C8, C9 and O, as shown in the Figure 3C) exhibit the energy and degree of localization from FERMO to HOMO. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms [26]. External electric fields oriented along the bond axis in a molecule induce significant ionicity, as well as changes in bond lengths, elongation frequencies and electronic characteristics. EEFs cause orbitals, whose mixing was prohibited in the absence of the field, to mix when the symmetry of their product is compatible with the symmetry of the applied field. As the product of the reaction has the same symmetry as an applied field along the bond axis, these two MOs will mix and hybridize, acquiring greater contributions in both the left and right atoms, leading to the development of the energetically stabilized dipole moment by the applied field [35].

Figure 4: TS between ethylene and nitrosoethylene. A) HOMO of TS without EEF; B) HOMO of TS with EEF; C) LUMO of TS without EEF; and D) LUMO of TS with EEF.

Table 4: Results for the degree of localization of MOs from TS between ethylene and nitrosoethylene.

Table 5: Values of activation barrier (?E#) with an external electric field applied in x-, y- and z-axes for two electric field magnitudes for substituents CH3/Cl and CH3/F.

As it can be seen in Table 5, only the substituent effect does not show a decrease in activation barriers, the value was 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcal.mol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. According to Jursic and Zdravkovski [29], the reaction between nitrosoethylene and ethylene, when catalyzed with borane, is a Diels-Alder reaction with inverse electron demand. Therefore, when we introduced electron donor groups in the diene, we would find a higher value in the activation barrier, as it can be seen in the tables. When we added the electric field, we were able to lower

this activation barrier. We realize that in fact the electric field acted as a catalyst.
Figure 5 shows the effect of the main catalysts on the activation barrier of the reaction between ethylene and nitrosoethylene. As can be seen, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Figure 5: Difference in the energy of the activation barrier without BH3, with the borane bonding in nitrogen and reaction with EEF.

Conclusion
In this study, the DA reaction between ethylene and nitrosoethylene with/without BH3, electric field and substituted dienophiles was studied theoretically using RHF and MP3 calculations aimed to determine which was the best catalyst to reaction. When the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst. We used the FERMO concept to understand how the electric field acted on the molecular orbitals of the studied reaction. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms. Only the substituent effect does not show a decrease in activation barriers. The values were 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcalmol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. Therefore, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Referências
1. Houk KN, Strozier RW (1973) On Lewis Acid Catalysis of Diels-Alder Reactions. J Am Chem Soc 95:4094?4096. https://doi.org/10.1021/ja00793a070
2. García JI, Martínez-Merino V, Mayoral JA, Salvatella L (1998) Density functional theory study of a Lewis acid catalyzed Diels-Alder reaction. The butadiene + acrolein paradigm. J Am Chem Soc 120:2415?2420. https://doi.org/10.1021/ja9722279
3. Domingo LR (2002) A density functional theory study for the Diels-Alder reaction between N-acyl-1-aza-1,3-butadienes and vinylamines. Lewis acid catalyst and solvent effects. Tetrahedron 58:3765?3774. https://doi.org/10.1016/S0040-4020(02)00326-5
4. Kang J, Rebek J (1997) Acceleration of a Diels-Alder reaction by a self-assembled molecular capsule. Nature 385:50?52. https://doi.org/10.1038/385050a0
5. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
6. Gatzenmeier T, Van Gemmeren M, Xie Y, et al (2016) Asymmetric Lewis acid organocatalysis of the Diels-Alder reaction by a silylated C-H acid. Science (80-) 351:949?952. https://doi.org/10.1126/science.aae0010
7. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
8. Dyan OT, Andreev R V., Zaikin PA (2021) Substituents effects in the Diels-Alder reaction of 1,1-difluoronaphthalen-2(1H)-ones with cyclopentadiene. J Fluor Chem 250:109859. https://doi.org/10.1016/j.jfluchem.2021.109859
9. Gara R, Zouaghi MO, ALshandoudi LMH, Arfaoui Y (2021) DFT investigation of solvent, substituent, and

catalysis effects on the intramolecular Diels-Alder reaction. J Mol Model 27:. https://doi.org/10.1007/s00894-021-04729-w
10. Hernández-Mancera JP, Rojas-Valencia N, Núñez-Zarur F (2022) Rationalizing the Substituent Effects in Diels-Alder Reactions of Triazolinediones with Anthracene. J Phys Chem A 126:6657?6667. https://doi.org/10.1021/ACS.JPCA.2C04970/SUPPL_FILE/JP2C04970_SI_001.PDF
11. Khan TS, Gupta S, Ahmad M, et al (2020) Effect of substituents and promoters on the Diels-Alder cycloaddition reaction in the biorenewable synthesis of trimellitic acid. RSC Adv 10:30656?30670. https://doi.org/10.1039/d0ra04318d
12. Aragonès AC, Haworth NL, Darwish N, et al (2016) Electrostatic catalysis of a Diels-Alder reaction. Nature 531:88?91. https://doi.org/10.1038/nature16989
13. Meir R, Chen H, Lai W, Shaik S (2010) Oriented electric fields accelerate diels-alder reactions and control the endo/exo selectivity. ChemPhysChem 11:301?310. https://doi.org/10.1002/cphc.200900848
14. Wang Z, Danovich D, Ramanan R, Shaik S (2018) Oriented-External Electric Fields Create Absolute Enantioselectivity in Diels-Alder Reactions: Importance of the Molecular Dipole Moment. J Am Chem Soc 140:13350?13359. https://doi.org/10.1021/jacs.8b08233
15. Gryn?ova G, Coote ML (2013) Origin and scope of long-range stabilizing interactions and associated SOMO-HOMO conversion in distonic radical anions. J Am Chem Soc 135:15392?15403. https://doi.org/10.1021/ja404279f
16. Shaik S, De Visser SP, Kumar D (2004) External electric field will control the selectivity of enzymatic-like bond activations. J Am Chem Soc 126:11746?11749. https://doi.org/10.1021/ja047432k
17. Andrés JL, Lledós A, Duran M, Bertrán J (1988) Electric fields acting as catalysts in chemical reactions. An ab initio study of the walden inversion reaction. Chem Phys Lett 153:82?86. https://doi.org/10.1016/0009-2614(88)80136-2
18. Carbonell E, Duran M, Lledós A, Bertrán J (1991) Catalysis of Friedel-Crafts reactions by electric fields. J Phys Chem 95:179?183. https://doi.org/10.1021/j100154a036
19. Huang X, Tang C, Li J, et al (2019) Electric field?induced selective catalysis of single-molecule reaction. Sci Adv 5:eaaw3072. https://doi.org/10.1126/sciadv.aaw3072
20. Léonard NG, Dhaoui R, Chantarojsiri T, Yang JY (2021) Electric Fields in Catalysis: From Enzymes to Molecular Catalysts. ACS Catal 11:10923?10932. https://doi.org/10.1021/acscatal.1c02084
21. Dubey KD, Stuyver T, Shaik S (2022) Local Electric Fields: From Enzyme Catalysis to Synthetic Catalyst Design. J Phys Chem B. https://doi.org/10.1021/ACS.JPCB.2C06422
22. Shaik S, Danovich D, Joy J, et al (2020) Electric-Field Mediated Chemistry: Uncovering and Exploiting the Potential of (Oriented) Electric Fields to Exert Chemical Catalysis and Reaction Control. J. Am. Chem. Soc. 142:12551?12562
23. Aitken HM, Coote ML (2018) Can electrostatic catalysis of Diels-Alder reactions be harnessed with pH-switchable charged functional groups? Phys Chem Chem Phys 20:10671?10676. https://doi.org/10.1039/c7cp07562f
24. G16_C01 (1)
25. Shaik S, Mandal D, Ramanan R (2016) Oriented electric fields as future smart reagents in chemistry. Nat Chem 8:1091?1098. https://doi.org/10.1038/nchem.2651
26. Braga LS, Moreira RA, Leal DHS, Ramalho TC (2019) Quantification of molecular orbitals based on projection operators: Methodological development and applications to basicity prediction of organic compounds in the gas phase. Chem Phys Lett 726:87?92. https://doi.org/10.1016/j.cplett.2019.04.023
27. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for

-Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:. https://doi.org/10.2174/1385272824666200204121044
28. Braga LS, Henriques Soares Leal D, Ramalho TC (2022) Rationalising the regioselectivity of substituted phenols from the FERMO concept: stereoelectronic effects on protonation and functionalization . https://doi.org/101080/0892702220222039390 48:610?620. https://doi.org /10.1080/08927022.2022.2039390
29. Jursic BS, Zdravkovski Z (1995) Theoretical Study of the BH3-Catalyzed Hetero Diels?Alder Reaction between Ethylene and Nitrosoethylene. J Org Chem 60:3163?3168. https://doi.org/10.1021/jo00115a036
30. Rowley D, Steiner H (1951) Kinetics of diene reactions at high temperatures. Discuss Faraday Soc 10:198?213. https://doi.org/10.1039/DF9511000198
31. Nori V, Pesciaioli F, Sinibaldi A, et al (2022) Boron-based lewis acid catalysis: Challenges and perspectives. Catalysts 12:. https://doi.org/10.3390/catal12010005
32. Toledo EJL, Custodio R, Ramalho TC, et al (2009) Electrical field effects on dipole moment, structure and energetic of (H2O)n (2 ? n ? 15) cluster. J Mol Struct THEOCHEM 915:170?177. https://doi.org /10.1016/j.theochem.2009.08.035
33. Mazurkiewicz J, Tomasik P (2012) Effect of external electric field upon charge distribution, energy and dipole moment of selected monosaccharide molecules. Nat Sci 04:276?285. https://doi.org/10.4236/ns .2012.45040
34. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for -Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:314?331. https://doi.org/10.2174/1385272824666200204121044
35. Stuyver T, Danovich D, Joy J, Shaik S (2020) External electric field effects on chemical structure and reactivity. Wiley Interdiscip Rev Comput Mol Sci 10:1?22. https://doi.org/10.1002/wcms.1438

Lewis Acid?E# Activation Barrier of paper [29](kcal.mol-1)MP3/6-31G(d)?E#Activation Barrier in this work (kcal.mol-1)MP3/6-31G(d)
Without BH320.344920.3624
BH3 bonding oxygen13.707813.7962
BH3 bonding nitrogen11.622311.6025

Electron-donating (X)Electron-withdrawing (Y)?E# (kcal.mol-1)MP3/6-31G(d)
CH3Cl23.3857
F23.2107

F (au)?E# (kcal.mol-1)MP3/6-31G(d)
xyz
0.08021.081118.007424.8302
-0.08017.945318.220118.3186
0.12520.981118.200018.6625
-0.1256.393818.000018.4103

Without EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.643098-140.30580.3750-181.10180.348421-225.0075

C20.158948-140.30580.2003-181.10180.550036-225.0075
C80.034416-140.30580.4971-181.10180.282893-225.0075
C90.174964-140.30580.2854-181.10180.550790-225.0075
With EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.637059-141.49040.342834-185.24800.370436-218.3439
C20.167188-141.49040.164733-185.24800.565620-218.3439
C80.042363-141.49040.505992-185.24800.214219-218.3439
C90.188071-141.49040.326526-185.24800.521364-218.3439

CH3/Cl
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08023.030622.212922.1533
-0.08022.006522.281322.2161
0.12522.750127.928225.7320
-0.12522.531722.206722.5455
CH3/F
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08022.121921.881022.1012
-0.08022.246222.976621.8747
0.12522.538022.725622.5361
-0.12521.499523.026934.5554

Toward Metal- and Catalyst-free Reactions: Deciphering the substituent and external electric field effects on the Diels-Alder reaction between Ethylene and Nitrosoethylene

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Abstract
The substituents on the diene and/or dienophile can contribute to the decrease or increase of this energy. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis. The existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy. So, the goal of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field, Lewis acid (BH3) as catalysts and the influence of substituents. All calculations were performed with Gaussian09 software, the compounds were fully optimized using the restricted Hartree-Fock method with the basis set 6-31G, single-point energies determined with MP3 method and basis set 6-31G. The effects of EEFs were studied using the ?Field = M ± N? keyword with F values (F=±0,125 au and ±0,080 au) along the preferred axis. The lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.
Keywords
Electric field catalysis, external electric fields, Lewis acid, Diels-Alder reaction, FERMO.

1 Introduction

According to the Lewis definition, acids are molecules or ions capable of coordinating with unshared electron pairs, and bases are molecules or ions with unshared electron pairs available to share with acids [1]?. To be acidic in the Lewis sense, a molecule must be deficient in electrons. This is the most general acid-base concept. All Lowry-Brönsted acids are also Lewis acids, but in addition, the Lewis definition includes many other reagents, such as boron trifluoride, aluminum chloride, among others [2].
Lewis acids catalyze Diels-Alder reactions. Some examples of these acids are: SnCl4, ZnCl2, BH3 or AlCl3 ,, which can accelerate cycloaddition reactions [3, 4]?, as occurs in the reaction catalyzed by AlCl3 of cycloalkenones with 1,3-butadienes [5, 6]. The effect of substituents in the components of the Diels-Alder reaction affect it according to the Frontier Molecular Orbital (FMO) theory, in which the reactivity, regiochemistry and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial phase interaction of the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other [7]?.
The separation between the HOMO-LUMO components controls the reactivity of the Diels-Alder reaction: the smaller the energy difference between these two orbitals, the smaller the difference in activation energy between the transition state and the reaction reactants [8?11]. The substituents on the diene and/or dienophile can contribute to decrease or increase this energy. Electron-withdrawing substituents decrease the energy of LUMO and increase of HOMO, while electron-donor groups increase the energy of LUMO and decrease of HOMO [7]??. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis [12?14].
Chemical reactions can be described by the movement of electrons as well as the movement of nuclei. Thinking about it, we can understand that they can then be influenced by external electric fieldsWhether the reaction is redox or not, some theoretical studies [12, 13, 15, 16]?? the stability of molecules involved in the reaction can be influenced by electrostatic effects: stabilizing or destabilizing resonance contributors separated by charge [13]?. This fact was announced some time ago by Shaik and collaborators for the Diels-Alder reaction [16] and in another work for simple reactions of halogen and hydrogen transfer by Bertrán and collaborators [17, 18]?. Thus, there is a great interest in metal-free catalysis and specifically in catalysis by hydrogen bonding models [19].
In this scenario, the existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy [12, 20?22]?. Meir et al (2010) explored by theoretical means the effect of targeted EEFs on the rate, mechanism and endo/exo selectivity of DA reactions between butadiene and ethylene and cyclopentadiene and maleic anhydride. According to the authors, it is necessary then that the electric field is aligned in order to attenuate or strengthen the dipole along the reaction axis [13, 23].
Theoretical predictions were confirmed experimentally in 2016 by means of intermittent tunneling scanning microscopy (STM) experiments [12]?. In summary, the experiment was carried out as follows: the diene and the dienophile were "attached" to the tip and plate of the STM, respectively, restricting their orientation , providing a means of controlling the stimulus of the electric field and measuring its effect on the reaction rate [23]?. They obtained as results that, in the tested range of field forces, the reaction rate was independent of the positive polarity of the field, but it was catalyzed by increasing the intensity of the field to negative polarization. Parallel quantum-chemical calculations of the same system under experimental conditions, which confirmed that these results were due to the effect of the field on the reaction barriers [23]?. Therefore, external electric fields instead of charged chemical species such as the ?catalyst?, can manipulate a much wider range of reactions, conveniently altering reactivity and selectivity in a tunable way

that can be predicted by theory [13].

As electrostatic catalysis is the least developed form of catalysis in synthetic chemistry [12]?, the aim of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field and a Lewis acid as catalysts, in addition to checking the influence of substituents on the reaction?s diene and dienophile, in order to determine if the electric field is the best catalyst for the reaction studied.

2 Methodology

Gaussian09 software was used for all calculations [24]. The optimization calculation for all compounds was performed with restricted Hartree-Fock method with the basis set 6-31G(d). No imaginary frequencies were found for the optimized reactants geometries, which were used in all subsequent calculations and had their single-point energies determined with MP3 method and the basis set 6-31G(d). GAMESS software for Linux, version 30 SEPT 2017 (R2) and MOLPROJ software, were used to analyze their MO eigenvectors and overlapping matrices of the reaction between ethylene and nitrosoethylene, both extracted from output files of single-point energy calculations with GAMESS.

The effects of EEFs were studied using the ?Field = M ± N? keyword, which defines in Gaussian09, the axis of the EEFs, its direction along that axis, and its magnitude. For each reaction, we initially evaluated the EEF effects at different Fx,y,z values, using single-point calculations on the critical species with F values (F=±0,125 au and ±0,080 au) along the preferred axis.

In opposition to the conventional definition in Physics, in Gaussian09, the positive direction of the electric field vector is defined from negative to positive charge [14]. Thus, whenever the dipole moment (?) and field vectors (F) are oriented opposite to each other, the EEF?s will stabilize the dipole, as shown in Scheme 1 for an X-EEF. The EEFs were further oriented along the X, Y and Z axes as defined in Scheme 1, where in each case the X axis defines the "reaction axis", which is approximately the direction along which two new C? C bonds are forming [13, 14, 25].

Scheme 1: Definitions of the x, y and z directions.

Figure 1: Reactants (A) nitrosoethylene and ethylene, (B) nitrosoethylene with borane connected to oxygen and ethylene and (C) nitrosoethylene with borane connected to nitrogen and ethylene.

The optimized compounds, as shown in Figure 1, were analyzed using the MOLPROJ software [26, 27]. The eigenvectors of the MOs and the matrices of were extracted from output files of single point energy calculations with GAMESS. The degree of location of each MO (2px-z orbitals of the carbon and oxygen atoms involved in the DA reaction) and their respective energies were calculated and analyzed. [28]. For comparison, degree of localization coefficients were calculated for the molecular orbitals ?HOMO and ?FERMO. We define that the degree of localization ?FERMO is the norm of an MO projected on the expected set of atomic orbitals (that participate in the reaction), as follows in Equation 1, where ?, is the matrix of molecular orbital coefficients and ? is the overlap matrix:

Equation 1: degree of localization ?FERMO

3 Results

3.1 Validation of the theoretical strategy: The Reaction of Ethylene and Nitrosoethylene - Catalysis of a Diels-Alder reaction using a Lewis acid.

The synthetic versatility of cycloaddition reactions was extended by introducing heterodienes, which allowed rapid access to various heterocycles. Nitrosoethylene compounds lead to valuable heterocyclic compounds with an N-O bond in the cycle. However, the reactivity of these compounds strongly depends on their structure and a catalyst. This is because nitrosoethylenes are generally unstable and are generated by base promoted elimination of -haloximes. Jursic and Zdravkovski, in 1995 [29], showed in a study the difference in the activation barrier when BH3 is used as a catalyst. According to literature, the activation barrier decreased by 2.08 kcal.mol-1 when borane is linked to nitrosoethylene nitrogen.
These same authors [29] used the reaction between ethylene and butadiene to compare the reliability of the results obtained computationally from the reaction between ethylene and nitrosoethylene with the experimental values of the first reaction. The activation energy for the ethylene and butadiene reaction was 25.98 kcal.mol-1 using MP3/6-31G(d), a value which is in reasonable agreement with the experimental value (25.4 and 27.5 kcal.mol-1) [30]. As our values were obtained with a difference of approximately 0.03 kcal.mol-1 in the activation barrier values of the base article, we consider that our results are also close to the experimental values, since there are no experimental studies of the reaction between ethylene and nitrosoethylene in literature.
Given the importance and versatility of this cycloaddition reaction, we sought validation (Table 1) of the author's results to compare them when we apply the electric field and use substituents as a catalyst. Figure 2 illustrates the energy profile for the reaction without and with the use of borane (bonded to oxygen and nitrogen atoms) as catalyst.
Table 1: Activation barrier of Lewis acid to trans reaction.

Figure 2: difference in the energy of the activation barrier without catalyst and with the catalyst borane bound to the oxygen atom and to the nitrogen atom.
As can be seen in Table 1, the lowest activation barrier found was for borane bound to nitrosethylene nitrogen. The borane-catalyzed reaction has a lower activation barrier than the uncatalyzed reaction [29]. Boron reagents are often employed as Lewis acids due to their strong electrophilic nature because of a vacant p orbital that can readily accept electrons from donor molecules [31]. So, as BH3 is acting as an electron acceptor, the reaction in question occurs with reverse electron demand. Therefore, borane as a catalyst has a profound influence on the reactivity of the system, decreasing the electron density in the diene and decreasing its LUMO energy.
Note that the values of the calculated activation barriers differ slightly from this current work [29]. This minimal difference in ?E# occurred because the coordinates of the structures were not made available by the researchers. Therefore, the difference in bond lengths in the optimization had a minimal influence on the activation barriers.

3.2 Effect of the substituents to check if the reaction rate becomes even lower when they are related to some type of catalyst
According to Frontier Molecular Orbital (FMO) theory, the reactivity, regiochemistry, and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial in-phase interaction of the HOMO molecular orbital of one component and the LUMO orbital of the other [7]. When the HOMO of the diene controls the reaction, the reaction can be accelerated by electron-donating substituents on the diene and by electron-withdrawing substituents on the dienophile, thus being a normal electron-demand Diels-Alder reaction. On the other hand, the Diels-Alder reactions controlled by the LUMO of the diene are influenced by the

electronic effects of the substituents in the opposite way, that is, it is a Diels-Alder reaction with inverse electron demand.
The influence were studied by considering the following substituents: CH3, Cl and F. Considering the reaction as a normal demand for electrons, the interactions occur from the HOMO/FERMO of the dienophile to the LUMO of the diene, as can be seen in Figure 3A. Table 2 shows the activation barrier values when we replace a diene hydrogen with X = methyl and a dienophile hydrogen with a halogen (Y = Cl and F).

Figure 3: reaction scheme for the Diels-Alder reaction between ethylene and substituted nitrosoehtylene. (A) structures of reactants (left), transition state (middle) and products (right); (B) molecular orbitals involved in the reaction; (C) numbering of the atoms involved in Diels-Alder reaction.
Table 2: activation barrier values when we replace a diene hydrogen with methyl and a dienophile hydrogen with a halogen (Cl and F).

As it can be seen, the substituents did not accelerate the reaction. According to Jursic and Zdravkovski [29], the reaction between ethylene and nitrosoethylene is an inverse demand reaction. Therefore, as we are treating it as a normal electron demand reaction, it is to be expected that the activation barrier will increase in value. This increase was approximately 3.02 kcalmol-1 in relation to the reaction without any type of catalyst (20.3624 kcal.mol-1).

3.3 Effect of the electric field in the reaction between ethylene and nitrosoethylene
Table 3 shows the EEF effects on the barriers for fields oriented along the x-, y- and z-axes in positive and negative directions. It is seen that Fy and Fz do not change the barrier, which remains constant at ~18.3(±2 .8) kcalmol-1. This is because the y,z-oriented EEFs stabilize both the reactant (R?) and the transition state (TS) to the same extent. However, when the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst.

Table 3: values of activation barrier (?E#) with electric field applied in x-, y- and z-axes for two magnitude values of electric field.

