LETÍCIA SANTOS BRAGA

ORBITAL SIGNATURES AS A DESCRIPTOR OF REGIOSELECTIVITY AND CHEMICAL REACTIVITY OF ORGANIC COMPOUNDS

LAVRAS – MG
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Dr. Teodorico de Castro Ramalho
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ORBITAIS COMO DESCRITORES DA REGIOSELETIVIDADE E REATIVIDADE QUÍMICA DE COMPOSTOS ORGÂNICOS

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"Happiness is only real when shared"

H. David Thoreau.

RESUMO

O formalismo HOMO-LUMO, desenvolvido mais como uma interpretação da reatividade, pode não ser adequado para descrever a reatividade de certas reações químicas. O conceito de FERMO, baseado em intuição química e em critérios de composição e localização para determinação correta do orbital molecular de fronteira que regula reações químicas, pode ser entendido como um complemento ao argumento HOMO–LUMO. O desenvolvimento do conceito do FERMO (Frontier Effective for Reaction Molecular Orbital) descreve a quebra e a formação de novas ligações químicas, fornecendo pistas importantes que modulam a reatividade química de átomos e moléculas. Por meio desse conceito, foi possível localizar os orbitais moleculares de fronteira envolvidos em reações de protonação de fenóis substituídos, uma vez que processos de protonação e desprotonação em moléculas aromáticas, como fenóis, são importantes em química orgânica e bioquímica. A análise foi realizada por meio do software MOLPROJ, para comparar os resultados computacionais com dados experimentais de RMN obtidos na literatura. Como resultado, foi obtido um percentual de acertos de aproximadamente 86% nos sítios de protonação. Em um outro estudo, analisamos as energias de ativação da reação orgânica entre o etileno e o nitrosoetileno, uma reação de Diels-Alder, catalisada por diferentes tipos de catalisadores: ácido de Lewis, campo elétrico orientado e substituintes doadores e retiradores de elétrons. Todos os cálculos foram realizados com o software Gaussian09. Os compostos foram totalmente otimizados usando o método Hartree-Fock restrito com o conjunto de base 6-31G. As energias de ponto único foram determinadas com o método MP3 e conjunto de base 6-31G. Foi observado que a barreira de ativação mais baixa foi encontrada quando o campo elétrico era aplicado, seguido pelo uso do ácido de Lewis. Vale a pena notar que o campo da catálise de campo elétrico ainda é relativamente novo, e pesquisas estão em andamento para explorar todo o seu potencial e aplicabilidade em diferentes reações químicas. Podemos perceber que a ideia FERMO é um conceito inovador que tem sido apontado como bastante promissor no estudo da importância dos orbitais moleculares para a reatividade química, e que tem sido aplicado com sucesso para descrever o comportamento ácido-base, reações químicas de compostos orgânicos e complexos inorgânicos, reações pericíclicas e sistemas biológicos. Compreender o comportamento dos orbitais moleculares é fundamental para entender melhor a química. Portanto, essas investigações levam a novas perspectivas e novas ideias sobre a reatividade das moléculas.

Palavras-chaves: FERMO. Reatividade. Orbitais moleculares. Reação de DA. Campo elétrico.

ABSTRACT

The HOMO-LUMO formalism, developed more as an interpretation of reactivity, may not be suitable for describing the reactivity of certain chemical reactions. The concept of FERMO, based on