As the field becomes more negative, the dipole moment becomes more positive. This change in dipole moment is accompanied by transferring charge between the reactants in the TS. As the value of Fx increases, the direction of charge transfer is reversed. Thus, the EEF not only reduces the energy of the TS , but also polarizes the TS and affects its electronic structure. In addition, the field also induces a charge transfer in its own direction, from nitrosoethylene to ethylene. In conclusion, it is apparent that when the electric field is oriented along the ?reaction axis?, which is the axis along which the two new C-C bonds are formed, it causes the reaction rate to accelerate by preferentially decreasing the transition state.
An EEF oriented in the direction of the ?reaction axis?, along which electronic reorganization takes place, can affect the reaction rate by orders of magnitude, becoming faster or slower, depending on the change in direction of the field. At the same time, the endo/exo stereoselectivity of the Diels-Alder reaction can be manipulated at will with EEFs oriented perpendicular to the reaction axis [13]. EEF changes distribution of

the electron density. Figure 4 show the molecular orbitals involved in the reaction with/without EEFs. Application of EEFs induce the polarizability of electrons, atoms and dipoles, resulting in an eventual reorientation of the molecules along the applied electric field of the molecules and the electron density redistribution at particular atoms [32]. As a general rule, one can module that two orbitals or states, which cannot mix by symmetry in the absence of a field, will do so when an EEF is applied along the axis that possesses the same symmetry as the direct product of the two orbitals/states [33].
We used the FERMO concept [26] to understand how the electric field acted on the molecular orbitals of the studied reaction. This concept is based on simultaneous analysis of composition and shapes of frontier molecular orbitals to determine the real molecular orbital governing a reaction. According to this approach, a frontier molecular orbital may even correspond to the FERMO for a given reaction and not for another. The HOMO itself would only be the orbital that rules a reaction if it fulfills the requirements to be the FERMO [34].
A strategy to quantify the location of the FERMO was developed, leading to the construction of the MOLPROJ software, based on the use of projection operators to build the molecular orbitals (MOs) by linear combination of atomic orbitals (AOs; the LCAO approach). Thus, the location of the FERMO would indicate the orbital in which the reaction occurs and, consequently, would point to the most favorable location for protonation [26, 28].
The values in Table 4 to four atoms involved in the Diels-Alder reaction (carbons: C2, C8, C9 and O, as shown in the Figure 3C) exhibit the energy and degree of localization from FERMO to HOMO. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms [26]. External electric fields oriented along the bond axis in a molecule induce significant ionicity, as well as changes in bond lengths, elongation frequencies and electronic characteristics. EEFs cause orbitals, whose mixing was prohibited in the absence of the field, to mix when the symmetry of their product is compatible with the symmetry of the applied field. As the product of the reaction has the same symmetry as an applied field along the bond axis, these two MOs will mix and hybridize, acquiring greater contributions in both the left and right atoms, leading to the development of the energetically stabilized dipole moment by the applied field [35].

Figure 4: TS between ethylene and nitrosoethylene. A) HOMO of TS without EEF; B) HOMO of TS with EEF; C) LUMO of TS without EEF; and D) LUMO of TS with EEF.

Table 4: Results for the degree of localization of MOs from TS between ethylene and nitrosoethylene.

Table 5: Values of activation barrier (?E#) with an external electric field applied in x-, y- and z-axes for two electric field magnitudes for substituents CH3/Cl and CH3/F.

As it can be seen in Table 5, only the substituent effect does not show a decrease in activation barriers, the value was 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcal.mol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. According to Jursic and Zdravkovski [29], the reaction between nitrosoethylene and ethylene, when catalyzed with borane, is a Diels-Alder reaction with inverse electron demand. Therefore, when we introduced electron donor groups in the diene, we would find a higher value in the activation barrier, as it can be seen in the tables. When we added the electric field, we were able to lower

this activation barrier. We realize that in fact the electric field acted as a catalyst.
Figure 5 shows the effect of the main catalysts on the activation barrier of the reaction between ethylene and nitrosoethylene. As can be seen, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Figure 5: Difference in the energy of the activation barrier without BH3, with the borane bonding in nitrogen and reaction with EEF.

Conclusion
In this study, the DA reaction between ethylene and nitrosoethylene with/without BH3, electric field and substituted dienophiles was studied theoretically using RHF and MP3 calculations aimed to determine which was the best catalyst to reaction. When the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst. We used the FERMO concept to understand how the electric field acted on the molecular orbitals of the studied reaction. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms. Only the substituent effect does not show a decrease in activation barriers. The values were 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcalmol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. Therefore, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Referências
1. Houk KN, Strozier RW (1973) On Lewis Acid Catalysis of Diels-Alder Reactions. J Am Chem Soc 95:4094?4096. https://doi.org/10.1021/ja00793a070
2. García JI, Martínez-Merino V, Mayoral JA, Salvatella L (1998) Density functional theory study of a Lewis acid catalyzed Diels-Alder reaction. The butadiene + acrolein paradigm. J Am Chem Soc 120:2415?2420. https://doi.org/10.1021/ja9722279
3. Domingo LR (2002) A density functional theory study for the Diels-Alder reaction between N-acyl-1-aza-1,3-butadienes and vinylamines. Lewis acid catalyst and solvent effects. Tetrahedron 58:3765?3774. https://doi.org/10.1016/S0040-4020(02)00326-5
4. Kang J, Rebek J (1997) Acceleration of a Diels-Alder reaction by a self-assembled molecular capsule. Nature 385:50?52. https://doi.org/10.1038/385050a0
5. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
6. Gatzenmeier T, Van Gemmeren M, Xie Y, et al (2016) Asymmetric Lewis acid organocatalysis of the Diels-Alder reaction by a silylated C-H acid. Science (80-) 351:949?952. https://doi.org/10.1126/science.aae0010
7. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
8. Dyan OT, Andreev R V., Zaikin PA (2021) Substituents effects in the Diels-Alder reaction of 1,1-difluoronaphthalen-2(1H)-ones with cyclopentadiene. J Fluor Chem 250:109859. https://doi.org/10.1016/j.jfluchem.2021.109859
9. Gara R, Zouaghi MO, ALshandoudi LMH, Arfaoui Y (2021) DFT investigation of solvent, substituent, and

catalysis effects on the intramolecular Diels-Alder reaction. J Mol Model 27:. https://doi.org/10.1007/s00894-021-04729-w
10. Hernández-Mancera JP, Rojas-Valencia N, Núñez-Zarur F (2022) Rationalizing the Substituent Effects in Diels-Alder Reactions of Triazolinediones with Anthracene. J Phys Chem A 126:6657?6667. https://doi.org/10.1021/ACS.JPCA.2C04970/SUPPL_FILE/JP2C04970_SI_001.PDF
11. Khan TS, Gupta S, Ahmad M, et al (2020) Effect of substituents and promoters on the Diels-Alder cycloaddition reaction in the biorenewable synthesis of trimellitic acid. RSC Adv 10:30656?30670. https://doi.org/10.1039/d0ra04318d
12. Aragonès AC, Haworth NL, Darwish N, et al (2016) Electrostatic catalysis of a Diels-Alder reaction. Nature 531:88?91. https://doi.org/10.1038/nature16989
13. Meir R, Chen H, Lai W, Shaik S (2010) Oriented electric fields accelerate diels-alder reactions and control the endo/exo selectivity. ChemPhysChem 11:301?310. https://doi.org/10.1002/cphc.200900848
14. Wang Z, Danovich D, Ramanan R, Shaik S (2018) Oriented-External Electric Fields Create Absolute Enantioselectivity in Diels-Alder Reactions: Importance of the Molecular Dipole Moment. J Am Chem Soc 140:13350?13359. https://doi.org/10.1021/jacs.8b08233
15. Gryn?ova G, Coote ML (2013) Origin and scope of long-range stabilizing interactions and associated SOMO-HOMO conversion in distonic radical anions. J Am Chem Soc 135:15392?15403. https://doi.org/10.1021/ja404279f
16. Shaik S, De Visser SP, Kumar D (2004) External electric field will control the selectivity of enzymatic-like bond activations. J Am Chem Soc 126:11746?11749. https://doi.org/10.1021/ja047432k
17. Andrés JL, Lledós A, Duran M, Bertrán J (1988) Electric fields acting as catalysts in chemical reactions. An ab initio study of the walden inversion reaction. Chem Phys Lett 153:82?86. https://doi.org/10.1016/0009-2614(88)80136-2
18. Carbonell E, Duran M, Lledós A, Bertrán J (1991) Catalysis of Friedel-Crafts reactions by electric fields. J Phys Chem 95:179?183. https://doi.org/10.1021/j100154a036
19. Huang X, Tang C, Li J, et al (2019) Electric field?induced selective catalysis of single-molecule reaction. Sci Adv 5:eaaw3072. https://doi.org/10.1126/sciadv.aaw3072
20. Léonard NG, Dhaoui R, Chantarojsiri T, Yang JY (2021) Electric Fields in Catalysis: From Enzymes to Molecular Catalysts. ACS Catal 11:10923?10932. https://doi.org/10.1021/acscatal.1c02084
21. Dubey KD, Stuyver T, Shaik S (2022) Local Electric Fields: From Enzyme Catalysis to Synthetic Catalyst Design. J Phys Chem B. https://doi.org/10.1021/ACS.JPCB.2C06422
22. Shaik S, Danovich D, Joy J, et al (2020) Electric-Field Mediated Chemistry: Uncovering and Exploiting the Potential of (Oriented) Electric Fields to Exert Chemical Catalysis and Reaction Control. J. Am. Chem. Soc. 142:12551?12562
23. Aitken HM, Coote ML (2018) Can electrostatic catalysis of Diels-Alder reactions be harnessed with pH-switchable charged functional groups? Phys Chem Chem Phys 20:10671?10676. https://doi.org/10.1039/c7cp07562f
24. G16_C01 (1)
25. Shaik S, Mandal D, Ramanan R (2016) Oriented electric fields as future smart reagents in chemistry. Nat Chem 8:1091?1098. https://doi.org/10.1038/nchem.2651
26. Braga LS, Moreira RA, Leal DHS, Ramalho TC (2019) Quantification of molecular orbitals based on projection operators: Methodological development and applications to basicity prediction of organic compounds in the gas phase. Chem Phys Lett 726:87?92. https://doi.org/10.1016/j.cplett.2019.04.023
27. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for

-Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:. https://doi.org/10.2174/1385272824666200204121044
28. Braga LS, Henriques Soares Leal D, Ramalho TC (2022) Rationalising the regioselectivity of substituted phenols from the FERMO concept: stereoelectronic effects on protonation and functionalization . https://doi.org/101080/0892702220222039390 48:610?620. https://doi.org /10.1080/08927022.2022.2039390
29. Jursic BS, Zdravkovski Z (1995) Theoretical Study of the BH3-Catalyzed Hetero Diels?Alder Reaction between Ethylene and Nitrosoethylene. J Org Chem 60:3163?3168. https://doi.org/10.1021/jo00115a036
30. Rowley D, Steiner H (1951) Kinetics of diene reactions at high temperatures. Discuss Faraday Soc 10:198?213. https://doi.org/10.1039/DF9511000198
31. Nori V, Pesciaioli F, Sinibaldi A, et al (2022) Boron-based lewis acid catalysis: Challenges and perspectives. Catalysts 12:. https://doi.org/10.3390/catal12010005
32. Toledo EJL, Custodio R, Ramalho TC, et al (2009) Electrical field effects on dipole moment, structure and energetic of (H2O)n (2 ? n ? 15) cluster. J Mol Struct THEOCHEM 915:170?177. https://doi.org /10.1016/j.theochem.2009.08.035
33. Mazurkiewicz J, Tomasik P (2012) Effect of external electric field upon charge distribution, energy and dipole moment of selected monosaccharide molecules. Nat Sci 04:276?285. https://doi.org/10.4236/ns .2012.45040
34. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for -Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:314?331. https://doi.org/10.2174/1385272824666200204121044
35. Stuyver T, Danovich D, Joy J, Shaik S (2020) External electric field effects on chemical structure and reactivity. Wiley Interdiscip Rev Comput Mol Sci 10:1?22. https://doi.org/10.1002/wcms.1438

Lewis Acid?E# Activation Barrier of paper [29](kcal.mol-1)MP3/6-31G(d)?E#Activation Barrier in this work (kcal.mol-1)MP3/6-31G(d)
Without BH320.344920.3624
BH3 bonding oxygen13.707813.7962
BH3 bonding nitrogen11.622311.6025

Electron-donating (X)Electron-withdrawing (Y)?E# (kcal.mol-1)MP3/6-31G(d)
CH3Cl23.3857
F23.2107

F (au)?E# (kcal.mol-1)MP3/6-31G(d)
xyz
0.08021.081118.007424.8302
-0.08017.945318.220118.3186
0.12520.981118.200018.6625
-0.1256.393818.000018.4103

Without EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.643098-140.30580.3750-181.10180.348421-225.0075

C20.158948-140.30580.2003-181.10180.550036-225.0075
C80.034416-140.30580.4971-181.10180.282893-225.0075
C90.174964-140.30580.2854-181.10180.550790-225.0075
With EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.637059-141.49040.342834-185.24800.370436-218.3439
C20.167188-141.49040.164733-185.24800.565620-218.3439
C80.042363-141.49040.505992-185.24800.214219-218.3439
C90.188071-141.49040.326526-185.24800.521364-218.3439

CH3/Cl
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08023.030622.212922.1533
-0.08022.006522.281322.2161
0.12522.750127.928225.7320
-0.12522.531722.206722.5455
CH3/F
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08022.121921.881022.1012
-0.08022.246222.976621.8747
0.12522.538022.725622.5361
-0.12521.499523.026934.5554

Toward Metal- and Catalyst-free Reactions: Deciphering the substituent and external electric field effects on the Diels-Alder reaction between Ethylene and Nitrosoethylene

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Abstract
The substituents on the diene and/or dienophile can contribute to the decrease or increase of this energy. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis. The existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy. So, the goal of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field, Lewis acid (BH3) as catalysts and the influence of substituents. All calculations were performed with Gaussian09 software, the compounds were fully optimized using the restricted Hartree-Fock method with the basis set 6-31G, single-point energies determined with MP3 method and basis set 6-31G. The effects of EEFs were studied using the ?Field = M ± N? keyword with F values (F=±0,125 au and ±0,080 au) along the preferred axis. The lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.
Keywords
Electric field catalysis, external electric fields, Lewis acid, Diels-Alder reaction, FERMO.

1 Introduction

According to the Lewis definition, acids are molecules or ions capable of coordinating with unshared electron pairs, and bases are molecules or ions with unshared electron pairs available to share with acids [1]?. To be acidic in the Lewis sense, a molecule must be deficient in electrons. This is the most general acid-base concept. All Lowry-Brönsted acids are also Lewis acids, but in addition, the Lewis definition includes many other reagents, such as boron trifluoride, aluminum chloride, among others [2].
Lewis acids catalyze Diels-Alder reactions. Some examples of these acids are: SnCl4, ZnCl2, BH3 or AlCl3 ,, which can accelerate cycloaddition reactions [3, 4]?, as occurs in the reaction catalyzed by AlCl3 of cycloalkenones with 1,3-butadienes [5, 6]. The effect of substituents in the components of the Diels-Alder reaction affect it according to the Frontier Molecular Orbital (FMO) theory, in which the reactivity, regiochemistry and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial phase interaction of the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other [7]?.
The separation between the HOMO-LUMO components controls the reactivity of the Diels-Alder reaction: the smaller the energy difference between these two orbitals, the smaller the difference in activation energy between the transition state and the reaction reactants [8?11]. The substituents on the diene and/or dienophile can contribute to decrease or increase this energy. Electron-withdrawing substituents decrease the energy of LUMO and increase of HOMO, while electron-donor groups increase the energy of LUMO and decrease of HOMO [7]??. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis [12?14].
Chemical reactions can be described by the movement of electrons as well as the movement of nuclei. Thinking about it, we can understand that they can then be influenced by external electric fieldsWhether the reaction is redox or not, some theoretical studies [12, 13, 15, 16]?? the stability of molecules involved in the reaction can be influenced by electrostatic effects: stabilizing or destabilizing resonance contributors separated by charge [13]?. This fact was announced some time ago by Shaik and collaborators for the Diels-Alder reaction [16] and in another work for simple reactions of halogen and hydrogen transfer by Bertrán and collaborators [17, 18]?. Thus, there is a great interest in metal-free catalysis and specifically in catalysis by hydrogen bonding models [19].
In this scenario, the existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy [12, 20?22]?. Meir et al (2010) explored by theoretical means the effect of targeted EEFs on the rate, mechanism and endo/exo selectivity of DA reactions between butadiene and ethylene and cyclopentadiene and maleic anhydride. According to the authors, it is necessary then that the electric field is aligned in order to attenuate or strengthen the dipole along the reaction axis [13, 23].
Theoretical predictions were confirmed experimentally in 2016 by means of intermittent tunneling scanning microscopy (STM) experiments [12]?. In summary, the experiment was carried out as follows: the diene and the dienophile were "attached" to the tip and plate of the STM, respectively, restricting their orientation , providing a means of controlling the stimulus of the electric field and measuring its effect on the reaction rate [23]?. They obtained as results that, in the tested range of field forces, the reaction rate was independent of the positive polarity of the field, but it was catalyzed by increasing the intensity of the field to negative polarization. Parallel quantum-chemical calculations of the same system under experimental conditions, which confirmed that these results were due to the effect of the field on the reaction barriers [23]?. Therefore, external electric fields instead of charged chemical species such as the ?catalyst?, can manipulate a much wider range of reactions, conveniently altering reactivity and selectivity in a tunable way

that can be predicted by theory [13].
As electrostatic catalysis is the least developed form of catalysis in synthetic chemistry [12]?, the aim of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field and a Lewis acid as catalysts, in addition to checking the influence of substituents on the reaction?s diene and dienophile, in order to determine if the electric field is the best catalyst for the reaction studied.

2 Methodology
Gaussian09 software was used for all calculations [24]. The optimization calculation for all compounds was performed with restricted Hartree-Fock method with the basis set 6-31G(d). No imaginary frequencies were found for the optimized reactants geometries, which were used in all subsequent calculations and had their single-point energies determined with MP3 method and the basis set 6-31G(d). GAMESS software for Linux, version 30 SEPT 2017 (R2) and MOLPROJ software, were used to analyze their MO eigenvectors and overlapping matrices of the reaction between ethylene and nitrosoethylene, both extracted from output files of single-point energy calculations with GAMESS.
The effects of EEFs were studied using the ?Field = M ± N? keyword, which defines in Gaussian09, the axis of the EEFs, its direction along that axis, and its magnitude. For each reaction, we initially evaluated the EEF effects at different Fx,y,z values, using single-point calculations on the critical species with F values (F=±0,125 au and ±0,080 au) along the preferred axis.
In opposition to the conventional definition in Physics, in Gaussian09, the positive direction of the electric field vector is defined from negative to positive charge [14]. Thus, whenever the dipole moment (?) and field vectors (F) are oriented opposite to each other, the EEF?s will stabilize the dipole, as shown in Scheme 1 for an X-EEF. The EEFs were further oriented along the X, Y and Z axes as defined in Scheme 1, where in each case the X axis defines the "reaction axis", which is approximately the direction along which two new C? C bonds are forming [13, 14, 25].

Scheme 1: Definitions of the x, y and z directions.

Figure 1: Reactants (A) nitrosoethylene and ethylene, (B) nitrosoethylene with borane connected to oxygen and ethylene and (C) nitrosoethylene with borane connected to nitrogen and ethylene.
The optimized compounds, as shown in Figure 1, were analyzed using the MOLPROJ software [26, 27]. The eigenvectors of the MOs and the matrices of were extracted from output files of single point energy calculations with GAMESS. The degree of location of each MO (2px-z orbitals of the carbon and oxygen atoms involved in the DA reaction) and their respective energies were calculated and analyzed. [28]. For comparison, degree of localization coefficients were calculated for the molecular orbitals ?HOMO and ?FERMO. We define that the degree of localization ?FERMO is the norm of an MO projected on the expected set of atomic orbitals (that participate in the reaction), as follows in Equation 1, where ?, is the matrix of molecular orbital coefficients and ? is the overlap matrix:

Equation 1: degree of localization ?FERMO
3 Results
3.1 Validation of the theoretical strategy: The Reaction of Ethylene and Nitrosoethylene - Catalysis of a Diels-Alder reaction using a Lewis acid.

The synthetic versatility of cycloaddition reactions was extended by introducing heterodienes, which allowed rapid access to various heterocycles. Nitrosoethylene compounds lead to valuable heterocyclic compounds with an N-O bond in the cycle. However, the reactivity of these compounds strongly depends on their structure and a catalyst. This is because nitrosoethylenes are generally unstable and are generated by base promoted elimination of -haloximes. Jursic and Zdravkovski, in 1995 [29], showed in a study the difference in the activation barrier when BH3 is used as a catalyst. According to literature, the activation barrier decreased by 2.08 kcal.mol-1 when borane is linked to nitrosoethylene nitrogen.
These same authors [29] used the reaction between ethylene and butadiene to compare the reliability of the results obtained computationally from the reaction between ethylene and nitrosoethylene with the experimental values of the first reaction. The activation energy for the ethylene and butadiene reaction was 25.98 kcal.mol-1 using MP3/6-31G(d), a value which is in reasonable agreement with the experimental value (25.4 and 27.5 kcal.mol-1) [30]. As our values were obtained with a difference of approximately 0.03 kcal.mol-1 in the activation barrier values of the base article, we consider that our results are also close to the experimental values, since there are no experimental studies of the reaction between ethylene and nitrosoethylene in literature.
Given the importance and versatility of this cycloaddition reaction, we sought validation (Table 1) of the author's results to compare them when we apply the electric field and use substituents as a catalyst. Figure 2 illustrates the energy profile for the reaction without and with the use of borane (bonded to oxygen and nitrogen atoms) as catalyst.
Table 1: Activation barrier of Lewis acid to trans reaction.

Figure 2: difference in the energy of the activation barrier without catalyst and with the catalyst borane bound to the oxygen atom and to the nitrogen atom.
As can be seen in Table 1, the lowest activation barrier found was for borane bound to nitrosethylene nitrogen. The borane-catalyzed reaction has a lower activation barrier than the uncatalyzed reaction [29]. Boron reagents are often employed as Lewis acids due to their strong electrophilic nature because of a vacant p orbital that can readily accept electrons from donor molecules [31]. So, as BH3 is acting as an electron acceptor, the reaction in question occurs with reverse electron demand. Therefore, borane as a catalyst has a profound influence on the reactivity of the system, decreasing the electron density in the diene and decreasing its LUMO energy.
Note that the values of the calculated activation barriers differ slightly from this current work [29]. This minimal difference in ?E# occurred because the coordinates of the structures were not made available by the researchers. Therefore, the difference in bond lengths in the optimization had a minimal influence on the activation barriers.

3.2 Effect of the substituents to check if the reaction rate becomes even lower when they are related to some type of catalyst
According to Frontier Molecular Orbital (FMO) theory, the reactivity, regiochemistry, and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial in-phase interaction of the HOMO molecular orbital of one component and the LUMO orbital of the other [7]. When the HOMO of the diene controls the reaction, the reaction can be accelerated by electron-donating substituents on the diene and by electron-withdrawing substituents on the dienophile, thus being a normal electron-demand Diels-Alder reaction. On the other hand, the Diels-Alder reactions controlled by the LUMO of the diene are influenced by the

electronic effects of the substituents in the opposite way, that is, it is a Diels-Alder reaction with inverse electron demand.
The influence were studied by considering the following substituents: CH3, Cl and F. Considering the reaction as a normal demand for electrons, the interactions occur from the HOMO/FERMO of the dienophile to the LUMO of the diene, as can be seen in Figure 3A. Table 2 shows the activation barrier values when we replace a diene hydrogen with X = methyl and a dienophile hydrogen with a halogen (Y = Cl and F).

Figure 3: reaction scheme for the Diels-Alder reaction between ethylene and substituted nitrosoehtylene. (A) structures of reactants (left), transition state (middle) and products (right); (B) molecular orbitals involved in the reaction; (C) numbering of the atoms involved in Diels-Alder reaction.
Table 2: activation barrier values when we replace a diene hydrogen with methyl and a dienophile hydrogen with a halogen (Cl and F).

As it can be seen, the substituents did not accelerate the reaction. According to Jursic and Zdravkovski [29], the reaction between ethylene and nitrosoethylene is an inverse demand reaction. Therefore, as we are treating it as a normal electron demand reaction, it is to be expected that the activation barrier will increase in value. This increase was approximately 3.02 kcalmol-1 in relation to the reaction without any type of catalyst (20.3624 kcal.mol-1).

3.3 Effect of the electric field in the reaction between ethylene and nitrosoethylene
Table 3 shows the EEF effects on the barriers for fields oriented along the x-, y- and z-axes in positive and negative directions. It is seen that Fy and Fz do not change the barrier, which remains constant at ~18.3(±2 .8) kcalmol-1. This is because the y,z-oriented EEFs stabilize both the reactant (R?) and the transition state (TS) to the same extent. However, when the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst.

Table 3: values of activation barrier (?E#) with electric field applied in x-, y- and z-axes for two magnitude values of electric field.

As the field becomes more negative, the dipole moment becomes more positive. This change in dipole moment is accompanied by transferring charge between the reactants in the TS. As the value of Fx increases, the direction of charge transfer is reversed. Thus, the EEF not only reduces the energy of the TS , but also polarizes the TS and affects its electronic structure. In addition, the field also induces a charge transfer in its own direction, from nitrosoethylene to ethylene. In conclusion, it is apparent that when the electric field is oriented along the ?reaction axis?, which is the axis along which the two new C-C bonds are formed, it causes the reaction rate to accelerate by preferentially decreasing the transition state.
An EEF oriented in the direction of the ?reaction axis?, along which electronic reorganization takes place, can affect the reaction rate by orders of magnitude, becoming faster or slower, depending on the change in direction of the field. At the same time, the endo/exo stereoselectivity of the Diels-Alder reaction can be manipulated at will with EEFs oriented perpendicular to the reaction axis [13]. EEF changes distribution of

the electron density. Figure 4 show the molecular orbitals involved in the reaction with/without EEFs. Application of EEFs induce the polarizability of electrons, atoms and dipoles, resulting in an eventual reorientation of the molecules along the applied electric field of the molecules and the electron density redistribution at particular atoms [32]. As a general rule, one can module that two orbitals or states, which cannot mix by symmetry in the absence of a field, will do so when an EEF is applied along the axis that possesses the same symmetry as the direct product of the two orbitals/states [33].
We used the FERMO concept [26] to understand how the electric field acted on the molecular orbitals of the studied reaction. This concept is based on simultaneous analysis of composition and shapes of frontier molecular orbitals to determine the real molecular orbital governing a reaction. According to this approach, a frontier molecular orbital may even correspond to the FERMO for a given reaction and not for another. The HOMO itself would only be the orbital that rules a reaction if it fulfills the requirements to be the FERMO [34].
A strategy to quantify the location of the FERMO was developed, leading to the construction of the MOLPROJ software, based on the use of projection operators to build the molecular orbitals (MOs) by linear combination of atomic orbitals (AOs; the LCAO approach). Thus, the location of the FERMO would indicate the orbital in which the reaction occurs and, consequently, would point to the most favorable location for protonation [26, 28].
The values in Table 4 to four atoms involved in the Diels-Alder reaction (carbons: C2, C8, C9 and O, as shown in the Figure 3C) exhibit the energy and degree of localization from FERMO to HOMO. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms [26]. External electric fields oriented along the bond axis in a molecule induce significant ionicity, as well as changes in bond lengths, elongation frequencies and electronic characteristics. EEFs cause orbitals, whose mixing was prohibited in the absence of the field, to mix when the symmetry of their product is compatible with the symmetry of the applied field. As the product of the reaction has the same symmetry as an applied field along the bond axis, these two MOs will mix and hybridize, acquiring greater contributions in both the left and right atoms, leading to the development of the energetically stabilized dipole moment by the applied field [35].

Figure 4: TS between ethylene and nitrosoethylene. A) HOMO of TS without EEF; B) HOMO of TS with EEF; C) LUMO of TS without EEF; and D) LUMO of TS with EEF.

Table 4: Results for the degree of localization of MOs from TS between ethylene and nitrosoethylene.

Table 5: Values of activation barrier (?E#) with an external electric field applied in x-, y- and z-axes for two electric field magnitudes for substituents CH3/Cl and CH3/F.

As it can be seen in Table 5, only the substituent effect does not show a decrease in activation barriers, the value was 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcal.mol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. According to Jursic and Zdravkovski [29], the reaction between nitrosoethylene and ethylene, when catalyzed with borane, is a Diels-Alder reaction with inverse electron demand. Therefore, when we introduced electron donor groups in the diene, we would find a higher value in the activation barrier, as it can be seen in the tables. When we added the electric field, we were able to lower

this activation barrier. We realize that in fact the electric field acted as a catalyst.
Figure 5 shows the effect of the main catalysts on the activation barrier of the reaction between ethylene and nitrosoethylene. As can be seen, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Figure 5: Difference in the energy of the activation barrier without BH3, with the borane bonding in nitrogen and reaction with EEF.

Conclusion
In this study, the DA reaction between ethylene and nitrosoethylene with/without BH3, electric field and substituted dienophiles was studied theoretically using RHF and MP3 calculations aimed to determine which was the best catalyst to reaction. When the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst. We used the FERMO concept to understand how the electric field acted on the molecular orbitals of the studied reaction. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms. Only the substituent effect does not show a decrease in activation barriers. The values were 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcalmol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. Therefore, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Referências
1. Houk KN, Strozier RW (1973) On Lewis Acid Catalysis of Diels-Alder Reactions. J Am Chem Soc 95:4094?4096. https://doi.org/10.1021/ja00793a070
2. García JI, Martínez-Merino V, Mayoral JA, Salvatella L (1998) Density functional theory study of a Lewis acid catalyzed Diels-Alder reaction. The butadiene + acrolein paradigm. J Am Chem Soc 120:2415?2420. https://doi.org/10.1021/ja9722279
3. Domingo LR (2002) A density functional theory study for the Diels-Alder reaction between N-acyl-1-aza-1,3-butadienes and vinylamines. Lewis acid catalyst and solvent effects. Tetrahedron 58:3765?3774. https://doi.org/10.1016/S0040-4020(02)00326-5
4. Kang J, Rebek J (1997) Acceleration of a Diels-Alder reaction by a self-assembled molecular capsule. Nature 385:50?52. https://doi.org/10.1038/385050a0
5. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
6. Gatzenmeier T, Van Gemmeren M, Xie Y, et al (2016) Asymmetric Lewis acid organocatalysis of the Diels-Alder reaction by a silylated C-H acid. Science (80-) 351:949?952. https://doi.org/10.1126/science.aae0010
7. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
8. Dyan OT, Andreev R V., Zaikin PA (2021) Substituents effects in the Diels-Alder reaction of 1,1-difluoronaphthalen-2(1H)-ones with cyclopentadiene. J Fluor Chem 250:109859. https://doi.org/10.1016/j.jfluchem.2021.109859
9. Gara R, Zouaghi MO, ALshandoudi LMH, Arfaoui Y (2021) DFT investigation of solvent, substituent, and

catalysis effects on the intramolecular Diels-Alder reaction. J Mol Model 27:. https://doi.org/10.1007/s00894-021-04729-w
10. Hernández-Mancera JP, Rojas-Valencia N, Núñez-Zarur F (2022) Rationalizing the Substituent Effects in Diels-Alder Reactions of Triazolinediones with Anthracene. J Phys Chem A 126:6657?6667. https://doi.org/10.1021/ACS.JPCA.2C04970/SUPPL_FILE/JP2C04970_SI_001.PDF
11. Khan TS, Gupta S, Ahmad M, et al (2020) Effect of substituents and promoters on the Diels-Alder cycloaddition reaction in the biorenewable synthesis of trimellitic acid. RSC Adv 10:30656?30670. https://doi.org/10.1039/d0ra04318d
12. Aragonès AC, Haworth NL, Darwish N, et al (2016) Electrostatic catalysis of a Diels-Alder reaction. Nature 531:88?91. https://doi.org/10.1038/nature16989
13. Meir R, Chen H, Lai W, Shaik S (2010) Oriented electric fields accelerate diels-alder reactions and control the endo/exo selectivity. ChemPhysChem 11:301?310. https://doi.org/10.1002/cphc.200900848
14. Wang Z, Danovich D, Ramanan R, Shaik S (2018) Oriented-External Electric Fields Create Absolute Enantioselectivity in Diels-Alder Reactions: Importance of the Molecular Dipole Moment. J Am Chem Soc 140:13350?13359. https://doi.org/10.1021/jacs.8b08233
15. Gryn?ova G, Coote ML (2013) Origin and scope of long-range stabilizing interactions and associated SOMO-HOMO conversion in distonic radical anions. J Am Chem Soc 135:15392?15403. https://doi.org/10.1021/ja404279f
16. Shaik S, De Visser SP, Kumar D (2004) External electric field will control the selectivity of enzymatic-like bond activations. J Am Chem Soc 126:11746?11749. https://doi.org/10.1021/ja047432k
17. Andrés JL, Lledós A, Duran M, Bertrán J (1988) Electric fields acting as catalysts in chemical reactions. An ab initio study of the walden inversion reaction. Chem Phys Lett 153:82?86. https://doi.org/10.1016/0009-2614(88)80136-2
18. Carbonell E, Duran M, Lledós A, Bertrán J (1991) Catalysis of Friedel-Crafts reactions by electric fields. J Phys Chem 95:179?183. https://doi.org/10.1021/j100154a036
19. Huang X, Tang C, Li J, et al (2019) Electric field?induced selective catalysis of single-molecule reaction. Sci Adv 5:eaaw3072. https://doi.org/10.1126/sciadv.aaw3072
20. Léonard NG, Dhaoui R, Chantarojsiri T, Yang JY (2021) Electric Fields in Catalysis: From Enzymes to Molecular Catalysts. ACS Catal 11:10923?10932. https://doi.org/10.1021/acscatal.1c02084
21. Dubey KD, Stuyver T, Shaik S (2022) Local Electric Fields: From Enzyme Catalysis to Synthetic Catalyst Design. J Phys Chem B. https://doi.org/10.1021/ACS.JPCB.2C06422
22. Shaik S, Danovich D, Joy J, et al (2020) Electric-Field Mediated Chemistry: Uncovering and Exploiting the Potential of (Oriented) Electric Fields to Exert Chemical Catalysis and Reaction Control. J. Am. Chem. Soc. 142:12551?12562
23. Aitken HM, Coote ML (2018) Can electrostatic catalysis of Diels-Alder reactions be harnessed with pH-switchable charged functional groups? Phys Chem Chem Phys 20:10671?10676. https://doi.org/10.1039/c7cp07562f
24. G16_C01 (1)
25. Shaik S, Mandal D, Ramanan R (2016) Oriented electric fields as future smart reagents in chemistry. Nat Chem 8:1091?1098. https://doi.org/10.1038/nchem.2651
26. Braga LS, Moreira RA, Leal DHS, Ramalho TC (2019) Quantification of molecular orbitals based on projection operators: Methodological development and applications to basicity prediction of organic compounds in the gas phase. Chem Phys Lett 726:87?92. https://doi.org/10.1016/j.cplett.2019.04.023
27. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for

-Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:. https://doi.org/10.2174/1385272824666200204121044
28. Braga LS, Henriques Soares Leal D, Ramalho TC (2022) Rationalising the regioselectivity of substituted phenols from the FERMO concept: stereoelectronic effects on protonation and functionalization . https://doi.org/101080/0892702220222039390 48:610?620. https://doi.org /10.1080/08927022.2022.2039390
29. Jursic BS, Zdravkovski Z (1995) Theoretical Study of the BH3-Catalyzed Hetero Diels?Alder Reaction between Ethylene and Nitrosoethylene. J Org Chem 60:3163?3168. https://doi.org/10.1021/jo00115a036
30. Rowley D, Steiner H (1951) Kinetics of diene reactions at high temperatures. Discuss Faraday Soc 10:198?213. https://doi.org/10.1039/DF9511000198
31. Nori V, Pesciaioli F, Sinibaldi A, et al (2022) Boron-based lewis acid catalysis: Challenges and perspectives. Catalysts 12:. https://doi.org/10.3390/catal12010005
32. Toledo EJL, Custodio R, Ramalho TC, et al (2009) Electrical field effects on dipole moment, structure and energetic of (H2O)n (2 ? n ? 15) cluster. J Mol Struct THEOCHEM 915:170?177. https://doi.org /10.1016/j.theochem.2009.08.035
33. Mazurkiewicz J, Tomasik P (2012) Effect of external electric field upon charge distribution, energy and dipole moment of selected monosaccharide molecules. Nat Sci 04:276?285. https://doi.org/10.4236/ns .2012.45040
34. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for -Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:314?331. https://doi.org/10.2174/1385272824666200204121044
35. Stuyver T, Danovich D, Joy J, Shaik S (2020) External electric field effects on chemical structure and reactivity. Wiley Interdiscip Rev Comput Mol Sci 10:1?22. https://doi.org/10.1002/wcms.1438

Lewis Acid?E# Activation Barrier of paper [29](kcal.mol-1)MP3/6-31G(d)?E#Activation Barrier in this work (kcal.mol-1)MP3/6-31G(d)
Without BH320.344920.3624
BH3 bonding oxygen13.707813.7962
BH3 bonding nitrogen11.622311.6025

Electron-donating (X)Electron-withdrawing (Y)?E# (kcal.mol-1)MP3/6-31G(d)
CH3Cl23.3857
F23.2107

F (au)?E# (kcal.mol-1)MP3/6-31G(d)
xyz
0.08021.081118.007424.8302
-0.08017.945318.220118.3186
0.12520.981118.200018.6625
-0.1256.393818.000018.4103

Without EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.643098-140.30580.3750-181.10180.348421-225.0075

C20.158948-140.30580.2003-181.10180.550036-225.0075
C80.034416-140.30580.4971-181.10180.282893-225.0075
C90.174964-140.30580.2854-181.10180.550790-225.0075
With EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.637059-141.49040.342834-185.24800.370436-218.3439
C20.167188-141.49040.164733-185.24800.565620-218.3439
C80.042363-141.49040.505992-185.24800.214219-218.3439
C90.188071-141.49040.326526-185.24800.521364-218.3439

CH3/Cl
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08023.030622.212922.1533
-0.08022.006522.281322.2161
0.12522.750127.928225.7320
-0.12522.531722.206722.5455
CH3/F
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08022.121921.881022.1012
-0.08022.246222.976621.8747
0.12522.538022.725622.5361
-0.12521.499523.026934.5554

Toward Metal- and Catalyst-free Reactions: Deciphering the substituent and external electric field effects on the Diels-Alder reaction between Ethylene and Nitrosoethylene

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Abstract
The substituents on the diene and/or dienophile can contribute to the decrease or increase of this energy. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis. The existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy. So, the goal of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field, Lewis acid (BH3) as catalysts and the influence of substituents. All calculations were performed with Gaussian09 software, the compounds were fully optimized using the restricted Hartree-Fock method with the basis set 6-31G, single-point energies determined with MP3 method and basis set 6-31G. The effects of EEFs were studied using the ?Field = M ± N? keyword with F values (F=±0,125 au and ±0,080 au) along the preferred axis. The lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.
Keywords
Electric field catalysis, external electric fields, Lewis acid, Diels-Alder reaction, FERMO.

1 Introduction

According to the Lewis definition, acids are molecules or ions capable of coordinating with unshared electron pairs, and bases are molecules or ions with unshared electron pairs available to share with acids [1]?. To be acidic in the Lewis sense, a molecule must be deficient in electrons. This is the most general acid-base concept. All Lowry-Brönsted acids are also Lewis acids, but in addition, the Lewis definition includes many other reagents, such as boron trifluoride, aluminum chloride, among others [2].
Lewis acids catalyze Diels-Alder reactions. Some examples of these acids are: SnCl4, ZnCl2, BH3 or AlCl3 ,, which can accelerate cycloaddition reactions [3, 4]?, as occurs in the reaction catalyzed by AlCl3 of cycloalkenones with 1,3-butadienes [5, 6]. The effect of substituents in the components of the Diels-Alder reaction affect it according to the Frontier Molecular Orbital (FMO) theory, in which the reactivity, regiochemistry and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial phase interaction of the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other [7]?.
The separation between the HOMO-LUMO components controls the reactivity of the Diels-Alder reaction: the smaller the energy difference between these two orbitals, the smaller the difference in activation energy between the transition state and the reaction reactants [8?11]. The substituents on the diene and/or dienophile can contribute to decrease or increase this energy. Electron-withdrawing substituents decrease the energy of LUMO and increase of HOMO, while electron-donor groups increase the energy of LUMO and decrease of HOMO [7]??. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis [12?14].
Chemical reactions can be described by the movement of electrons as well as the movement of nuclei. Thinking about it, we can understand that they can then be influenced by external electric fieldsWhether the reaction is redox or not, some theoretical studies [12, 13, 15, 16]?? the stability of molecules involved in the reaction can be influenced by electrostatic effects: stabilizing or destabilizing resonance contributors separated by charge [13]?. This fact was announced some time ago by Shaik and collaborators for the Diels-Alder reaction [16] and in another work for simple reactions of halogen and hydrogen transfer by Bertrán and collaborators [17, 18]?. Thus, there is a great interest in metal-free catalysis and specifically in catalysis by hydrogen bonding models [19].
In this scenario, the existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy [12, 20?22]?. Meir et al (2010) explored by theoretical means the effect of targeted EEFs on the rate, mechanism and endo/exo selectivity of DA reactions between butadiene and ethylene and cyclopentadiene and maleic anhydride. According to the authors, it is necessary then that the electric field is aligned in order to attenuate or strengthen the dipole along the reaction axis [13, 23].
Theoretical predictions were confirmed experimentally in 2016 by means of intermittent tunneling scanning microscopy (STM) experiments [12]?. In summary, the experiment was carried out as follows: the diene and the dienophile were "attached" to the tip and plate of the STM, respectively, restricting their orientation , providing a means of controlling the stimulus of the electric field and measuring its effect on the reaction rate [23]?. They obtained as results that, in the tested range of field forces, the reaction rate was independent of the positive polarity of the field, but it was catalyzed by increasing the intensity of the field to negative polarization. Parallel quantum-chemical calculations of the same system under experimental conditions, which confirmed that these results were due to the effect of the field on the reaction barriers [23]?. Therefore, external electric fields instead of charged chemical species such as the ?catalyst?, can manipulate a much wider range of reactions, conveniently altering reactivity and selectivity in a tunable way

that can be predicted by theory [13].
As electrostatic catalysis is the least developed form of catalysis in synthetic chemistry [12]?, the aim of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field and a Lewis acid as catalysts, in addition to checking the influence of substituents on the reaction?s diene and dienophile, in order to determine if the electric field is the best catalyst for the reaction studied.

2 Methodology
Gaussian09 software was used for all calculations [24]. The optimization calculation for all compounds was performed with restricted Hartree-Fock method with the basis set 6-31G(d). No imaginary frequencies were found for the optimized reactants geometries, which were used in all subsequent calculations and had their single-point energies determined with MP3 method and the basis set 6-31G(d). GAMESS software for Linux, version 30 SEPT 2017 (R2) and MOLPROJ software, were used to analyze their MO eigenvectors and overlapping matrices of the reaction between ethylene and nitrosoethylene, both extracted from output files of single-point energy calculations with GAMESS.
The effects of EEFs were studied using the ?Field = M ± N? keyword, which defines in Gaussian09, the axis of the EEFs, its direction along that axis, and its magnitude. For each reaction, we initially evaluated the EEF effects at different Fx,y,z values, using single-point calculations on the critical species with F values (F=±0,125 au and ±0,080 au) along the preferred axis.
In opposition to the conventional definition in Physics, in Gaussian09, the positive direction of the electric field vector is defined from negative to positive charge [14]. Thus, whenever the dipole moment (?) and field vectors (F) are oriented opposite to each other, the EEF?s will stabilize the dipole, as shown in Scheme 1 for an X-EEF. The EEFs were further oriented along the X, Y and Z axes as defined in Scheme 1, where in each case the X axis defines the "reaction axis", which is approximately the direction along which two new C? C bonds are forming [13, 14, 25].

Scheme 1: Definitions of the x, y and z directions.

Figure 1: Reactants (A) nitrosoethylene and ethylene, (B) nitrosoethylene with borane connected to oxygen and ethylene and (C) nitrosoethylene with borane connected to nitrogen and ethylene.
The optimized compounds, as shown in Figure 1, were analyzed using the MOLPROJ software [26, 27]. The eigenvectors of the MOs and the matrices of were extracted from output files of single point energy calculations with GAMESS. The degree of location of each MO (2px-z orbitals of the carbon and oxygen atoms involved in the DA reaction) and their respective energies were calculated and analyzed. [28]. For comparison, degree of localization coefficients were calculated for the molecular orbitals ?HOMO and ?FERMO. We define that the degree of localization ?FERMO is the norm of an MO projected on the expected set of atomic orbitals (that participate in the reaction), as follows in Equation 1, where ?, is the matrix of molecular orbital coefficients and ? is the overlap matrix:

Equation 1: degree of localization ?FERMO
3 Results
3.1 Validation of the theoretical strategy: The Reaction of Ethylene and Nitrosoethylene - Catalysis of a Diels-Alder reaction using a Lewis acid.

The synthetic versatility of cycloaddition reactions was extended by introducing heterodienes, which allowed rapid access to various heterocycles. Nitrosoethylene compounds lead to valuable heterocyclic compounds with an N-O bond in the cycle. However, the reactivity of these compounds strongly depends on their structure and a catalyst. This is because nitrosoethylenes are generally unstable and are generated by base promoted elimination of -haloximes. Jursic and Zdravkovski, in 1995 [29], showed in a study the difference in the activation barrier when BH3 is used as a catalyst. According to literature, the activation barrier decreased by 2.08 kcal.mol-1 when borane is linked to nitrosoethylene nitrogen.
These same authors [29] used the reaction between ethylene and butadiene to compare the reliability of the results obtained computationally from the reaction between ethylene and nitrosoethylene with the experimental values of the first reaction. The activation energy for the ethylene and butadiene reaction was 25.98 kcal.mol-1 using MP3/6-31G(d), a value which is in reasonable agreement with the experimental value (25.4 and 27.5 kcal.mol-1) [30]. As our values were obtained with a difference of approximately 0.03 kcal.mol-1 in the activation barrier values of the base article, we consider that our results are also close to the experimental values, since there are no experimental studies of the reaction between ethylene and nitrosoethylene in literature.
Given the importance and versatility of this cycloaddition reaction, we sought validation (Table 1) of the author's results to compare them when we apply the electric field and use substituents as a catalyst. Figure 2 illustrates the energy profile for the reaction without and with the use of borane (bonded to oxygen and nitrogen atoms) as catalyst.
Table 1: Activation barrier of Lewis acid to trans reaction.

Figure 2: difference in the energy of the activation barrier without catalyst and with the catalyst borane bound to the oxygen atom and to the nitrogen atom.
As can be seen in Table 1, the lowest activation barrier found was for borane bound to nitrosethylene nitrogen. The borane-catalyzed reaction has a lower activation barrier than the uncatalyzed reaction [29]. Boron reagents are often employed as Lewis acids due to their strong electrophilic nature because of a vacant p orbital that can readily accept electrons from donor molecules [31]. So, as BH3 is acting as an electron acceptor, the reaction in question occurs with reverse electron demand. Therefore, borane as a catalyst has a profound influence on the reactivity of the system, decreasing the electron density in the diene and decreasing its LUMO energy.
Note that the values of the calculated activation barriers differ slightly from this current work [29]. This minimal difference in ?E# occurred because the coordinates of the structures were not made available by the researchers. Therefore, the difference in bond lengths in the optimization had a minimal influence on the activation barriers.

3.2 Effect of the substituents to check if the reaction rate becomes even lower when they are related to some type of catalyst
According to Frontier Molecular Orbital (FMO) theory, the reactivity, regiochemistry, and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial in-phase interaction of the HOMO molecular orbital of one component and the LUMO orbital of the other [7]. When the HOMO of the diene controls the reaction, the reaction can be accelerated by electron-donating substituents on the diene and by electron-withdrawing substituents on the dienophile, thus being a normal electron-demand Diels-Alder reaction. On the other hand, the Diels-Alder reactions controlled by the LUMO of the diene are influenced by the

electronic effects of the substituents in the opposite way, that is, it is a Diels-Alder reaction with inverse electron demand.
The influence were studied by considering the following substituents: CH3, Cl and F. Considering the reaction as a normal demand for electrons, the interactions occur from the HOMO/FERMO of the dienophile to the LUMO of the diene, as can be seen in Figure 3A. Table 2 shows the activation barrier values when we replace a diene hydrogen with X = methyl and a dienophile hydrogen with a halogen (Y = Cl and F).

Figure 3: reaction scheme for the Diels-Alder reaction between ethylene and substituted nitrosoehtylene. (A) structures of reactants (left), transition state (middle) and products (right); (B) molecular orbitals involved in the reaction; (C) numbering of the atoms involved in Diels-Alder reaction.
Table 2: activation barrier values when we replace a diene hydrogen with methyl and a dienophile hydrogen with a halogen (Cl and F).

As it can be seen, the substituents did not accelerate the reaction. According to Jursic and Zdravkovski [29], the reaction between ethylene and nitrosoethylene is an inverse demand reaction. Therefore, as we are treating it as a normal electron demand reaction, it is to be expected that the activation barrier will increase in value. This increase was approximately 3.02 kcalmol-1 in relation to the reaction without any type of catalyst (20.3624 kcal.mol-1).

3.3 Effect of the electric field in the reaction between ethylene and nitrosoethylene
Table 3 shows the EEF effects on the barriers for fields oriented along the x-, y- and z-axes in positive and negative directions. It is seen that Fy and Fz do not change the barrier, which remains constant at ~18.3(±2 .8) kcalmol-1. This is because the y,z-oriented EEFs stabilize both the reactant (R?) and the transition state (TS) to the same extent. However, when the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst.

Table 3: values of activation barrier (?E#) with electric field applied in x-, y- and z-axes for two magnitude values of electric field.

As the field becomes more negative, the dipole moment becomes more positive. This change in dipole moment is accompanied by transferring charge between the reactants in the TS. As the value of Fx increases, the direction of charge transfer is reversed. Thus, the EEF not only reduces the energy of the TS , but also polarizes the TS and affects its electronic structure. In addition, the field also induces a charge transfer in its own direction, from nitrosoethylene to ethylene. In conclusion, it is apparent that when the electric field is oriented along the ?reaction axis?, which is the axis along which the two new C-C bonds are formed, it causes the reaction rate to accelerate by preferentially decreasing the transition state.
An EEF oriented in the direction of the ?reaction axis?, along which electronic reorganization takes place, can affect the reaction rate by orders of magnitude, becoming faster or slower, depending on the change in direction of the field. At the same time, the endo/exo stereoselectivity of the Diels-Alder reaction can be manipulated at will with EEFs oriented perpendicular to the reaction axis [13]. EEF changes distribution of

the electron density. Figure 4 show the molecular orbitals involved in the reaction with/without EEFs. Application of EEFs induce the polarizability of electrons, atoms and dipoles, resulting in an eventual reorientation of the molecules along the applied electric field of the molecules and the electron density redistribution at particular atoms [32]. As a general rule, one can module that two orbitals or states, which cannot mix by symmetry in the absence of a field, will do so when an EEF is applied along the axis that possesses the same symmetry as the direct product of the two orbitals/states [33].
We used the FERMO concept [26] to understand how the electric field acted on the molecular orbitals of the studied reaction. This concept is based on simultaneous analysis of composition and shapes of frontier molecular orbitals to determine the real molecular orbital governing a reaction. According to this approach, a frontier molecular orbital may even correspond to the FERMO for a given reaction and not for another. The HOMO itself would only be the orbital that rules a reaction if it fulfills the requirements to be the FERMO [34].
A strategy to quantify the location of the FERMO was developed, leading to the construction of the MOLPROJ software, based on the use of projection operators to build the molecular orbitals (MOs) by linear combination of atomic orbitals (AOs; the LCAO approach). Thus, the location of the FERMO would indicate the orbital in which the reaction occurs and, consequently, would point to the most favorable location for protonation [26, 28].
The values in Table 4 to four atoms involved in the Diels-Alder reaction (carbons: C2, C8, C9 and O, as shown in the Figure 3C) exhibit the energy and degree of localization from FERMO to HOMO. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms [26]. External electric fields oriented along the bond axis in a molecule induce significant ionicity, as well as changes in bond lengths, elongation frequencies and electronic characteristics. EEFs cause orbitals, whose mixing was prohibited in the absence of the field, to mix when the symmetry of their product is compatible with the symmetry of the applied field. As the product of the reaction has the same symmetry as an applied field along the bond axis, these two MOs will mix and hybridize, acquiring greater contributions in both the left and right atoms, leading to the development of the energetically stabilized dipole moment by the applied field [35].

Figure 4: TS between ethylene and nitrosoethylene. A) HOMO of TS without EEF; B) HOMO of TS with EEF; C) LUMO of TS without EEF; and D) LUMO of TS with EEF.

Table 4: Results for the degree of localization of MOs from TS between ethylene and nitrosoethylene.

Table 5: Values of activation barrier (?E#) with an external electric field applied in x-, y- and z-axes for two electric field magnitudes for substituents CH3/Cl and CH3/F.

As it can be seen in Table 5, only the substituent effect does not show a decrease in activation barriers, the value was 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcal.mol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. According to Jursic and Zdravkovski [29], the reaction between nitrosoethylene and ethylene, when catalyzed with borane, is a Diels-Alder reaction with inverse electron demand. Therefore, when we introduced electron donor groups in the diene, we would find a higher value in the activation barrier, as it can be seen in the tables. When we added the electric field, we were able to lower

this activation barrier. We realize that in fact the electric field acted as a catalyst.
Figure 5 shows the effect of the main catalysts on the activation barrier of the reaction between ethylene and nitrosoethylene. As can be seen, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Figure 5: Difference in the energy of the activation barrier without BH3, with the borane bonding in nitrogen and reaction with EEF.

Conclusion
In this study, the DA reaction between ethylene and nitrosoethylene with/without BH3, electric field and substituted dienophiles was studied theoretically using RHF and MP3 calculations aimed to determine which was the best catalyst to reaction. When the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst. We used the FERMO concept to understand how the electric field acted on the molecular orbitals of the studied reaction. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms. Only the substituent effect does not show a decrease in activation barriers. The values were 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcalmol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. Therefore, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Referências
1. Houk KN, Strozier RW (1973) On Lewis Acid Catalysis of Diels-Alder Reactions. J Am Chem Soc 95:4094?4096. https://doi.org/10.1021/ja00793a070
2. García JI, Martínez-Merino V, Mayoral JA, Salvatella L (1998) Density functional theory study of a Lewis acid catalyzed Diels-Alder reaction. The butadiene + acrolein paradigm. J Am Chem Soc 120:2415?2420. https://doi.org/10.1021/ja9722279
3. Domingo LR (2002) A density functional theory study for the Diels-Alder reaction between N-acyl-1-aza-1,3-butadienes and vinylamines. Lewis acid catalyst and solvent effects. Tetrahedron 58:3765?3774. https://doi.org/10.1016/S0040-4020(02)00326-5
4. Kang J, Rebek J (1997) Acceleration of a Diels-Alder reaction by a self-assembled molecular capsule. Nature 385:50?52. https://doi.org/10.1038/385050a0
5. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
6. Gatzenmeier T, Van Gemmeren M, Xie Y, et al (2016) Asymmetric Lewis acid organocatalysis of the Diels-Alder reaction by a silylated C-H acid. Science (80-) 351:949?952. https://doi.org/10.1126/science.aae0010
7. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
8. Dyan OT, Andreev R V., Zaikin PA (2021) Substituents effects in the Diels-Alder reaction of 1,1-difluoronaphthalen-2(1H)-ones with cyclopentadiene. J Fluor Chem 250:109859. https://doi.org/10.1016/j.jfluchem.2021.109859
9. Gara R, Zouaghi MO, ALshandoudi LMH, Arfaoui Y (2021) DFT investigation of solvent, substituent, and

catalysis effects on the intramolecular Diels-Alder reaction. J Mol Model 27:. https://doi.org/10.1007/s00894-021-04729-w
10. Hernández-Mancera JP, Rojas-Valencia N, Núñez-Zarur F (2022) Rationalizing the Substituent Effects in Diels-Alder Reactions of Triazolinediones with Anthracene. J Phys Chem A 126:6657?6667. https://doi.org/10.1021/ACS.JPCA.2C04970/SUPPL_FILE/JP2C04970_SI_001.PDF
11. Khan TS, Gupta S, Ahmad M, et al (2020) Effect of substituents and promoters on the Diels-Alder cycloaddition reaction in the biorenewable synthesis of trimellitic acid. RSC Adv 10:30656?30670. https://doi.org/10.1039/d0ra04318d
12. Aragonès AC, Haworth NL, Darwish N, et al (2016) Electrostatic catalysis of a Diels-Alder reaction. Nature 531:88?91. https://doi.org/10.1038/nature16989
13. Meir R, Chen H, Lai W, Shaik S (2010) Oriented electric fields accelerate diels-alder reactions and control the endo/exo selectivity. ChemPhysChem 11:301?310. https://doi.org/10.1002/cphc.200900848
14. Wang Z, Danovich D, Ramanan R, Shaik S (2018) Oriented-External Electric Fields Create Absolute Enantioselectivity in Diels-Alder Reactions: Importance of the Molecular Dipole Moment. J Am Chem Soc 140:13350?13359. https://doi.org/10.1021/jacs.8b08233
15. Gryn?ova G, Coote ML (2013) Origin and scope of long-range stabilizing interactions and associated SOMO-HOMO conversion in distonic radical anions. J Am Chem Soc 135:15392?15403. https://doi.org/10.1021/ja404279f
16. Shaik S, De Visser SP, Kumar D (2004) External electric field will control the selectivity of enzymatic-like bond activations. J Am Chem Soc 126:11746?11749. https://doi.org/10.1021/ja047432k
17. Andrés JL, Lledós A, Duran M, Bertrán J (1988) Electric fields acting as catalysts in chemical reactions. An ab initio study of the walden inversion reaction. Chem Phys Lett 153:82?86. https://doi.org/10.1016/0009-2614(88)80136-2
18. Carbonell E, Duran M, Lledós A, Bertrán J (1991) Catalysis of Friedel-Crafts reactions by electric fields. J Phys Chem 95:179?183. https://doi.org/10.1021/j100154a036
19. Huang X, Tang C, Li J, et al (2019) Electric field?induced selective catalysis of single-molecule reaction. Sci Adv 5:eaaw3072. https://doi.org/10.1126/sciadv.aaw3072
20. Léonard NG, Dhaoui R, Chantarojsiri T, Yang JY (2021) Electric Fields in Catalysis: From Enzymes to Molecular Catalysts. ACS Catal 11:10923?10932. https://doi.org/10.1021/acscatal.1c02084
21. Dubey KD, Stuyver T, Shaik S (2022) Local Electric Fields: From Enzyme Catalysis to Synthetic Catalyst Design. J Phys Chem B. https://doi.org/10.1021/ACS.JPCB.2C06422
22. Shaik S, Danovich D, Joy J, et al (2020) Electric-Field Mediated Chemistry: Uncovering and Exploiting the Potential of (Oriented) Electric Fields to Exert Chemical Catalysis and Reaction Control. J. Am. Chem. Soc. 142:12551?12562
23. Aitken HM, Coote ML (2018) Can electrostatic catalysis of Diels-Alder reactions be harnessed with pH-switchable charged functional groups? Phys Chem Chem Phys 20:10671?10676. https://doi.org/10.1039/c7cp07562f
24. G16_C01 (1)
25. Shaik S, Mandal D, Ramanan R (2016) Oriented electric fields as future smart reagents in chemistry. Nat Chem 8:1091?1098. https://doi.org/10.1038/nchem.2651
26. Braga LS, Moreira RA, Leal DHS, Ramalho TC (2019) Quantification of molecular orbitals based on projection operators: Methodological development and applications to basicity prediction of organic compounds in the gas phase. Chem Phys Lett 726:87?92. https://doi.org/10.1016/j.cplett.2019.04.023
27. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for

-Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:. https://doi.org/10.2174/1385272824666200204121044
28. Braga LS, Henriques Soares Leal D, Ramalho TC (2022) Rationalising the regioselectivity of substituted phenols from the FERMO concept: stereoelectronic effects on protonation and functionalization . https://doi.org/101080/0892702220222039390 48:610?620. https://doi.org /10.1080/08927022.2022.2039390
29. Jursic BS, Zdravkovski Z (1995) Theoretical Study of the BH3-Catalyzed Hetero Diels?Alder Reaction between Ethylene and Nitrosoethylene. J Org Chem 60:3163?3168. https://doi.org/10.1021/jo00115a036
30. Rowley D, Steiner H (1951) Kinetics of diene reactions at high temperatures. Discuss Faraday Soc 10:198?213. https://doi.org/10.1039/DF9511000198
31. Nori V, Pesciaioli F, Sinibaldi A, et al (2022) Boron-based lewis acid catalysis: Challenges and perspectives. Catalysts 12:. https://doi.org/10.3390/catal12010005
32. Toledo EJL, Custodio R, Ramalho TC, et al (2009) Electrical field effects on dipole moment, structure and energetic of (H2O)n (2 ? n ? 15) cluster. J Mol Struct THEOCHEM 915:170?177. https://doi.org /10.1016/j.theochem.2009.08.035
33. Mazurkiewicz J, Tomasik P (2012) Effect of external electric field upon charge distribution, energy and dipole moment of selected monosaccharide molecules. Nat Sci 04:276?285. https://doi.org/10.4236/ns .2012.45040
34. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for -Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:314?331. https://doi.org/10.2174/1385272824666200204121044
35. Stuyver T, Danovich D, Joy J, Shaik S (2020) External electric field effects on chemical structure and reactivity. Wiley Interdiscip Rev Comput Mol Sci 10:1?22. https://doi.org/10.1002/wcms.1438

Lewis Acid?E# Activation Barrier of paper [29](kcal.mol-1)MP3/6-31G(d)?E#Activation Barrier in this work (kcal.mol-1)MP3/6-31G(d)
Without BH320.344920.3624
BH3 bonding oxygen13.707813.7962
BH3 bonding nitrogen11.622311.6025

Electron-donating (X)Electron-withdrawing (Y)?E# (kcal.mol-1)MP3/6-31G(d)
CH3Cl23.3857
F23.2107

F (au)?E# (kcal.mol-1)MP3/6-31G(d)
xyz
0.08021.081118.007424.8302
-0.08017.945318.220118.3186
0.12520.981118.200018.6625
-0.1256.393818.000018.4103

Without EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.643098-140.30580.3750-181.10180.348421-225.0075

C20.158948-140.30580.2003-181.10180.550036-225.0075
C80.034416-140.30580.4971-181.10180.282893-225.0075
C90.174964-140.30580.2854-181.10180.550790-225.0075
With EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.637059-141.49040.342834-185.24800.370436-218.3439
C20.167188-141.49040.164733-185.24800.565620-218.3439
C80.042363-141.49040.505992-185.24800.214219-218.3439
C90.188071-141.49040.326526-185.24800.521364-218.3439

CH3/Cl
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08023.030622.212922.1533
-0.08022.006522.281322.2161
0.12522.750127.928225.7320
-0.12522.531722.206722.5455
CH3/F
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08022.121921.881022.1012
-0.08022.246222.976621.8747
0.12522.538022.725622.5361
-0.12521.499523.026934.5554

Toward Metal- and Catalyst-free Reactions: Deciphering the substituent and external electric field effects on the Diels-Alder reaction between Ethylene and Nitrosoethylene

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Abstract
The substituents on the diene and/or dienophile can contribute to the decrease or increase of this energy. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis. The existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy. So, the goal of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field, Lewis acid (BH3) as catalysts and the influence of substituents. All calculations were performed with Gaussian09 software, the compounds were fully optimized using the restricted Hartree-Fock method with the basis set 6-31G, single-point energies determined with MP3 method and basis set 6-31G. The effects of EEFs were studied using the ?Field = M ± N? keyword with F values (F=±0,125 au and ±0,080 au) along the preferred axis. The lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.
Keywords
Electric field catalysis, external electric fields, Lewis acid, Diels-Alder reaction, FERMO.

1 Introduction

According to the Lewis definition, acids are molecules or ions capable of coordinating with unshared electron pairs, and bases are molecules or ions with unshared electron pairs available to share with acids [1]?. To be acidic in the Lewis sense, a molecule must be deficient in electrons. This is the most general acid-base concept. All Lowry-Brönsted acids are also Lewis acids, but in addition, the Lewis definition includes many other reagents, such as boron trifluoride, aluminum chloride, among others [2].
Lewis acids catalyze Diels-Alder reactions. Some examples of these acids are: SnCl4, ZnCl2, BH3 or AlCl3 ,, which can accelerate cycloaddition reactions [3, 4]?, as occurs in the reaction catalyzed by AlCl3 of cycloalkenones with 1,3-butadienes [5, 6]. The effect of substituents in the components of the Diels-Alder reaction affect it according to the Frontier Molecular Orbital (FMO) theory, in which the reactivity, regiochemistry and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial phase interaction of the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other [7]?.
The separation between the HOMO-LUMO components controls the reactivity of the Diels-Alder reaction: the smaller the energy difference between these two orbitals, the smaller the difference in activation energy between the transition state and the reaction reactants [8?11]. The substituents on the diene and/or dienophile can contribute to decrease or increase this energy. Electron-withdrawing substituents decrease the energy of LUMO and increase of HOMO, while electron-donor groups increase the energy of LUMO and decrease of HOMO [7]??. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis [12?14].
Chemical reactions can be described by the movement of electrons as well as the movement of nuclei. Thinking about it, we can understand that they can then be influenced by external electric fieldsWhether the reaction is redox or not, some theoretical studies [12, 13, 15, 16]?? the stability of molecules involved in the reaction can be influenced by electrostatic effects: stabilizing or destabilizing resonance contributors separated by charge [13]?. This fact was announced some time ago by Shaik and collaborators for the Diels-Alder reaction [16] and in another work for simple reactions of halogen and hydrogen transfer by Bertrán and collaborators [17, 18]?. Thus, there is a great interest in metal-free catalysis and specifically in catalysis by hydrogen bonding models [19].
In this scenario, the existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy [12, 20?22]?. Meir et al (2010) explored by theoretical means the effect of targeted EEFs on the rate, mechanism and endo/exo selectivity of DA reactions between butadiene and ethylene and cyclopentadiene and maleic anhydride. According to the authors, it is necessary then that the electric field is aligned in order to attenuate or strengthen the dipole along the reaction axis [13, 23].
Theoretical predictions were confirmed experimentally in 2016 by means of intermittent tunneling scanning microscopy (STM) experiments [12]?. In summary, the experiment was carried out as follows: the diene and the dienophile were "attached" to the tip and plate of the STM, respectively, restricting their orientation , providing a means of controlling the stimulus of the electric field and measuring its effect on the reaction rate [23]?. They obtained as results that, in the tested range of field forces, the reaction rate was independent of the positive polarity of the field, but it was catalyzed by increasing the intensity of the field to negative polarization. Parallel quantum-chemical calculations of the same system under experimental conditions, which confirmed that these results were due to the effect of the field on the reaction barriers [23]?. Therefore, external electric fields instead of charged chemical species such as the ?catalyst?, can manipulate a much wider range of reactions, conveniently altering reactivity and selectivity in a tunable way

that can be predicted by theory [13].
As electrostatic catalysis is the least developed form of catalysis in synthetic chemistry [12]?, the aim of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field and a Lewis acid as catalysts, in addition to checking the influence of substituents on the reaction?s diene and dienophile, in order to determine if the electric field is the best catalyst for the reaction studied.

2 Methodology
Gaussian09 software was used for all calculations [24]. The optimization calculation for all compounds was performed with restricted Hartree-Fock method with the basis set 6-31G(d). No imaginary frequencies were found for the optimized reactants geometries, which were used in all subsequent calculations and had their single-point energies determined with MP3 method and the basis set 6-31G(d). GAMESS software for Linux, version 30 SEPT 2017 (R2) and MOLPROJ software, were used to analyze their MO eigenvectors and overlapping matrices of the reaction between ethylene and nitrosoethylene, both extracted from output files of single-point energy calculations with GAMESS.
The effects of EEFs were studied using the ?Field = M ± N? keyword, which defines in Gaussian09, the axis of the EEFs, its direction along that axis, and its magnitude. For each reaction, we initially evaluated the EEF effects at different Fx,y,z values, using single-point calculations on the critical species with F values (F=±0,125 au and ±0,080 au) along the preferred axis.
In opposition to the conventional definition in Physics, in Gaussian09, the positive direction of the electric field vector is defined from negative to positive charge [14]. Thus, whenever the dipole moment (?) and field vectors (F) are oriented opposite to each other, the EEF?s will stabilize the dipole, as shown in Scheme 1 for an X-EEF. The EEFs were further oriented along the X, Y and Z axes as defined in Scheme 1, where in each case the X axis defines the "reaction axis", which is approximately the direction along which two new C? C bonds are forming [13, 14, 25].

Scheme 1: Definitions of the x, y and z directions.

Figure 1: Reactants (A) nitrosoethylene and ethylene, (B) nitrosoethylene with borane connected to oxygen and ethylene and (C) nitrosoethylene with borane connected to nitrogen and ethylene.
The optimized compounds, as shown in Figure 1, were analyzed using the MOLPROJ software [26, 27]. The eigenvectors of the MOs and the matrices of were extracted from output files of single point energy calculations with GAMESS. The degree of location of each MO (2px-z orbitals of the carbon and oxygen atoms involved in the DA reaction) and their respective energies were calculated and analyzed. [28]. For comparison, degree of localization coefficients were calculated for the molecular orbitals ?HOMO and ?FERMO. We define that the degree of localization ?FERMO is the norm of an MO projected on the expected set of atomic orbitals (that participate in the reaction), as follows in Equation 1, where ?, is the matrix of molecular orbital coefficients and ? is the overlap matrix:

Equation 1: degree of localization ?FERMO
3 Results
3.1 Validation of the theoretical strategy: The Reaction of Ethylene and Nitrosoethylene - Catalysis of a Diels-Alder reaction using a Lewis acid.

The synthetic versatility of cycloaddition reactions was extended by introducing heterodienes, which allowed rapid access to various heterocycles. Nitrosoethylene compounds lead to valuable heterocyclic compounds with an N-O bond in the cycle. However, the reactivity of these compounds strongly depends on their structure and a catalyst. This is because nitrosoethylenes are generally unstable and are generated by base promoted elimination of -haloximes. Jursic and Zdravkovski, in 1995 [29], showed in a study the difference in the activation barrier when BH3 is used as a catalyst. According to literature, the activation barrier decreased by 2.08 kcal.mol-1 when borane is linked to nitrosoethylene nitrogen.
These same authors [29] used the reaction between ethylene and butadiene to compare the reliability of the results obtained computationally from the reaction between ethylene and nitrosoethylene with the experimental values of the first reaction. The activation energy for the ethylene and butadiene reaction was 25.98 kcal.mol-1 using MP3/6-31G(d), a value which is in reasonable agreement with the experimental value (25.4 and 27.5 kcal.mol-1) [30]. As our values were obtained with a difference of approximately 0.03 kcal.mol-1 in the activation barrier values of the base article, we consider that our results are also close to the experimental values, since there are no experimental studies of the reaction between ethylene and nitrosoethylene in literature.
Given the importance and versatility of this cycloaddition reaction, we sought validation (Table 1) of the author's results to compare them when we apply the electric field and use substituents as a catalyst. Figure 2 illustrates the energy profile for the reaction without and with the use of borane (bonded to oxygen and nitrogen atoms) as catalyst.
Table 1: Activation barrier of Lewis acid to trans reaction.

Figure 2: difference in the energy of the activation barrier without catalyst and with the catalyst borane bound to the oxygen atom and to the nitrogen atom.
As can be seen in Table 1, the lowest activation barrier found was for borane bound to nitrosethylene nitrogen. The borane-catalyzed reaction has a lower activation barrier than the uncatalyzed reaction [29]. Boron reagents are often employed as Lewis acids due to their strong electrophilic nature because of a vacant p orbital that can readily accept electrons from donor molecules [31]. So, as BH3 is acting as an electron acceptor, the reaction in question occurs with reverse electron demand. Therefore, borane as a catalyst has a profound influence on the reactivity of the system, decreasing the electron density in the diene and decreasing its LUMO energy.
Note that the values of the calculated activation barriers differ slightly from this current work [29]. This minimal difference in ?E# occurred because the coordinates of the structures were not made available by the researchers. Therefore, the difference in bond lengths in the optimization had a minimal influence on the activation barriers.

3.2 Effect of the substituents to check if the reaction rate becomes even lower when they are related to some type of catalyst
According to Frontier Molecular Orbital (FMO) theory, the reactivity, regiochemistry, and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial in-phase interaction of the HOMO molecular orbital of one component and the LUMO orbital of the other [7]. When the HOMO of the diene controls the reaction, the reaction can be accelerated by electron-donating substituents on the diene and by electron-withdrawing substituents on the dienophile, thus being a normal electron-demand Diels-Alder reaction. On the other hand, the Diels-Alder reactions controlled by the LUMO of the diene are influenced by the

electronic effects of the substituents in the opposite way, that is, it is a Diels-Alder reaction with inverse electron demand.
The influence were studied by considering the following substituents: CH3, Cl and F. Considering the reaction as a normal demand for electrons, the interactions occur from the HOMO/FERMO of the dienophile to the LUMO of the diene, as can be seen in Figure 3A. Table 2 shows the activation barrier values when we replace a diene hydrogen with X = methyl and a dienophile hydrogen with a halogen (Y = Cl and F).

Figure 3: reaction scheme for the Diels-Alder reaction between ethylene and substituted nitrosoehtylene. (A) structures of reactants (left), transition state (middle) and products (right); (B) molecular orbitals involved in the reaction; (C) numbering of the atoms involved in Diels-Alder reaction.
Table 2: activation barrier values when we replace a diene hydrogen with methyl and a dienophile hydrogen with a halogen (Cl and F).

As it can be seen, the substituents did not accelerate the reaction. According to Jursic and Zdravkovski [29], the reaction between ethylene and nitrosoethylene is an inverse demand reaction. Therefore, as we are treating it as a normal electron demand reaction, it is to be expected that the activation barrier will increase in value. This increase was approximately 3.02 kcalmol-1 in relation to the reaction without any type of catalyst (20.3624 kcal.mol-1).

3.3 Effect of the electric field in the reaction between ethylene and nitrosoethylene
Table 3 shows the EEF effects on the barriers for fields oriented along the x-, y- and z-axes in positive and negative directions. It is seen that Fy and Fz do not change the barrier, which remains constant at ~18.3(±2 .8) kcalmol-1. This is because the y,z-oriented EEFs stabilize both the reactant (R?) and the transition state (TS) to the same extent. However, when the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst.

Table 3: values of activation barrier (?E#) with electric field applied in x-, y- and z-axes for two magnitude values of electric field.

As the field becomes more negative, the dipole moment becomes more positive. This change in dipole moment is accompanied by transferring charge between the reactants in the TS. As the value of Fx increases, the direction of charge transfer is reversed. Thus, the EEF not only reduces the energy of the TS , but also polarizes the TS and affects its electronic structure. In addition, the field also induces a charge transfer in its own direction, from nitrosoethylene to ethylene. In conclusion, it is apparent that when the electric field is oriented along the ?reaction axis?, which is the axis along which the two new C-C bonds are formed, it causes the reaction rate to accelerate by preferentially decreasing the transition state.
An EEF oriented in the direction of the ?reaction axis?, along which electronic reorganization takes place, can affect the reaction rate by orders of magnitude, becoming faster or slower, depending on the change in direction of the field. At the same time, the endo/exo stereoselectivity of the Diels-Alder reaction can be manipulated at will with EEFs oriented perpendicular to the reaction axis [13]. EEF changes distribution of

the electron density. Figure 4 show the molecular orbitals involved in the reaction with/without EEFs. Application of EEFs induce the polarizability of electrons, atoms and dipoles, resulting in an eventual reorientation of the molecules along the applied electric field of the molecules and the electron density redistribution at particular atoms [32]. As a general rule, one can module that two orbitals or states, which cannot mix by symmetry in the absence of a field, will do so when an EEF is applied along the axis that possesses the same symmetry as the direct product of the two orbitals/states [33].
We used the FERMO concept [26] to understand how the electric field acted on the molecular orbitals of the studied reaction. This concept is based on simultaneous analysis of composition and shapes of frontier molecular orbitals to determine the real molecular orbital governing a reaction. According to this approach, a frontier molecular orbital may even correspond to the FERMO for a given reaction and not for another. The HOMO itself would only be the orbital that rules a reaction if it fulfills the requirements to be the FERMO [34].
A strategy to quantify the location of the FERMO was developed, leading to the construction of the MOLPROJ software, based on the use of projection operators to build the molecular orbitals (MOs) by linear combination of atomic orbitals (AOs; the LCAO approach). Thus, the location of the FERMO would indicate the orbital in which the reaction occurs and, consequently, would point to the most favorable location for protonation [26, 28].
The values in Table 4 to four atoms involved in the Diels-Alder reaction (carbons: C2, C8, C9 and O, as shown in the Figure 3C) exhibit the energy and degree of localization from FERMO to HOMO. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms [26]. External electric fields oriented along the bond axis in a molecule induce significant ionicity, as well as changes in bond lengths, elongation frequencies and electronic characteristics. EEFs cause orbitals, whose mixing was prohibited in the absence of the field, to mix when the symmetry of their product is compatible with the symmetry of the applied field. As the product of the reaction has the same symmetry as an applied field along the bond axis, these two MOs will mix and hybridize, acquiring greater contributions in both the left and right atoms, leading to the development of the energetically stabilized dipole moment by the applied field [35].

Figure 4: TS between ethylene and nitrosoethylene. A) HOMO of TS without EEF; B) HOMO of TS with EEF; C) LUMO of TS without EEF; and D) LUMO of TS with EEF.

Table 4: Results for the degree of localization of MOs from TS between ethylene and nitrosoethylene.

Table 5: Values of activation barrier (?E#) with an external electric field applied in x-, y- and z-axes for two electric field magnitudes for substituents CH3/Cl and CH3/F.

As it can be seen in Table 5, only the substituent effect does not show a decrease in activation barriers, the value was 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcal.mol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. According to Jursic and Zdravkovski [29], the reaction between nitrosoethylene and ethylene, when catalyzed with borane, is a Diels-Alder reaction with inverse electron demand. Therefore, when we introduced electron donor groups in the diene, we would find a higher value in the activation barrier, as it can be seen in the tables. When we added the electric field, we were able to lower

this activation barrier. We realize that in fact the electric field acted as a catalyst.
Figure 5 shows the effect of the main catalysts on the activation barrier of the reaction between ethylene and nitrosoethylene. As can be seen, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Figure 5: Difference in the energy of the activation barrier without BH3, with the borane bonding in nitrogen and reaction with EEF.

Conclusion
In this study, the DA reaction between ethylene and nitrosoethylene with/without BH3, electric field and substituted dienophiles was studied theoretically using RHF and MP3 calculations aimed to determine which was the best catalyst to reaction. When the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst. We used the FERMO concept to understand how the electric field acted on the molecular orbitals of the studied reaction. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms. Only the substituent effect does not show a decrease in activation barriers. The values were 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcalmol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. Therefore, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Referências
1. Houk KN, Strozier RW (1973) On Lewis Acid Catalysis of Diels-Alder Reactions. J Am Chem Soc 95:4094?4096. https://doi.org/10.1021/ja00793a070
2. García JI, Martínez-Merino V, Mayoral JA, Salvatella L (1998) Density functional theory study of a Lewis acid catalyzed Diels-Alder reaction. The butadiene + acrolein paradigm. J Am Chem Soc 120:2415?2420. https://doi.org/10.1021/ja9722279
3. Domingo LR (2002) A density functional theory study for the Diels-Alder reaction between N-acyl-1-aza-1,3-butadienes and vinylamines. Lewis acid catalyst and solvent effects. Tetrahedron 58:3765?3774. https://doi.org/10.1016/S0040-4020(02)00326-5
4. Kang J, Rebek J (1997) Acceleration of a Diels-Alder reaction by a self-assembled molecular capsule. Nature 385:50?52. https://doi.org/10.1038/385050a0
5. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
6. Gatzenmeier T, Van Gemmeren M, Xie Y, et al (2016) Asymmetric Lewis acid organocatalysis of the Diels-Alder reaction by a silylated C-H acid. Science (80-) 351:949?952. https://doi.org/10.1126/science.aae0010
7. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
8. Dyan OT, Andreev R V., Zaikin PA (2021) Substituents effects in the Diels-Alder reaction of 1,1-difluoronaphthalen-2(1H)-ones with cyclopentadiene. J Fluor Chem 250:109859. https://doi.org/10.1016/j.jfluchem.2021.109859
9. Gara R, Zouaghi MO, ALshandoudi LMH, Arfaoui Y (2021) DFT investigation of solvent, substituent, and

catalysis effects on the intramolecular Diels-Alder reaction. J Mol Model 27:. https://doi.org/10.1007/s00894-021-04729-w
10. Hernández-Mancera JP, Rojas-Valencia N, Núñez-Zarur F (2022) Rationalizing the Substituent Effects in Diels-Alder Reactions of Triazolinediones with Anthracene. J Phys Chem A 126:6657?6667. https://doi.org/10.1021/ACS.JPCA.2C04970/SUPPL_FILE/JP2C04970_SI_001.PDF
11. Khan TS, Gupta S, Ahmad M, et al (2020) Effect of substituents and promoters on the Diels-Alder cycloaddition reaction in the biorenewable synthesis of trimellitic acid. RSC Adv 10:30656?30670. https://doi.org/10.1039/d0ra04318d
12. Aragonès AC, Haworth NL, Darwish N, et al (2016) Electrostatic catalysis of a Diels-Alder reaction. Nature 531:88?91. https://doi.org/10.1038/nature16989
13. Meir R, Chen H, Lai W, Shaik S (2010) Oriented electric fields accelerate diels-alder reactions and control the endo/exo selectivity. ChemPhysChem 11:301?310. https://doi.org/10.1002/cphc.200900848
14. Wang Z, Danovich D, Ramanan R, Shaik S (2018) Oriented-External Electric Fields Create Absolute Enantioselectivity in Diels-Alder Reactions: Importance of the Molecular Dipole Moment. J Am Chem Soc 140:13350?13359. https://doi.org/10.1021/jacs.8b08233
15. Gryn?ova G, Coote ML (2013) Origin and scope of long-range stabilizing interactions and associated SOMO-HOMO conversion in distonic radical anions. J Am Chem Soc 135:15392?15403. https://doi.org/10.1021/ja404279f
16. Shaik S, De Visser SP, Kumar D (2004) External electric field will control the selectivity of enzymatic-like bond activations. J Am Chem Soc 126:11746?11749. https://doi.org/10.1021/ja047432k
17. Andrés JL, Lledós A, Duran M, Bertrán J (1988) Electric fields acting as catalysts in chemical reactions. An ab initio study of the walden inversion reaction. Chem Phys Lett 153:82?86. https://doi.org/10.1016/0009-2614(88)80136-2
18. Carbonell E, Duran M, Lledós A, Bertrán J (1991) Catalysis of Friedel-Crafts reactions by electric fields. J Phys Chem 95:179?183. https://doi.org/10.1021/j100154a036
19. Huang X, Tang C, Li J, et al (2019) Electric field?induced selective catalysis of single-molecule reaction. Sci Adv 5:eaaw3072. https://doi.org/10.1126/sciadv.aaw3072
20. Léonard NG, Dhaoui R, Chantarojsiri T, Yang JY (2021) Electric Fields in Catalysis: From Enzymes to Molecular Catalysts. ACS Catal 11:10923?10932. https://doi.org/10.1021/acscatal.1c02084
21. Dubey KD, Stuyver T, Shaik S (2022) Local Electric Fields: From Enzyme Catalysis to Synthetic Catalyst Design. J Phys Chem B. https://doi.org/10.1021/ACS.JPCB.2C06422
22. Shaik S, Danovich D, Joy J, et al (2020) Electric-Field Mediated Chemistry: Uncovering and Exploiting the Potential of (Oriented) Electric Fields to Exert Chemical Catalysis and Reaction Control. J. Am. Chem. Soc. 142:12551?12562
23. Aitken HM, Coote ML (2018) Can electrostatic catalysis of Diels-Alder reactions be harnessed with pH-switchable charged functional groups? Phys Chem Chem Phys 20:10671?10676. https://doi.org/10.1039/c7cp07562f
24. G16_C01 (1)
25. Shaik S, Mandal D, Ramanan R (2016) Oriented electric fields as future smart reagents in chemistry. Nat Chem 8:1091?1098. https://doi.org/10.1038/nchem.2651
26. Braga LS, Moreira RA, Leal DHS, Ramalho TC (2019) Quantification of molecular orbitals based on projection operators: Methodological development and applications to basicity prediction of organic compounds in the gas phase. Chem Phys Lett 726:87?92. https://doi.org/10.1016/j.cplett.2019.04.023
27. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for

-Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:. https://doi.org/10.2174/1385272824666200204121044
28. Braga LS, Henriques Soares Leal D, Ramalho TC (2022) Rationalising the regioselectivity of substituted phenols from the FERMO concept: stereoelectronic effects on protonation and functionalization . https://doi.org/101080/0892702220222039390 48:610?620. https://doi.org /10.1080/08927022.2022.2039390
29. Jursic BS, Zdravkovski Z (1995) Theoretical Study of the BH3-Catalyzed Hetero Diels?Alder Reaction between Ethylene and Nitrosoethylene. J Org Chem 60:3163?3168. https://doi.org/10.1021/jo00115a036
30. Rowley D, Steiner H (1951) Kinetics of diene reactions at high temperatures. Discuss Faraday Soc 10:198?213. https://doi.org/10.1039/DF9511000198
31. Nori V, Pesciaioli F, Sinibaldi A, et al (2022) Boron-based lewis acid catalysis: Challenges and perspectives. Catalysts 12:. https://doi.org/10.3390/catal12010005
32. Toledo EJL, Custodio R, Ramalho TC, et al (2009) Electrical field effects on dipole moment, structure and energetic of (H2O)n (2 ? n ? 15) cluster. J Mol Struct THEOCHEM 915:170?177. https://doi.org /10.1016/j.theochem.2009.08.035
33. Mazurkiewicz J, Tomasik P (2012) Effect of external electric field upon charge distribution, energy and dipole moment of selected monosaccharide molecules. Nat Sci 04:276?285. https://doi.org/10.4236/ns .2012.45040
34. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for -Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:314?331. https://doi.org/10.2174/1385272824666200204121044
35. Stuyver T, Danovich D, Joy J, Shaik S (2020) External electric field effects on chemical structure and reactivity. Wiley Interdiscip Rev Comput Mol Sci 10:1?22. https://doi.org/10.1002/wcms.1438

Lewis Acid?E# Activation Barrier of paper [29](kcal.mol-1)MP3/6-31G(d)?E#Activation Barrier in this work (kcal.mol-1)MP3/6-31G(d)
Without BH320.344920.3624
BH3 bonding oxygen13.707813.7962
BH3 bonding nitrogen11.622311.6025

Electron-donating (X)Electron-withdrawing (Y)?E# (kcal.mol-1)MP3/6-31G(d)
CH3Cl23.3857
F23.2107

F (au)?E# (kcal.mol-1)MP3/6-31G(d)
xyz
0.08021.081118.007424.8302
-0.08017.945318.220118.3186
0.12520.981118.200018.6625
-0.1256.393818.000018.4103

Without EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.643098-140.30580.3750-181.10180.348421-225.0075

C20.158948-140.30580.2003-181.10180.550036-225.0075
C80.034416-140.30580.4971-181.10180.282893-225.0075
C90.174964-140.30580.2854-181.10180.550790-225.0075
With EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.637059-141.49040.342834-185.24800.370436-218.3439
C20.167188-141.49040.164733-185.24800.565620-218.3439
C80.042363-141.49040.505992-185.24800.214219-218.3439
C90.188071-141.49040.326526-185.24800.521364-218.3439

CH3/Cl
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08023.030622.212922.1533
-0.08022.006522.281322.2161
0.12522.750127.928225.7320
-0.12522.531722.206722.5455
CH3/F
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08022.121921.881022.1012
-0.08022.246222.976621.8747
0.12522.538022.725622.5361
-0.12521.499523.026934.5554

Toward Metal- and Catalyst-free Reactions: Deciphering the substituent and external electric field effects on the Diels-Alder reaction between Ethylene and Nitrosoethylene

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Abstract
The substituents on the diene and/or dienophile can contribute to the decrease or increase of this energy. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis. The existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy. So, the goal of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field, Lewis acid (BH3) as catalysts and the influence of substituents. All calculations were performed with Gaussian09 software, the compounds were fully optimized using the restricted Hartree-Fock method with the basis set 6-31G, single-point energies determined with MP3 method and basis set 6-31G. The effects of EEFs were studied using the ?Field = M ± N? keyword with F values (F=±0,125 au and ±0,080 au) along the preferred axis. The lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.
Keywords
Electric field catalysis, external electric fields, Lewis acid, Diels-Alder reaction, FERMO.

1 Introduction

According to the Lewis definition, acids are molecules or ions capable of coordinating with unshared electron pairs, and bases are molecules or ions with unshared electron pairs available to share with acids [1]?. To be acidic in the Lewis sense, a molecule must be deficient in electrons. This is the most general acid-base concept. All Lowry-Brönsted acids are also Lewis acids, but in addition, the Lewis definition includes many other reagents, such as boron trifluoride, aluminum chloride, among others [2].
Lewis acids catalyze Diels-Alder reactions. Some examples of these acids are: SnCl4, ZnCl2, BH3 or AlCl3 ,, which can accelerate cycloaddition reactions [3, 4]?, as occurs in the reaction catalyzed by AlCl3 of cycloalkenones with 1,3-butadienes [5, 6]. The effect of substituents in the components of the Diels-Alder reaction affect it according to the Frontier Molecular Orbital (FMO) theory, in which the reactivity, regiochemistry and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial phase interaction of the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other [7]?.
The separation between the HOMO-LUMO components controls the reactivity of the Diels-Alder reaction: the smaller the energy difference between these two orbitals, the smaller the difference in activation energy between the transition state and the reaction reactants [8?11]. The substituents on the diene and/or dienophile can contribute to decrease or increase this energy. Electron-withdrawing substituents decrease the energy of LUMO and increase of HOMO, while electron-donor groups increase the energy of LUMO and decrease of HOMO [7]??. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis [12?14].
Chemical reactions can be described by the movement of electrons as well as the movement of nuclei. Thinking about it, we can understand that they can then be influenced by external electric fieldsWhether the reaction is redox or not, some theoretical studies [12, 13, 15, 16]?? the stability of molecules involved in the reaction can be influenced by electrostatic effects: stabilizing or destabilizing resonance contributors separated by charge [13]?. This fact was announced some time ago by Shaik and collaborators for the Diels-Alder reaction [16] and in another work for simple reactions of halogen and hydrogen transfer by Bertrán and collaborators [17, 18]?. Thus, there is a great interest in metal-free catalysis and specifically in catalysis by hydrogen bonding models [19].
In this scenario, the existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy [12, 20?22]?. Meir et al (2010) explored by theoretical means the effect of targeted EEFs on the rate, mechanism and endo/exo selectivity of DA reactions between butadiene and ethylene and cyclopentadiene and maleic anhydride. According to the authors, it is necessary then that the electric field is aligned in order to attenuate or strengthen the dipole along the reaction axis [13, 23].
Theoretical predictions were confirmed experimentally in 2016 by means of intermittent tunneling scanning microscopy (STM) experiments [12]?. In summary, the experiment was carried out as follows: the diene and the dienophile were "attached" to the tip and plate of the STM, respectively, restricting their orientation , providing a means of controlling the stimulus of the electric field and measuring its effect on the reaction rate [23]?. They obtained as results that, in the tested range of field forces, the reaction rate was independent of the positive polarity of the field, but it was catalyzed by increasing the intensity of the field to negative polarization. Parallel quantum-chemical calculations of the same system under experimental conditions, which confirmed that these results were due to the effect of the field on the reaction barriers [23]?. Therefore, external electric fields instead of charged chemical species such as the ?catalyst?, can manipulate a much wider range of reactions, conveniently altering reactivity and selectivity in a tunable way

that can be predicted by theory [13].
As electrostatic catalysis is the least developed form of catalysis in synthetic chemistry [12]?, the aim of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field and a Lewis acid as catalysts, in addition to checking the influence of substituents on the reaction?s diene and dienophile, in order to determine if the electric field is the best catalyst for the reaction studied.

2 Methodology
Gaussian09 software was used for all calculations [24]. The optimization calculation for all compounds was performed with restricted Hartree-Fock method with the basis set 6-31G(d). No imaginary frequencies were found for the optimized reactants geometries, which were used in all subsequent calculations and had their single-point energies determined with MP3 method and the basis set 6-31G(d). GAMESS software for Linux, version 30 SEPT 2017 (R2) and MOLPROJ software, were used to analyze their MO eigenvectors and overlapping matrices of the reaction between ethylene and nitrosoethylene, both extracted from output files of single-point energy calculations with GAMESS.
The effects of EEFs were studied using the ?Field = M ± N? keyword, which defines in Gaussian09, the axis of the EEFs, its direction along that axis, and its magnitude. For each reaction, we initially evaluated the EEF effects at different Fx,y,z values, using single-point calculations on the critical species with F values (F=±0,125 au and ±0,080 au) along the preferred axis.
In opposition to the conventional definition in Physics, in Gaussian09, the positive direction of the electric field vector is defined from negative to positive charge [14]. Thus, whenever the dipole moment (?) and field vectors (F) are oriented opposite to each other, the EEF?s will stabilize the dipole, as shown in Scheme 1 for an X-EEF. The EEFs were further oriented along the X, Y and Z axes as defined in Scheme 1, where in each case the X axis defines the "reaction axis", which is approximately the direction along which two new C? C bonds are forming [13, 14, 25].

Scheme 1: Definitions of the x, y and z directions.

Figure 1: Reactants (A) nitrosoethylene and ethylene, (B) nitrosoethylene with borane connected to oxygen and ethylene and (C) nitrosoethylene with borane connected to nitrogen and ethylene.
The optimized compounds, as shown in Figure 1, were analyzed using the MOLPROJ software [26, 27]. The eigenvectors of the MOs and the matrices of were extracted from output files of single point energy calculations with GAMESS. The degree of location of each MO (2px-z orbitals of the carbon and oxygen atoms involved in the DA reaction) and their respective energies were calculated and analyzed. [28]. For comparison, degree of localization coefficients were calculated for the molecular orbitals ?HOMO and ?FERMO. We define that the degree of localization ?FERMO is the norm of an MO projected on the expected set of atomic orbitals (that participate in the reaction), as follows in Equation 1, where ?, is the matrix of molecular orbital coefficients and ? is the overlap matrix:

Equation 1: degree of localization ?FERMO
3 Results
3.1 Validation of the theoretical strategy: The Reaction of Ethylene and Nitrosoethylene - Catalysis of a Diels-Alder reaction using a Lewis acid.

The synthetic versatility of cycloaddition reactions was extended by introducing heterodienes, which allowed rapid access to various heterocycles. Nitrosoethylene compounds lead to valuable heterocyclic compounds with an N-O bond in the cycle. However, the reactivity of these compounds strongly depends on their structure and a catalyst. This is because nitrosoethylenes are generally unstable and are generated by base promoted elimination of -haloximes. Jursic and Zdravkovski, in 1995 [29], showed in a study the difference in the activation barrier when BH3 is used as a catalyst. According to literature, the activation barrier decreased by 2.08 kcal.mol-1 when borane is linked to nitrosoethylene nitrogen.
These same authors [29] used the reaction between ethylene and butadiene to compare the reliability of the results obtained computationally from the reaction between ethylene and nitrosoethylene with the experimental values of the first reaction. The activation energy for the ethylene and butadiene reaction was 25.98 kcal.mol-1 using MP3/6-31G(d), a value which is in reasonable agreement with the experimental value (25.4 and 27.5 kcal.mol-1) [30]. As our values were obtained with a difference of approximately 0.03 kcal.mol-1 in the activation barrier values of the base article, we consider that our results are also close to the experimental values, since there are no experimental studies of the reaction between ethylene and nitrosoethylene in literature.
Given the importance and versatility of this cycloaddition reaction, we sought validation (Table 1) of the author's results to compare them when we apply the electric field and use substituents as a catalyst. Figure 2 illustrates the energy profile for the reaction without and with the use of borane (bonded to oxygen and nitrogen atoms) as catalyst.
Table 1: Activation barrier of Lewis acid to trans reaction.

Figure 2: difference in the energy of the activation barrier without catalyst and with the catalyst borane bound to the oxygen atom and to the nitrogen atom.
As can be seen in Table 1, the lowest activation barrier found was for borane bound to nitrosethylene nitrogen. The borane-catalyzed reaction has a lower activation barrier than the uncatalyzed reaction [29]. Boron reagents are often employed as Lewis acids due to their strong electrophilic nature because of a vacant p orbital that can readily accept electrons from donor molecules [31]. So, as BH3 is acting as an electron acceptor, the reaction in question occurs with reverse electron demand. Therefore, borane as a catalyst has a profound influence on the reactivity of the system, decreasing the electron density in the diene and decreasing its LUMO energy.
Note that the values of the calculated activation barriers differ slightly from this current work [29]. This minimal difference in ?E# occurred because the coordinates of the structures were not made available by the researchers. Therefore, the difference in bond lengths in the optimization had a minimal influence on the activation barriers.

3.2 Effect of the substituents to check if the reaction rate becomes even lower when they are related to some type of catalyst
According to Frontier Molecular Orbital (FMO) theory, the reactivity, regiochemistry, and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial in-phase interaction of the HOMO molecular orbital of one component and the LUMO orbital of the other [7]. When the HOMO of the diene controls the reaction, the reaction can be accelerated by electron-donating substituents on the diene and by electron-withdrawing substituents on the dienophile, thus being a normal electron-demand Diels-Alder reaction. On the other hand, the Diels-Alder reactions controlled by the LUMO of the diene are influenced by the

electronic effects of the substituents in the opposite way, that is, it is a Diels-Alder reaction with inverse electron demand.
The influence were studied by considering the following substituents: CH3, Cl and F. Considering the reaction as a normal demand for electrons, the interactions occur from the HOMO/FERMO of the dienophile to the LUMO of the diene, as can be seen in Figure 3A. Table 2 shows the activation barrier values when we replace a diene hydrogen with X = methyl and a dienophile hydrogen with a halogen (Y = Cl and F).

Figure 3: reaction scheme for the Diels-Alder reaction between ethylene and substituted nitrosoehtylene. (A) structures of reactants (left), transition state (middle) and products (right); (B) molecular orbitals involved in the reaction; (C) numbering of the atoms involved in Diels-Alder reaction.
Table 2: activation barrier values when we replace a diene hydrogen with methyl and a dienophile hydrogen with a halogen (Cl and F).

As it can be seen, the substituents did not accelerate the reaction. According to Jursic and Zdravkovski [29], the reaction between ethylene and nitrosoethylene is an inverse demand reaction. Therefore, as we are treating it as a normal electron demand reaction, it is to be expected that the activation barrier will increase in value. This increase was approximately 3.02 kcalmol-1 in relation to the reaction without any type of catalyst (20.3624 kcal.mol-1).

3.3 Effect of the electric field in the reaction between ethylene and nitrosoethylene
Table 3 shows the EEF effects on the barriers for fields oriented along the x-, y- and z-axes in positive and negative directions. It is seen that Fy and Fz do not change the barrier, which remains constant at ~18.3(±2 .8) kcalmol-1. This is because the y,z-oriented EEFs stabilize both the reactant (R?) and the transition state (TS) to the same extent. However, when the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst.

Table 3: values of activation barrier (?E#) with electric field applied in x-, y- and z-axes for two magnitude values of electric field.

As the field becomes more negative, the dipole moment becomes more positive. This change in dipole moment is accompanied by transferring charge between the reactants in the TS. As the value of Fx increases, the direction of charge transfer is reversed. Thus, the EEF not only reduces the energy of the TS , but also polarizes the TS and affects its electronic structure. In addition, the field also induces a charge transfer in its own direction, from nitrosoethylene to ethylene. In conclusion, it is apparent that when the electric field is oriented along the ?reaction axis?, which is the axis along which the two new C-C bonds are formed, it causes the reaction rate to accelerate by preferentially decreasing the transition state.
An EEF oriented in the direction of the ?reaction axis?, along which electronic reorganization takes place, can affect the reaction rate by orders of magnitude, becoming faster or slower, depending on the change in direction of the field. At the same time, the endo/exo stereoselectivity of the Diels-Alder reaction can be manipulated at will with EEFs oriented perpendicular to the reaction axis [13]. EEF changes distribution of

the electron density. Figure 4 show the molecular orbitals involved in the reaction with/without EEFs. Application of EEFs induce the polarizability of electrons, atoms and dipoles, resulting in an eventual reorientation of the molecules along the applied electric field of the molecules and the electron density redistribution at particular atoms [32]. As a general rule, one can module that two orbitals or states, which cannot mix by symmetry in the absence of a field, will do so when an EEF is applied along the axis that possesses the same symmetry as the direct product of the two orbitals/states [33].
We used the FERMO concept [26] to understand how the electric field acted on the molecular orbitals of the studied reaction. This concept is based on simultaneous analysis of composition and shapes of frontier molecular orbitals to determine the real molecular orbital governing a reaction. According to this approach, a frontier molecular orbital may even correspond to the FERMO for a given reaction and not for another. The HOMO itself would only be the orbital that rules a reaction if it fulfills the requirements to be the FERMO [34].
A strategy to quantify the location of the FERMO was developed, leading to the construction of the MOLPROJ software, based on the use of projection operators to build the molecular orbitals (MOs) by linear combination of atomic orbitals (AOs; the LCAO approach). Thus, the location of the FERMO would indicate the orbital in which the reaction occurs and, consequently, would point to the most favorable location for protonation [26, 28].
The values in Table 4 to four atoms involved in the Diels-Alder reaction (carbons: C2, C8, C9 and O, as shown in the Figure 3C) exhibit the energy and degree of localization from FERMO to HOMO. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms [26]. External electric fields oriented along the bond axis in a molecule induce significant ionicity, as well as changes in bond lengths, elongation frequencies and electronic characteristics. EEFs cause orbitals, whose mixing was prohibited in the absence of the field, to mix when the symmetry of their product is compatible with the symmetry of the applied field. As the product of the reaction has the same symmetry as an applied field along the bond axis, these two MOs will mix and hybridize, acquiring greater contributions in both the left and right atoms, leading to the development of the energetically stabilized dipole moment by the applied field [35].

Figure 4: TS between ethylene and nitrosoethylene. A) HOMO of TS without EEF; B) HOMO of TS with EEF; C) LUMO of TS without EEF; and D) LUMO of TS with EEF.

Table 4: Results for the degree of localization of MOs from TS between ethylene and nitrosoethylene.

Table 5: Values of activation barrier (?E#) with an external electric field applied in x-, y- and z-axes for two electric field magnitudes for substituents CH3/Cl and CH3/F.

As it can be seen in Table 5, only the substituent effect does not show a decrease in activation barriers, the value was 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcal.mol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. According to Jursic and Zdravkovski [29], the reaction between nitrosoethylene and ethylene, when catalyzed with borane, is a Diels-Alder reaction with inverse electron demand. Therefore, when we introduced electron donor groups in the diene, we would find a higher value in the activation barrier, as it can be seen in the tables. When we added the electric field, we were able to lower

this activation barrier. We realize that in fact the electric field acted as a catalyst.
Figure 5 shows the effect of the main catalysts on the activation barrier of the reaction between ethylene and nitrosoethylene. As can be seen, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Figure 5: Difference in the energy of the activation barrier without BH3, with the borane bonding in nitrogen and reaction with EEF.

Conclusion
In this study, the DA reaction between ethylene and nitrosoethylene with/without BH3, electric field and substituted dienophiles was studied theoretically using RHF and MP3 calculations aimed to determine which was the best catalyst to reaction. When the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst. We used the FERMO concept to understand how the electric field acted on the molecular orbitals of the studied reaction. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms. Only the substituent effect does not show a decrease in activation barriers. The values were 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcalmol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. Therefore, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Referências
1. Houk KN, Strozier RW (1973) On Lewis Acid Catalysis of Diels-Alder Reactions. J Am Chem Soc 95:4094?4096. https://doi.org/10.1021/ja00793a070
2. García JI, Martínez-Merino V, Mayoral JA, Salvatella L (1998) Density functional theory study of a Lewis acid catalyzed Diels-Alder reaction. The butadiene + acrolein paradigm. J Am Chem Soc 120:2415?2420. https://doi.org/10.1021/ja9722279
3. Domingo LR (2002) A density functional theory study for the Diels-Alder reaction between N-acyl-1-aza-1,3-butadienes and vinylamines. Lewis acid catalyst and solvent effects. Tetrahedron 58:3765?3774. https://doi.org/10.1016/S0040-4020(02)00326-5
4. Kang J, Rebek J (1997) Acceleration of a Diels-Alder reaction by a self-assembled molecular capsule. Nature 385:50?52. https://doi.org/10.1038/385050a0
5. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
6. Gatzenmeier T, Van Gemmeren M, Xie Y, et al (2016) Asymmetric Lewis acid organocatalysis of the Diels-Alder reaction by a silylated C-H acid. Science (80-) 351:949?952. https://doi.org/10.1126/science.aae0010
7. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
8. Dyan OT, Andreev R V., Zaikin PA (2021) Substituents effects in the Diels-Alder reaction of 1,1-difluoronaphthalen-2(1H)-ones with cyclopentadiene. J Fluor Chem 250:109859. https://doi.org/10.1016/j.jfluchem.2021.109859
9. Gara R, Zouaghi MO, ALshandoudi LMH, Arfaoui Y (2021) DFT investigation of solvent, substituent, and

catalysis effects on the intramolecular Diels-Alder reaction. J Mol Model 27:. https://doi.org/10.1007/s00894-021-04729-w
10. Hernández-Mancera JP, Rojas-Valencia N, Núñez-Zarur F (2022) Rationalizing the Substituent Effects in Diels-Alder Reactions of Triazolinediones with Anthracene. J Phys Chem A 126:6657?6667. https://doi.org/10.1021/ACS.JPCA.2C04970/SUPPL_FILE/JP2C04970_SI_001.PDF
11. Khan TS, Gupta S, Ahmad M, et al (2020) Effect of substituents and promoters on the Diels-Alder cycloaddition reaction in the biorenewable synthesis of trimellitic acid. RSC Adv 10:30656?30670. https://doi.org/10.1039/d0ra04318d
12. Aragonès AC, Haworth NL, Darwish N, et al (2016) Electrostatic catalysis of a Diels-Alder reaction. Nature 531:88?91. https://doi.org/10.1038/nature16989
13. Meir R, Chen H, Lai W, Shaik S (2010) Oriented electric fields accelerate diels-alder reactions and control the endo/exo selectivity. ChemPhysChem 11:301?310. https://doi.org/10.1002/cphc.200900848
14. Wang Z, Danovich D, Ramanan R, Shaik S (2018) Oriented-External Electric Fields Create Absolute Enantioselectivity in Diels-Alder Reactions: Importance of the Molecular Dipole Moment. J Am Chem Soc 140:13350?13359. https://doi.org/10.1021/jacs.8b08233
15. Gryn?ova G, Coote ML (2013) Origin and scope of long-range stabilizing interactions and associated SOMO-HOMO conversion in distonic radical anions. J Am Chem Soc 135:15392?15403. https://doi.org/10.1021/ja404279f
16. Shaik S, De Visser SP, Kumar D (2004) External electric field will control the selectivity of enzymatic-like bond activations. J Am Chem Soc 126:11746?11749. https://doi.org/10.1021/ja047432k
17. Andrés JL, Lledós A, Duran M, Bertrán J (1988) Electric fields acting as catalysts in chemical reactions. An ab initio study of the walden inversion reaction. Chem Phys Lett 153:82?86. https://doi.org/10.1016/0009-2614(88)80136-2
18. Carbonell E, Duran M, Lledós A, Bertrán J (1991) Catalysis of Friedel-Crafts reactions by electric fields. J Phys Chem 95:179?183. https://doi.org/10.1021/j100154a036
19. Huang X, Tang C, Li J, et al (2019) Electric field?induced selective catalysis of single-molecule reaction. Sci Adv 5:eaaw3072. https://doi.org/10.1126/sciadv.aaw3072
20. Léonard NG, Dhaoui R, Chantarojsiri T, Yang JY (2021) Electric Fields in Catalysis: From Enzymes to Molecular Catalysts. ACS Catal 11:10923?10932. https://doi.org/10.1021/acscatal.1c02084
21. Dubey KD, Stuyver T, Shaik S (2022) Local Electric Fields: From Enzyme Catalysis to Synthetic Catalyst Design. J Phys Chem B. https://doi.org/10.1021/ACS.JPCB.2C06422
22. Shaik S, Danovich D, Joy J, et al (2020) Electric-Field Mediated Chemistry: Uncovering and Exploiting the Potential of (Oriented) Electric Fields to Exert Chemical Catalysis and Reaction Control. J. Am. Chem. Soc. 142:12551?12562
23. Aitken HM, Coote ML (2018) Can electrostatic catalysis of Diels-Alder reactions be harnessed with pH-switchable charged functional groups? Phys Chem Chem Phys 20:10671?10676. https://doi.org/10.1039/c7cp07562f
24. G16_C01 (1)
25. Shaik S, Mandal D, Ramanan R (2016) Oriented electric fields as future smart reagents in chemistry. Nat Chem 8:1091?1098. https://doi.org/10.1038/nchem.2651
26. Braga LS, Moreira RA, Leal DHS, Ramalho TC (2019) Quantification of molecular orbitals based on projection operators: Methodological development and applications to basicity prediction of organic compounds in the gas phase. Chem Phys Lett 726:87?92. https://doi.org/10.1016/j.cplett.2019.04.023
27. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for

-Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:. https://doi.org/10.2174/1385272824666200204121044
28. Braga LS, Henriques Soares Leal D, Ramalho TC (2022) Rationalising the regioselectivity of substituted phenols from the FERMO concept: stereoelectronic effects on protonation and functionalization . https://doi.org/101080/0892702220222039390 48:610?620. https://doi.org /10.1080/08927022.2022.2039390
29. Jursic BS, Zdravkovski Z (1995) Theoretical Study of the BH3-Catalyzed Hetero Diels?Alder Reaction between Ethylene and Nitrosoethylene. J Org Chem 60:3163?3168. https://doi.org/10.1021/jo00115a036
30. Rowley D, Steiner H (1951) Kinetics of diene reactions at high temperatures. Discuss Faraday Soc 10:198?213. https://doi.org/10.1039/DF9511000198
31. Nori V, Pesciaioli F, Sinibaldi A, et al (2022) Boron-based lewis acid catalysis: Challenges and perspectives. Catalysts 12:. https://doi.org/10.3390/catal12010005
32. Toledo EJL, Custodio R, Ramalho TC, et al (2009) Electrical field effects on dipole moment, structure and energetic of (H2O)n (2 ? n ? 15) cluster. J Mol Struct THEOCHEM 915:170?177. https://doi.org /10.1016/j.theochem.2009.08.035
33. Mazurkiewicz J, Tomasik P (2012) Effect of external electric field upon charge distribution, energy and dipole moment of selected monosaccharide molecules. Nat Sci 04:276?285. https://doi.org/10.4236/ns .2012.45040
34. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for -Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:314?331. https://doi.org/10.2174/1385272824666200204121044
35. Stuyver T, Danovich D, Joy J, Shaik S (2020) External electric field effects on chemical structure and reactivity. Wiley Interdiscip Rev Comput Mol Sci 10:1?22. https://doi.org/10.1002/wcms.1438

Lewis Acid?E# Activation Barrier of paper [29](kcal.mol-1)MP3/6-31G(d)?E#Activation Barrier in this work (kcal.mol-1)MP3/6-31G(d)
Without BH320.344920.3624
BH3 bonding oxygen13.707813.7962
BH3 bonding nitrogen11.622311.6025

Electron-donating (X)Electron-withdrawing (Y)?E# (kcal.mol-1)MP3/6-31G(d)
CH3Cl23.3857
F23.2107

F (au)?E# (kcal.mol-1)MP3/6-31G(d)
xyz
0.08021.081118.007424.8302
-0.08017.945318.220118.3186
0.12520.981118.200018.6625
-0.1256.393818.000018.4103

Without EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.643098-140.30580.3750-181.10180.348421-225.0075

C20.158948-140.30580.2003-181.10180.550036-225.0075
C80.034416-140.30580.4971-181.10180.282893-225.0075
C90.174964-140.30580.2854-181.10180.550790-225.0075
With EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.637059-141.49040.342834-185.24800.370436-218.3439
C20.167188-141.49040.164733-185.24800.565620-218.3439
C80.042363-141.49040.505992-185.24800.214219-218.3439
C90.188071-141.49040.326526-185.24800.521364-218.3439

CH3/Cl
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08023.030622.212922.1533
-0.08022.006522.281322.2161
0.12522.750127.928225.7320
-0.12522.531722.206722.5455
CH3/F
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08022.121921.881022.1012
-0.08022.246222.976621.8747
0.12522.538022.725622.5361
-0.12521.499523.026934.5554

Toward Metal- and Catalyst-free Reactions: Deciphering the substituent and external electric field effects on the Diels-Alder reaction between Ethylene and Nitrosoethylene

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Abstract
The substituents on the diene and/or dienophile can contribute to the decrease or increase of this energy. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis. The existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy. So, the goal of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field, Lewis acid (BH3) as catalysts and the influence of substituents. All calculations were performed with Gaussian09 software, the compounds were fully optimized using the restricted Hartree-Fock method with the basis set 6-31G, single-point energies determined with MP3 method and basis set 6-31G. The effects of EEFs were studied using the ?Field = M ± N? keyword with F values (F=±0,125 au and ±0,080 au) along the preferred axis. The lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.
Keywords
Electric field catalysis, external electric fields, Lewis acid, Diels-Alder reaction, FERMO.

1 Introduction

According to the Lewis definition, acids are molecules or ions capable of coordinating with unshared electron pairs, and bases are molecules or ions with unshared electron pairs available to share with acids [1]?. To be acidic in the Lewis sense, a molecule must be deficient in electrons. This is the most general acid-base concept. All Lowry-Brönsted acids are also Lewis acids, but in addition, the Lewis definition includes many other reagents, such as boron trifluoride, aluminum chloride, among others [2].
Lewis acids catalyze Diels-Alder reactions. Some examples of these acids are: SnCl4, ZnCl2, BH3 or AlCl3 ,, which can accelerate cycloaddition reactions [3, 4]?, as occurs in the reaction catalyzed by AlCl3 of cycloalkenones with 1,3-butadienes [5, 6]. The effect of substituents in the components of the Diels-Alder reaction affect it according to the Frontier Molecular Orbital (FMO) theory, in which the reactivity, regiochemistry and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial phase interaction of the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other [7]?.
The separation between the HOMO-LUMO components controls the reactivity of the Diels-Alder reaction: the smaller the energy difference between these two orbitals, the smaller the difference in activation energy between the transition state and the reaction reactants [8?11]. The substituents on the diene and/or dienophile can contribute to decrease or increase this energy. Electron-withdrawing substituents decrease the energy of LUMO and increase of HOMO, while electron-donor groups increase the energy of LUMO and decrease of HOMO [7]??. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis [12?14].
Chemical reactions can be described by the movement of electrons as well as the movement of nuclei. Thinking about it, we can understand that they can then be influenced by external electric fieldsWhether the reaction is redox or not, some theoretical studies [12, 13, 15, 16]?? the stability of molecules involved in the reaction can be influenced by electrostatic effects: stabilizing or destabilizing resonance contributors separated by charge [13]?. This fact was announced some time ago by Shaik and collaborators for the Diels-Alder reaction [16] and in another work for simple reactions of halogen and hydrogen transfer by Bertrán and collaborators [17, 18]?. Thus, there is a great interest in metal-free catalysis and specifically in catalysis by hydrogen bonding models [19].
In this scenario, the existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy [12, 20?22]?. Meir et al (2010) explored by theoretical means the effect of targeted EEFs on the rate, mechanism and endo/exo selectivity of DA reactions between butadiene and ethylene and cyclopentadiene and maleic anhydride. According to the authors, it is necessary then that the electric field is aligned in order to attenuate or strengthen the dipole along the reaction axis [13, 23].
Theoretical predictions were confirmed experimentally in 2016 by means of intermittent tunneling scanning microscopy (STM) experiments [12]?. In summary, the experiment was carried out as follows: the diene and the dienophile were "attached" to the tip and plate of the STM, respectively, restricting their orientation , providing a means of controlling the stimulus of the electric field and measuring its effect on the reaction rate [23]?. They obtained as results that, in the tested range of field forces, the reaction rate was independent of the positive polarity of the field, but it was catalyzed by increasing the intensity of the field to negative polarization. Parallel quantum-chemical calculations of the same system under experimental conditions, which confirmed that these results were due to the effect of the field on the reaction barriers [23]?. Therefore, external electric fields instead of charged chemical species such as the ?catalyst?, can manipulate a much wider range of reactions, conveniently altering reactivity and selectivity in a tunable way

that can be predicted by theory [13].

As electrostatic catalysis is the least developed form of catalysis in synthetic chemistry [12]?, the aim of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field and a Lewis acid as catalysts, in addition to checking the influence of substituents on the reaction?s diene and dienophile, in order to determine if the electric field is the best catalyst for the reaction studied.

2 Methodology

Gaussian09 software was used for all calculations [24]. The optimization calculation for all compounds was performed with restricted Hartree-Fock method with the basis set 6-31G(d). No imaginary frequencies were found for the optimized reactants geometries, which were used in all subsequent calculations and had their single-point energies determined with MP3 method and the basis set 6-31G(d). GAMESS software for Linux, version 30 SEPT 2017 (R2) and MOLPROJ software, were used to analyze their MO eigenvectors and overlapping matrices of the reaction between ethylene and nitrosoethylene, both extracted from output files of single-point energy calculations with GAMESS.

The effects of EEFs were studied using the ?Field = M ± N? keyword, which defines in Gaussian09, the axis of the EEFs, its direction along that axis, and its magnitude. For each reaction, we initially evaluated the EEF effects at different Fx,y,z values, using single-point calculations on the critical species with F values (F=±0,125 au and ±0,080 au) along the preferred axis.

In opposition to the conventional definition in Physics, in Gaussian09, the positive direction of the electric field vector is defined from negative to positive charge [14]. Thus, whenever the dipole moment (?) and field vectors (F) are oriented opposite to each other, the EEF?s will stabilize the dipole, as shown in Scheme 1 for an X-EEF. The EEFs were further oriented along the X, Y and Z axes as defined in Scheme 1, where in each case the X axis defines the "reaction axis", which is approximately the direction along which two new C? C bonds are forming [13, 14, 25].

Scheme 1: Definitions of the x, y and z directions.

Figure 1: Reactants (A) nitrosoethylene and ethylene, (B) nitrosoethylene with borane connected to oxygen and ethylene and (C) nitrosoethylene with borane connected to nitrogen and ethylene.

The optimized compounds, as shown in Figure 1, were analyzed using the MOLPROJ software [26, 27]. The eigenvectors of the MOs and the matrices of were extracted from output files of single point energy calculations with GAMESS. The degree of location of each MO (2px-z orbitals of the carbon and oxygen atoms involved in the DA reaction) and their respective energies were calculated and analyzed. [28]. For comparison, degree of localization coefficients were calculated for the molecular orbitals ?HOMO and ?FERMO. We define that the degree of localization ?FERMO is the norm of an MO projected on the expected set of atomic orbitals (that participate in the reaction), as follows in Equation 1, where ?, is the matrix of molecular orbital coefficients and ? is the overlap matrix:

Equation 1: degree of localization ?FERMO

3 Results

3.1 Validation of the theoretical strategy: The Reaction of Ethylene and Nitrosoethylene - Catalysis of a Diels-Alder reaction using a Lewis acid.

The synthetic versatility of cycloaddition reactions was extended by introducing heterodienes, which allowed rapid access to various heterocycles. Nitrosoethylene compounds lead to valuable heterocyclic compounds with an N-O bond in the cycle. However, the reactivity of these compounds strongly depends on their structure and a catalyst. This is because nitrosoethylenes are generally unstable and are generated by base promoted elimination of -haloximes. Jursic and Zdravkovski, in 1995 [29], showed in a study the difference in the activation barrier when BH3 is used as a catalyst. According to literature, the activation barrier decreased by 2.08 kcal.mol-1 when borane is linked to nitrosoethylene nitrogen.
These same authors [29] used the reaction between ethylene and butadiene to compare the reliability of the results obtained computationally from the reaction between ethylene and nitrosoethylene with the experimental values of the first reaction. The activation energy for the ethylene and butadiene reaction was 25.98 kcal.mol-1 using MP3/6-31G(d), a value which is in reasonable agreement with the experimental value (25.4 and 27.5 kcal.mol-1) [30]. As our values were obtained with a difference of approximately 0.03 kcal.mol-1 in the activation barrier values of the base article, we consider that our results are also close to the experimental values, since there are no experimental studies of the reaction between ethylene and nitrosoethylene in literature.
Given the importance and versatility of this cycloaddition reaction, we sought validation (Table 1) of the author's results to compare them when we apply the electric field and use substituents as a catalyst. Figure 2 illustrates the energy profile for the reaction without and with the use of borane (bonded to oxygen and nitrogen atoms) as catalyst.
Table 1: Activation barrier of Lewis acid to trans reaction.

Figure 2: difference in the energy of the activation barrier without catalyst and with the catalyst borane bound to the oxygen atom and to the nitrogen atom.
As can be seen in Table 1, the lowest activation barrier found was for borane bound to nitrosethylene nitrogen. The borane-catalyzed reaction has a lower activation barrier than the uncatalyzed reaction [29]. Boron reagents are often employed as Lewis acids due to their strong electrophilic nature because of a vacant p orbital that can readily accept electrons from donor molecules [31]. So, as BH3 is acting as an electron acceptor, the reaction in question occurs with reverse electron demand. Therefore, borane as a catalyst has a profound influence on the reactivity of the system, decreasing the electron density in the diene and decreasing its LUMO energy.
Note that the values of the calculated activation barriers differ slightly from this current work [29]. This minimal difference in ?E# occurred because the coordinates of the structures were not made available by the researchers. Therefore, the difference in bond lengths in the optimization had a minimal influence on the activation barriers.

3.2 Effect of the substituents to check if the reaction rate becomes even lower when they are related to some type of catalyst
According to Frontier Molecular Orbital (FMO) theory, the reactivity, regiochemistry, and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial in-phase interaction of the HOMO molecular orbital of one component and the LUMO orbital of the other [7]. When the HOMO of the diene controls the reaction, the reaction can be accelerated by electron-donating substituents on the diene and by electron-withdrawing substituents on the dienophile, thus being a normal electron-demand Diels-Alder reaction. On the other hand, the Diels-Alder reactions controlled by the LUMO of the diene are influenced by the

electronic effects of the substituents in the opposite way, that is, it is a Diels-Alder reaction with inverse electron demand.
The influence were studied by considering the following substituents: CH3, Cl and F. Considering the reaction as a normal demand for electrons, the interactions occur from the HOMO/FERMO of the dienophile to the LUMO of the diene, as can be seen in Figure 3A. Table 2 shows the activation barrier values when we replace a diene hydrogen with X = methyl and a dienophile hydrogen with a halogen (Y = Cl and F).

Figure 3: reaction scheme for the Diels-Alder reaction between ethylene and substituted nitrosoehtylene. (A) structures of reactants (left), transition state (middle) and products (right); (B) molecular orbitals involved in the reaction; (C) numbering of the atoms involved in Diels-Alder reaction.
Table 2: activation barrier values when we replace a diene hydrogen with methyl and a dienophile hydrogen with a halogen (Cl and F).

As it can be seen, the substituents did not accelerate the reaction. According to Jursic and Zdravkovski [29], the reaction between ethylene and nitrosoethylene is an inverse demand reaction. Therefore, as we are treating it as a normal electron demand reaction, it is to be expected that the activation barrier will increase in value. This increase was approximately 3.02 kcalmol-1 in relation to the reaction without any type of catalyst (20.3624 kcal.mol-1).

3.3 Effect of the electric field in the reaction between ethylene and nitrosoethylene
Table 3 shows the EEF effects on the barriers for fields oriented along the x-, y- and z-axes in positive and negative directions. It is seen that Fy and Fz do not change the barrier, which remains constant at ~18.3(±2 .8) kcalmol-1. This is because the y,z-oriented EEFs stabilize both the reactant (R?) and the transition state (TS) to the same extent. However, when the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst.

Table 3: values of activation barrier (?E#) with electric field applied in x-, y- and z-axes for two magnitude values of electric field.

As the field becomes more negative, the dipole moment becomes more positive. This change in dipole moment is accompanied by transferring charge between the reactants in the TS. As the value of Fx increases, the direction of charge transfer is reversed. Thus, the EEF not only reduces the energy of the TS , but also polarizes the TS and affects its electronic structure. In addition, the field also induces a charge transfer in its own direction, from nitrosoethylene to ethylene. In conclusion, it is apparent that when the electric field is oriented along the ?reaction axis?, which is the axis along which the two new C-C bonds are formed, it causes the reaction rate to accelerate by preferentially decreasing the transition state.
An EEF oriented in the direction of the ?reaction axis?, along which electronic reorganization takes place, can affect the reaction rate by orders of magnitude, becoming faster or slower, depending on the change in direction of the field. At the same time, the endo/exo stereoselectivity of the Diels-Alder reaction can be manipulated at will with EEFs oriented perpendicular to the reaction axis [13]. EEF changes distribution of

the electron density. Figure 4 show the molecular orbitals involved in the reaction with/without EEFs. Application of EEFs induce the polarizability of electrons, atoms and dipoles, resulting in an eventual reorientation of the molecules along the applied electric field of the molecules and the electron density redistribution at particular atoms [32]. As a general rule, one can module that two orbitals or states, which cannot mix by symmetry in the absence of a field, will do so when an EEF is applied along the axis that possesses the same symmetry as the direct product of the two orbitals/states [33].
We used the FERMO concept [26] to understand how the electric field acted on the molecular orbitals of the studied reaction. This concept is based on simultaneous analysis of composition and shapes of frontier molecular orbitals to determine the real molecular orbital governing a reaction. According to this approach, a frontier molecular orbital may even correspond to the FERMO for a given reaction and not for another. The HOMO itself would only be the orbital that rules a reaction if it fulfills the requirements to be the FERMO [34].
A strategy to quantify the location of the FERMO was developed, leading to the construction of the MOLPROJ software, based on the use of projection operators to build the molecular orbitals (MOs) by linear combination of atomic orbitals (AOs; the LCAO approach). Thus, the location of the FERMO would indicate the orbital in which the reaction occurs and, consequently, would point to the most favorable location for protonation [26, 28].
The values in Table 4 to four atoms involved in the Diels-Alder reaction (carbons: C2, C8, C9 and O, as shown in the Figure 3C) exhibit the energy and degree of localization from FERMO to HOMO. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms [26]. External electric fields oriented along the bond axis in a molecule induce significant ionicity, as well as changes in bond lengths, elongation frequencies and electronic characteristics. EEFs cause orbitals, whose mixing was prohibited in the absence of the field, to mix when the symmetry of their product is compatible with the symmetry of the applied field. As the product of the reaction has the same symmetry as an applied field along the bond axis, these two MOs will mix and hybridize, acquiring greater contributions in both the left and right atoms, leading to the development of the energetically stabilized dipole moment by the applied field [35].

Figure 4: TS between ethylene and nitrosoethylene. A) HOMO of TS without EEF; B) HOMO of TS with EEF; C) LUMO of TS without EEF; and D) LUMO of TS with EEF.

Table 4: Results for the degree of localization of MOs from TS between ethylene and nitrosoethylene.

Table 5: Values of activation barrier (?E#) with an external electric field applied in x-, y- and z-axes for two electric field magnitudes for substituents CH3/Cl and CH3/F.

As it can be seen in Table 5, only the substituent effect does not show a decrease in activation barriers, the value was 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcal.mol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. According to Jursic and Zdravkovski [29], the reaction between nitrosoethylene and ethylene, when catalyzed with borane, is a Diels-Alder reaction with inverse electron demand. Therefore, when we introduced electron donor groups in the diene, we would find a higher value in the activation barrier, as it can be seen in the tables. When we added the electric field, we were able to lower

this activation barrier. We realize that in fact the electric field acted as a catalyst.
Figure 5 shows the effect of the main catalysts on the activation barrier of the reaction between ethylene and nitrosoethylene. As can be seen, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Figure 5: Difference in the energy of the activation barrier without BH3, with the borane bonding in nitrogen and reaction with EEF.

Conclusion
In this study, the DA reaction between ethylene and nitrosoethylene with/without BH3, electric field and substituted dienophiles was studied theoretically using RHF and MP3 calculations aimed to determine which was the best catalyst to reaction. When the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst. We used the FERMO concept to understand how the electric field acted on the molecular orbitals of the studied reaction. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms. Only the substituent effect does not show a decrease in activation barriers. The values were 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcalmol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. Therefore, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Referências
1. Houk KN, Strozier RW (1973) On Lewis Acid Catalysis of Diels-Alder Reactions. J Am Chem Soc 95:4094?4096. https://doi.org/10.1021/ja00793a070
2. García JI, Martínez-Merino V, Mayoral JA, Salvatella L (1998) Density functional theory study of a Lewis acid catalyzed Diels-Alder reaction. The butadiene + acrolein paradigm. J Am Chem Soc 120:2415?2420. https://doi.org/10.1021/ja9722279
3. Domingo LR (2002) A density functional theory study for the Diels-Alder reaction between N-acyl-1-aza-1,3-butadienes and vinylamines. Lewis acid catalyst and solvent effects. Tetrahedron 58:3765?3774. https://doi.org/10.1016/S0040-4020(02)00326-5
4. Kang J, Rebek J (1997) Acceleration of a Diels-Alder reaction by a self-assembled molecular capsule. Nature 385:50?52. https://doi.org/10.1038/385050a0
5. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
6. Gatzenmeier T, Van Gemmeren M, Xie Y, et al (2016) Asymmetric Lewis acid organocatalysis of the Diels-Alder reaction by a silylated C-H acid. Science (80-) 351:949?952. https://doi.org/10.1126/science.aae0010
7. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
8. Dyan OT, Andreev R V., Zaikin PA (2021) Substituents effects in the Diels-Alder reaction of 1,1-difluoronaphthalen-2(1H)-ones with cyclopentadiene. J Fluor Chem 250:109859. https://doi.org/10.1016/j.jfluchem.2021.109859
9. Gara R, Zouaghi MO, ALshandoudi LMH, Arfaoui Y (2021) DFT investigation of solvent, substituent, and

catalysis effects on the intramolecular Diels-Alder reaction. J Mol Model 27:. https://doi.org/10.1007/s00894-021-04729-w
10. Hernández-Mancera JP, Rojas-Valencia N, Núñez-Zarur F (2022) Rationalizing the Substituent Effects in Diels-Alder Reactions of Triazolinediones with Anthracene. J Phys Chem A 126:6657?6667. https://doi.org/10.1021/ACS.JPCA.2C04970/SUPPL_FILE/JP2C04970_SI_001.PDF
11. Khan TS, Gupta S, Ahmad M, et al (2020) Effect of substituents and promoters on the Diels-Alder cycloaddition reaction in the biorenewable synthesis of trimellitic acid. RSC Adv 10:30656?30670. https://doi.org/10.1039/d0ra04318d
12. Aragonès AC, Haworth NL, Darwish N, et al (2016) Electrostatic catalysis of a Diels-Alder reaction. Nature 531:88?91. https://doi.org/10.1038/nature16989
13. Meir R, Chen H, Lai W, Shaik S (2010) Oriented electric fields accelerate diels-alder reactions and control the endo/exo selectivity. ChemPhysChem 11:301?310. https://doi.org/10.1002/cphc.200900848
14. Wang Z, Danovich D, Ramanan R, Shaik S (2018) Oriented-External Electric Fields Create Absolute Enantioselectivity in Diels-Alder Reactions: Importance of the Molecular Dipole Moment. J Am Chem Soc 140:13350?13359. https://doi.org/10.1021/jacs.8b08233
15. Gryn?ova G, Coote ML (2013) Origin and scope of long-range stabilizing interactions and associated SOMO-HOMO conversion in distonic radical anions. J Am Chem Soc 135:15392?15403. https://doi.org/10.1021/ja404279f
16. Shaik S, De Visser SP, Kumar D (2004) External electric field will control the selectivity of enzymatic-like bond activations. J Am Chem Soc 126:11746?11749. https://doi.org/10.1021/ja047432k
17. Andrés JL, Lledós A, Duran M, Bertrán J (1988) Electric fields acting as catalysts in chemical reactions. An ab initio study of the walden inversion reaction. Chem Phys Lett 153:82?86. https://doi.org/10.1016/0009-2614(88)80136-2
18. Carbonell E, Duran M, Lledós A, Bertrán J (1991) Catalysis of Friedel-Crafts reactions by electric fields. J Phys Chem 95:179?183. https://doi.org/10.1021/j100154a036
19. Huang X, Tang C, Li J, et al (2019) Electric field?induced selective catalysis of single-molecule reaction. Sci Adv 5:eaaw3072. https://doi.org/10.1126/sciadv.aaw3072
20. Léonard NG, Dhaoui R, Chantarojsiri T, Yang JY (2021) Electric Fields in Catalysis: From Enzymes to Molecular Catalysts. ACS Catal 11:10923?10932. https://doi.org/10.1021/acscatal.1c02084
21. Dubey KD, Stuyver T, Shaik S (2022) Local Electric Fields: From Enzyme Catalysis to Synthetic Catalyst Design. J Phys Chem B. https://doi.org/10.1021/ACS.JPCB.2C06422
22. Shaik S, Danovich D, Joy J, et al (2020) Electric-Field Mediated Chemistry: Uncovering and Exploiting the Potential of (Oriented) Electric Fields to Exert Chemical Catalysis and Reaction Control. J. Am. Chem. Soc. 142:12551?12562
23. Aitken HM, Coote ML (2018) Can electrostatic catalysis of Diels-Alder reactions be harnessed with pH-switchable charged functional groups? Phys Chem Chem Phys 20:10671?10676. https://doi.org/10.1039/c7cp07562f
24. G16_C01 (1)
25. Shaik S, Mandal D, Ramanan R (2016) Oriented electric fields as future smart reagents in chemistry. Nat Chem 8:1091?1098. https://doi.org/10.1038/nchem.2651
26. Braga LS, Moreira RA, Leal DHS, Ramalho TC (2019) Quantification of molecular orbitals based on projection operators: Methodological development and applications to basicity prediction of organic compounds in the gas phase. Chem Phys Lett 726:87?92. https://doi.org/10.1016/j.cplett.2019.04.023
27. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for

-Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:. https://doi.org/10.2174/1385272824666200204121044
28. Braga LS, Henriques Soares Leal D, Ramalho TC (2022) Rationalising the regioselectivity of substituted phenols from the FERMO concept: stereoelectronic effects on protonation and functionalization . https://doi.org/101080/0892702220222039390 48:610?620. https://doi.org /10.1080/08927022.2022.2039390
29. Jursic BS, Zdravkovski Z (1995) Theoretical Study of the BH3-Catalyzed Hetero Diels?Alder Reaction between Ethylene and Nitrosoethylene. J Org Chem 60:3163?3168. https://doi.org/10.1021/jo00115a036
30. Rowley D, Steiner H (1951) Kinetics of diene reactions at high temperatures. Discuss Faraday Soc 10:198?213. https://doi.org/10.1039/DF9511000198
31. Nori V, Pesciaioli F, Sinibaldi A, et al (2022) Boron-based lewis acid catalysis: Challenges and perspectives. Catalysts 12:. https://doi.org/10.3390/catal12010005
32. Toledo EJL, Custodio R, Ramalho TC, et al (2009) Electrical field effects on dipole moment, structure and energetic of (H2O)n (2 ? n ? 15) cluster. J Mol Struct THEOCHEM 915:170?177. https://doi.org /10.1016/j.theochem.2009.08.035
33. Mazurkiewicz J, Tomasik P (2012) Effect of external electric field upon charge distribution, energy and dipole moment of selected monosaccharide molecules. Nat Sci 04:276?285. https://doi.org/10.4236/ns .2012.45040
34. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for -Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:314?331. https://doi.org/10.2174/1385272824666200204121044
35. Stuyver T, Danovich D, Joy J, Shaik S (2020) External electric field effects on chemical structure and reactivity. Wiley Interdiscip Rev Comput Mol Sci 10:1?22. https://doi.org/10.1002/wcms.1438

Lewis Acid?E# Activation Barrier of paper [29](kcal.mol-1)MP3/6-31G(d)?E#Activation Barrier in this work (kcal.mol-1)MP3/6-31G(d)
Without BH320.344920.3624
BH3 bonding oxygen13.707813.7962
BH3 bonding nitrogen11.622311.6025

Electron-donating (X)Electron-withdrawing (Y)?E# (kcal.mol-1)MP3/6-31G(d)
CH3Cl23.3857
F23.2107

F (au)?E# (kcal.mol-1)MP3/6-31G(d)
xyz
0.08021.081118.007424.8302
-0.08017.945318.220118.3186
0.12520.981118.200018.6625
-0.1256.393818.000018.4103

Without EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.643098-140.30580.3750-181.10180.348421-225.0075

C20.158948-140.30580.2003-181.10180.550036-225.0075
C80.034416-140.30580.4971-181.10180.282893-225.0075
C90.174964-140.30580.2854-181.10180.550790-225.0075
With EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.637059-141.49040.342834-185.24800.370436-218.3439
C20.167188-141.49040.164733-185.24800.565620-218.3439
C80.042363-141.49040.505992-185.24800.214219-218.3439
C90.188071-141.49040.326526-185.24800.521364-218.3439

CH3/Cl
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08023.030622.212922.1533
-0.08022.006522.281322.2161
0.12522.750127.928225.7320
-0.12522.531722.206722.5455
CH3/F
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08022.121921.881022.1012
-0.08022.246222.976621.8747
0.12522.538022.725622.5361
-0.12521.499523.026934.5554

Toward Metal- and Catalyst-free Reactions: Deciphering the substituent and external electric field effects on the Diels-Alder reaction between Ethylene and Nitrosoethylene

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Abstract
The substituents on the diene and/or dienophile can contribute to the decrease or increase of this energy. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis. The existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy. So, the goal of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field, Lewis acid (BH3) as catalysts and the influence of substituents. All calculations were performed with Gaussian09 software, the compounds were fully optimized using the restricted Hartree-Fock method with the basis set 6-31G, single-point energies determined with MP3 method and basis set 6-31G. The effects of EEFs were studied using the ?Field = M ± N? keyword with F values (F=±0,125 au and ±0,080 au) along the preferred axis. The lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.
Keywords
Electric field catalysis, external electric fields, Lewis acid, Diels-Alder reaction, FERMO.

1 Introduction

According to the Lewis definition, acids are molecules or ions capable of coordinating with unshared

electron pairs, and bases are molecules or ions with unshared electron pairs available to share with acids [1]?. To be acidic in the Lewis sense, a molecule must be deficient in electrons. This is the most general acid-base concept. All Lowry-Brönsted acids are also Lewis acids, but in addition, the Lewis definition includes many other reagents, such as boron trifluoride, aluminum chloride, among others [2].
Lewis acids catalyze Diels-Alder reactions. Some examples of these acids are: SnCl4, ZnCl2, BH3 or AlCl3 ,, which can accelerate cycloaddition reactions [3, 4]?, as occurs in the reaction catalyzed by AlCl3 of cycloalkenones with 1,3-butadienes [5, 6]. The effect of substituents in the components of the Diels-Alder reaction affect it according to the Frontier Molecular Orbital (FMO) theory, in which the reactivity, regiochemistry and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial phase interaction of the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other [7]?.
The separation between the HOMO-LUMO components controls the reactivity of the Diels-Alder reaction: the smaller the energy difference between these two orbitals, the smaller the difference in activation energy between the transition state and the reaction reactants [8?11]. The substituents on the diene and/or dienophile can contribute to decrease or increase this energy. Electron-withdrawing substituents decrease the energy of LUMO and increase of HOMO, while electron-donor groups increase the energy of LUMO and decrease of HOMO [7]??. However, there are other artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field on the reaction axis [12?14].
Chemical reactions can be described by the movement of electrons as well as the movement of nuclei. Thinking about it, we can understand that they can then be influenced by external electric fieldsWhether the reaction is redox or not, some theoretical studies [12, 13, 15, 16]?? the stability of molecules involved in the reaction can be influenced by electrostatic effects: stabilizing or destabilizing resonance contributors separated by charge [13]?. This fact was announced some time ago by Shaik and collaborators for the Diels-Alder reaction [16] and in another work for simple reactions of halogen and hydrogen transfer by Bertrán and collaborators [17, 18]?. Thus, there is a great interest in metal-free catalysis and specifically in catalysis by hydrogen bonding models [19].
In this scenario, the existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these charge transfer contributors and thus influence the energy [12, 20?22]?. Meir et al (2010) explored by theoretical means the effect of targeted EEFs on the rate, mechanism and endo/exo selectivity of DA reactions between butadiene and ethylene and cyclopentadiene and maleic anhydride. According to the authors, it is necessary then that the electric field is aligned in order to attenuate or strengthen the dipole along the reaction axis [13, 23].
Theoretical predictions were confirmed experimentally in 2016 by means of intermittent tunneling scanning microscopy (STM) experiments [12]?. In summary, the experiment was carried out as follows: the diene and the dienophile were "attached" to the tip and plate of the STM, respectively, restricting their orientation , providing a means of controlling the stimulus of the electric field and measuring its effect on the reaction rate [23]?. They obtained as results that, in the tested range of field forces, the reaction rate was independent of the positive polarity of the field, but it was catalyzed by increasing the intensity of the field to negative polarization. Parallel quantum-chemical calculations of the same system under experimental conditions, which confirmed that these results were due to the effect of the field on the reaction barriers [23]?. Therefore, external electric fields instead of charged chemical species such as the ?catalyst?, can manipulate a much wider range of reactions, conveniently altering reactivity and selectivity in a tunable way that can be predicted by theory [13].

As electrostatic catalysis is the least developed form of catalysis in synthetic chemistry [12]?, the aim of this study was to compare the activation energies of the Diels-Alder reaction between ethylene and nitrosoethylene, using an electric field and a Lewis acid as catalysts, in addition to checking the influence of substituents on the reaction?s diene and dienophile, in order to determine if the electric field is the best catalyst for the reaction studied.

2 Methodology

Gaussian09 software was used for all calculations [24]. The optimization calculation for all compounds was performed with restricted Hartree-Fock method with the basis set 6-31G(d). No imaginary frequencies were found for the optimized reactants geometries, which were used in all subsequent calculations and had their single-point energies determined with MP3 method and the basis set 6-31G(d). GAMESS software for Linux, version 30 SEPT 2017 (R2) and MOLPROJ software, were used to analyze their MO eigenvectors and overlapping matrices of the reaction between ethylene and nitrosoethylene, both extracted from output files of single-point energy calculations with GAMESS.

The effects of EEFs were studied using the ?Field = M ± N? keyword, which defines in Gaussian09, the axis of the EEFs, its direction along that axis, and its magnitude. For each reaction, we initially evaluated the EEF effects at different Fx,y,z values, using single-point calculations on the critical species with F values (F=±0,125 au and ±0,080 au) along the preferred axis.

In opposition to the conventional definition in Physics, in Gaussian09, the positive direction of the electric field vector is defined from negative to positive charge [14]. Thus, whenever the dipole moment (?) and field vectors (F) are oriented opposite to each other, the EEF?s will stabilize the dipole, as shown in Scheme 1 for an X-EEF. The EEFs were further oriented along the X, Y and Z axes as defined in Scheme 1, where in each case the X axis defines the "reaction axis", which is approximately the direction along which two new C? C bonds are forming [13, 14, 25].

Scheme 1: Definitions of the x, y and z directions.

Figure 1: Reactants (A) nitrosoethylene and ethylene, (B) nitrosoethylene with borane connected to oxygen and ethylene and (C) nitrosoethylene with borane connected to nitrogen and ethylene.

The optimized compounds, as shown in Figure 1, were analyzed using the MOLPROJ software [26, 27]. The eigenvectors of the MOs and the matrices of were extracted from output files of single point energy calculations with GAMESS. The degree of location of each MO (2px-z orbitals of the carbon and oxygen atoms involved in the DA reaction) and their respective energies were calculated and analyzed. [28]. For comparison, degree of localization coefficients were calculated for the molecular orbitals ?HOMO and ?FERMO. We define that the degree of localization ?FERMO is the norm of an MO projected on the expected set of atomic orbitals (that participate in the reaction), as follows in Equation 1, where ?, is the matrix of molecular orbital coefficients and ? is the overlap matrix:

Equation 1: degree of localization ?FERMO

3 Results

3.1 Validation of the theoretical strategy: The Reaction of Ethylene and Nitrosoethylene - Catalysis of a Diels-Alder reaction using a Lewis acid.

The synthetic versatility of cycloaddition reactions was extended by introducing heterodienes, which

allowed rapid access to various heterocycles. Nitrosoethylene compounds lead to valuable heterocyclic compounds with an N-O bond in the cycle. However, the reactivity of these compounds strongly depends on their structure and a catalyst. This is because nitrosoethylenes are generally unstable and are generated by base promoted elimination of -haloximes. Jursic and Zdravkovski, in 1995 [29], showed in a study the difference in the activation barrier when BH3 is used as a catalyst. According to literature, the activation barrier decreased by 2.08 kcal.mol-1 when borane is linked to nitrosoethylene nitrogen.
These same authors [29] used the reaction between ethylene and butadiene to compare the reliability of the results obtained computationally from the reaction between ethylene and nitrosoethylene with the experimental values of the first reaction. The activation energy for the ethylene and butadiene reaction was 25.98 kcal.mol-1 using MP3/6-31G(d), a value which is in reasonable agreement with the experimental value (25.4 and 27.5 kcal.mol-1) [30]. As our values were obtained with a difference of approximately 0.03 kcal.mol-1 in the activation barrier values of the base article, we consider that our results are also close to the experimental values, since there are no experimental studies of the reaction between ethylene and nitrosoethylene in literature.
Given the importance and versatility of this cycloaddition reaction, we sought validation (Table 1) of the author's results to compare them when we apply the electric field and use substituents as a catalyst. Figure 2 illustrates the energy profile for the reaction without and with the use of borane (bonded to oxygen and nitrogen atoms) as catalyst.
Table 1: Activation barrier of Lewis acid to trans reaction.

Figure 2: difference in the energy of the activation barrier without catalyst and with the catalyst borane bound to the oxygen atom and to the nitrogen atom.
As can be seen in Table 1, the lowest activation barrier found was for borane bound to nitrosethylene nitrogen. The borane-catalyzed reaction has a lower activation barrier than the uncatalyzed reaction [29]. Boron reagents are often employed as Lewis acids due to their strong electrophilic nature because of a vacant p orbital that can readily accept electrons from donor molecules [31]. So, as BH3 is acting as an electron acceptor, the reaction in question occurs with reverse electron demand. Therefore, borane as a catalyst has a profound influence on the reactivity of the system, decreasing the electron density in the diene and decreasing its LUMO energy.
Note that the values of the calculated activation barriers differ slightly from this current work [29]. This minimal difference in ?E# occurred because the coordinates of the structures were not made available by the researchers. Therefore, the difference in bond lengths in the optimization had a minimal influence on the activation barriers.

3.2 Effect of the substituents to check if the reaction rate becomes even lower when they are related to some type of catalyst
According to Frontier Molecular Orbital (FMO) theory, the reactivity, regiochemistry, and stereochemistry of the Diels-Alder reaction are controlled by the suprafacial in-phase interaction of the HOMO molecular orbital of one component and the LUMO orbital of the other [7]. When the HOMO of the diene controls the reaction, the reaction can be accelerated by electron-donating substituents on the diene and by electron-withdrawing substituents on the dienophile, thus being a normal electron-demand Diels-Alder reaction. On the other hand, the Diels-Alder reactions controlled by the LUMO of the diene are influenced by the electronic effects of the substituents in the opposite way, that is, it is a Diels-Alder reaction with inverse

electron demand.
The influence were studied by considering the following substituents: CH3, Cl and F. Considering the reaction as a normal demand for electrons, the interactions occur from the HOMO/FERMO of the dienophile to the LUMO of the diene, as can be seen in Figure 3A. Table 2 shows the activation barrier values when we replace a diene hydrogen with X = methyl and a dienophile hydrogen with a halogen (Y = Cl and F).

Figure 3: reaction scheme for the Diels-Alder reaction between ethylene and substituted nitrosoehtylene. (A) structures of reactants (left), transition state (middle) and products (right); (B) molecular orbitals involved in the reaction; (C) numbering of the atoms involved in Diels-Alder reaction.
Table 2: activation barrier values when we replace a diene hydrogen with methyl and a dienophile hydrogen with a halogen (Cl and F).

As it can be seen, the substituents did not accelerate the reaction. According to Jursic and Zdravkovski [29], the reaction between ethylene and nitrosoethylene is an inverse demand reaction. Therefore, as we are treating it as a normal electron demand reaction, it is to be expected that the activation barrier will increase in value. This increase was approximately 3.02 kcalmol-1 in relation to the reaction without any type of catalyst (20.3624 kcal.mol-1).

3.3 Effect of the electric field in the reaction between ethylene and nitrosoethylene
Table 3 shows the EEF effects on the barriers for fields oriented along the x-, y- and z-axes in positive and negative directions. It is seen that Fy and Fz do not change the barrier, which remains constant at ~18.3(±2 .8) kcalmol-1. This is because the y,z-oriented EEFs stabilize both the reactant (R?) and the transition state (TS) to the same extent. However, when the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst.

Table 3: values of activation barrier (?E#) with electric field applied in x-, y- and z-axes for two magnitude values of electric field.

As the field becomes more negative, the dipole moment becomes more positive. This change in dipole moment is accompanied by transferring charge between the reactants in the TS. As the value of Fx increases, the direction of charge transfer is reversed. Thus, the EEF not only reduces the energy of the TS , but also polarizes the TS and affects its electronic structure. In addition, the field also induces a charge transfer in its own direction, from nitrosoethylene to ethylene. In conclusion, it is apparent that when the electric field is oriented along the ?reaction axis?, which is the axis along which the two new C-C bonds are formed, it causes the reaction rate to accelerate by preferentially decreasing the transition state.
An EEF oriented in the direction of the ?reaction axis?, along which electronic reorganization takes place, can affect the reaction rate by orders of magnitude, becoming faster or slower, depending on the change in direction of the field. At the same time, the endo/exo stereoselectivity of the Diels-Alder reaction can be manipulated at will with EEFs oriented perpendicular to the reaction axis [13]. EEF changes distribution of the electron density. Figure 4 show the molecular orbitals involved in the reaction with/without EEFs.

Application of EEFs induce the polarizability of electrons, atoms and dipoles, resulting in an eventual reorientation of the molecules along the applied electric field of the molecules and the electron density redistribution at particular atoms [32]. As a general rule, one can module that two orbitals or states, which cannot mix by symmetry in the absence of a field, will do so when an EEF is applied along the axis that possesses the same symmetry as the direct product of the two orbitals/states [33].
We used the FERMO concept [26] to understand how the electric field acted on the molecular orbitals of the studied reaction. This concept is based on simultaneous analysis of composition and shapes of frontier molecular orbitals to determine the real molecular orbital governing a reaction. According to this approach, a frontier molecular orbital may even correspond to the FERMO for a given reaction and not for another. The HOMO itself would only be the orbital that rules a reaction if it fulfills the requirements to be the FERMO [34].
A strategy to quantify the location of the FERMO was developed, leading to the construction of the MOLPROJ software, based on the use of projection operators to build the molecular orbitals (MOs) by linear combination of atomic orbitals (AOs; the LCAO approach). Thus, the location of the FERMO would indicate the orbital in which the reaction occurs and, consequently, would point to the most favorable location for protonation [26, 28].
The values in Table 4 to four atoms involved in the Diels-Alder reaction (carbons: C2, C8, C9 and O, as shown in the Figure 3C) exhibit the energy and degree of localization from FERMO to HOMO. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms [26]. External electric fields oriented along the bond axis in a molecule induce significant ionicity, as well as changes in bond lengths, elongation frequencies and electronic characteristics. EEFs cause orbitals, whose mixing was prohibited in the absence of the field, to mix when the symmetry of their product is compatible with the symmetry of the applied field. As the product of the reaction has the same symmetry as an applied field along the bond axis, these two MOs will mix and hybridize, acquiring greater contributions in both the left and right atoms, leading to the development of the energetically stabilized dipole moment by the applied field [35].

Figure 4: TS between ethylene and nitrosoethylene. A) HOMO of TS without EEF; B) HOMO of TS with EEF; C) LUMO of TS without EEF; and D) LUMO of TS with EEF.

Table 4: Results for the degree of localization of MOs from TS between ethylene and nitrosoethylene.

Table 5: Values of activation barrier (?E#) with an external electric field applied in x-, y- and z-axes for two electric field magnitudes for substituents CH3/Cl and CH3/F.

As it can be seen in Table 5, only the substituent effect does not show a decrease in activation barriers, the value was 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcal.mol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. According to Jursic and Zdravkovski [29], the reaction between nitrosoethylene and ethylene, when catalyzed with borane, is a Diels-Alder reaction with inverse electron demand. Therefore, when we introduced electron donor groups in the diene, we would find a higher value in the activation barrier, as it can be seen in the tables. When we added the electric field, we were able to lower this activation barrier. We realize that in fact the electric field acted as a catalyst.

Figure 5 shows the effect of the main catalysts on the activation barrier of the reaction between ethylene and nitrosoethylene. As can be seen, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Figure 5: Difference in the energy of the activation barrier without BH3, with the borane bonding in nitrogen and reaction with EEF.

Conclusion

In this study, the DA reaction between ethylene and nitrosoethylene with/without BH3, electric field and substituted dienophiles was studied theoretically using RHF and MP3 calculations aimed to determine which was the best catalyst to reaction. When the EEF is oriented along the ?reaction axis? x, the effect is seen to be different. In the positive fields, with Fx >0, the barrier remains constant. However, when Fx is negative (Fx <0) in 0.125 au, the TS is preferentially stabilized, and the barrier gradually decreases. At the highest field strength, the barrier is lowered by 5.28 kcal.mol-1, when compared the borane catalyst. We used the FERMO concept to understand how the electric field acted on the molecular orbitals of the studied reaction. The degree of localization from FERMO to HOMO increases with the application of EEF to carbon atoms. Only the substituent effect does not show a decrease in activation barriers. The values were 23.3857 and 23.2107 kcal.mol-1 to CH3/Cl and CH3/F, respectively. However, when the electric field is applied, its value decreases by around ±1.0 kcalmol-1. We can explain this small change in the barrier by the fact that we replace the hydrogen with electron withdrawing groups in the dienophile and donor groups in the diene. Therefore, the lowest activation barrier is encountered when the electric field is applied, followed by the use of borane as the Lewis acid.

Referências

1. Houk KN, Strozier RW (1973) On Lewis Acid Catalysis of Diels-Alder Reactions. J Am Chem Soc 95:4094?4096. https://doi.org/10.1021/ja00793a070
2. García JI, Martínez-Merino V, Mayoral JA, Salvatella L (1998) Density functional theory study of a Lewis acid catalyzed Diels-Alder reaction. The butadiene + acrolein paradigm. J Am Chem Soc 120:2415?2420. https://doi.org/10.1021/ja9722279
3. Domingo LR (2002) A density functional theory study for the Diels-Alder reaction between N-acyl-1-aza-1,3-butadienes and vinylamines. Lewis acid catalyst and solvent effects. Tetrahedron 58:3765?3774. https://doi.org/10.1016/S0040-4020(02)00326-5
4. Kang J, Rebek J (1997) Acceleration of a Diels-Alder reaction by a self-assembled molecular capsule. Nature 385:50?52. https://doi.org/10.1038/385050a0
5. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
6. Gatzenmeier T, Van Gemmeren M, Xie Y, et al (2016) Asymmetric Lewis acid organocatalysis of the Diels-Alder reaction by a silylated C-H acid. Science (80-) 351:949?952. https://doi.org/10.1126/science.aae0010
7. Fringuelli F, Taticchi A (1988) The Diels±Alder Reaction
8. Dyan OT, Andreev R V., Zaikin PA (2021) Substituents effects in the Diels-Alder reaction of 1,1-difluoronaphthalen-2(1H)-ones with cyclopentadiene. J Fluor Chem 250:109859. https://doi.org/10.1016/j.jfluchem.2021.109859
9. Gara R, Zouaghi MO, ALshandoudi LMH, Arfaoui Y (2021) DFT investigation of solvent, substituent, and catalysis effects on the intramolecular Diels-Alder reaction. J Mol Model 27:. https://doi.org/10.1007/s00894

-021-04729-w
10. Hernández-Mancera JP, Rojas-Valencia N, Núñez-Zarur F (2022) Rationalizing the Substituent Effects in Diels-Alder Reactions of Triazolinediones with Anthracene. J Phys Chem A 126:6657?6667. https://doi.org/10.1021/ACS.JPCA.2C04970/SUPPL_FILE/JP2C04970_SI_001.PDF
11. Khan TS, Gupta S, Ahmad M, et al (2020) Effect of substituents and promoters on the Diels-Alder cycloaddition reaction in the biorenewable synthesis of trimellitic acid. RSC Adv 10:30656?30670. https://doi.org/10.1039/d0ra04318d
12. Aragonès AC, Haworth NL, Darwish N, et al (2016) Electrostatic catalysis of a Diels-Alder reaction. Nature 531:88?91. https://doi.org/10.1038/nature16989
13. Meir R, Chen H, Lai W, Shaik S (2010) Oriented electric fields accelerate diels-alder reactions and control the endo/exo selectivity. ChemPhysChem 11:301?310. https://doi.org/10.1002/cphc.200900848
14. Wang Z, Danovich D, Ramanan R, Shaik S (2018) Oriented-External Electric Fields Create Absolute Enantioselectivity in Diels-Alder Reactions: Importance of the Molecular Dipole Moment. J Am Chem Soc 140:13350?13359. https://doi.org/10.1021/jacs.8b08233
15. Gryn?ova G, Coote ML (2013) Origin and scope of long-range stabilizing interactions and associated SOMO-HOMO conversion in distonic radical anions. J Am Chem Soc 135:15392?15403. https://doi.org/10.1021/ja404279f
16. Shaik S, De Visser SP, Kumar D (2004) External electric field will control the selectivity of enzymatic-like bond activations. J Am Chem Soc 126:11746?11749. https://doi.org/10.1021/ja047432k
17. Andrés JL, Lledós A, Duran M, Bertrán J (1988) Electric fields acting as catalysts in chemical reactions. An ab initio study of the walden inversion reaction. Chem Phys Lett 153:82?86. https://doi.org/10.1016/0009-2614(88)80136-2
18. Carbonell E, Duran M, Lledós A, Bertrán J (1991) Catalysis of Friedel-Crafts reactions by electric fields. J Phys Chem 95:179?183. https://doi.org/10.1021/j100154a036
19. Huang X, Tang C, Li J, et al (2019) Electric field?induced selective catalysis of single-molecule reaction. Sci Adv 5:eaaw3072. https://doi.org/10.1126/sciadv.aaw3072
20. Léonard NG, Dhaoui R, Chantarojsiri T, Yang JY (2021) Electric Fields in Catalysis: From Enzymes to Molecular Catalysts. ACS Catal 11:10923?10932. https://doi.org/10.1021/acscatal.1c02084
21. Dubey KD, Stuyver T, Shaik S (2022) Local Electric Fields: From Enzyme Catalysis to Synthetic Catalyst Design. J Phys Chem B. https://doi.org/10.1021/ACS.JPCB.2C06422
22. Shaik S, Danovich D, Joy J, et al (2020) Electric-Field Mediated Chemistry: Uncovering and Exploiting the Potential of (Oriented) Electric Fields to Exert Chemical Catalysis and Reaction Control. J. Am. Chem. Soc. 142:12551?12562
23. Aitken HM, Coote ML (2018) Can electrostatic catalysis of Diels-Alder reactions be harnessed with pH-switchable charged functional groups? Phys Chem Chem Phys 20:10671?10676. https://doi.org/10.1039/c7cp07562f
24. G16_C01 (1)
25. Shaik S, Mandal D, Ramanan R (2016) Oriented electric fields as future smart reagents in chemistry. Nat Chem 8:1091?1098. https://doi.org/10.1038/nchem.2651
26. Braga LS, Moreira RA, Leal DHS, Ramalho TC (2019) Quantification of molecular orbitals based on projection operators: Methodological development and applications to basicity prediction of organic compounds in the gas phase. Chem Phys Lett 726:87?92. https://doi.org/10.1016/j.cplett.2019.04.023
27. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for-Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org

Chem 24:. https://doi.org/10.2174/1385272824666200204121044
28. Braga LS, Henriques Soares Leal D, Ramalho TC (2022) Rationalising the regioselectivity of substituted phenols from the FERMO concept: stereoelectronic effects on protonation and functionalization . https://doi.org/101080/0892702220222039390 48:610?620. https://doi.org /10.1080/08927022.2022.2039390
29. Jursic BS, Zdravkovski Z (1995) Theoretical Study of the BH3-Catalyzed Hetero Diels?Alder Reaction between Ethylene and Nitrosoethylene. J Org Chem 60:3163?3168. https://doi.org/10.1021/jo00115a036
30. Rowley D, Steiner H (1951) Kinetics of diene reactions at high temperatures. Discuss Faraday Soc 10:198?213. https://doi.org/10.1039/DF9511000198
31. Nori V, Pesciaioli F, Sinibaldi A, et al (2022) Boron-based lewis acid catalysis: Challenges and perspectives. Catalysts 12:. https://doi.org/10.3390/catal12010005
32. Toledo EJL, Custodio R, Ramalho TC, et al (2009) Electrical field effects on dipole moment, structure and energetic of (H2O)n (2 ? n ? 15) cluster. J Mol Struct THEOCHEM 915:170?177. https://doi.org /10.1016/j.theochem.2009.08.035
33. Mazurkiewicz J, Tomasik P (2012) Effect of external electric field upon charge distribution, energy and dipole moment of selected monosaccharide molecules. Nat Sci 04:276?285. https://doi.org/10.4236/ns .2012.45040
34. Braga LS, Leal DHS, Kuca K, Ramalho TC (2020) Perspectives on the Role of the Frontier Effective-for -Reaction Molecular Orbital (FERMO) in the Study of Chemical Reactivity: An Updated Review. Curr Org Chem 24:314?331. https://doi.org/10.2174/1385272824666200204121044
35. Stuyver T, Danovich D, Joy J, Shaik S (2020) External electric field effects on chemical structure and reactivity. Wiley Interdiscip Rev Comput Mol Sci 10:1?22. https://doi.org/10.1002/wcms.1438

Lewis Acid?E# Activation Barrier of paper [29](kcal.mol-1)MP3/6-31G(d)?E#Activation Barrier in this work (kcal.mol-1)MP3/6-31G(d)
Without BH320.344920.3624
BH3 bonding oxygen13.707813.7962
BH3 bonding nitrogen11.622311.6025

Electron-donating (X)Electron-withdrawing (Y)?E# (kcal.mol-1)MP3/6-31G(d)
CH3Cl23.3857
F23.2107

F (au)?E# (kcal.mol-1)MP3/6-31G(d)
xyz
0.08021.081118.007424.8302
-0.08017.945318.220118.3186
0.12520.981118.200018.6625
-0.1256.393818.000018.4103

Without EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.643098-140.30580.3750-181.10180.348421-225.0075
C20.158948-140.30580.2003-181.10180.550036-225.0075

C80.034416-140.30580.4971-181.10180.282893-225.0075
C90.174964-140.30580.2854-181.10180.550790-225.0075
With EEF
AtomHOMOEnergy (eV)HOMO-1Energy (eV)HOMO-2Energy (eV)
O0.637059-141.49040.342834-185.24800.370436-218.3439
C20.167188-141.49040.164733-185.24800.565620-218.3439
C80.042363-141.49040.505992-185.24800.214219-218.3439
C90.188071-141.49040.326526-185.24800.521364-218.3439

CH3/Cl
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08023.030622.212922.1533
-0.08022.006522.281322.2161
0.12522.750127.928225.7320
-0.12522.531722.206722.5455
CH3/F
F (au)?E# (kcal.mol-1)MP3/6-31G(d)
x-axisy-axisz-axis
0.08022.121921.881022.1012
-0.08022.246222.976621.8747
0.12522.538022.725622.5361
-0.12521.499523.026934.5554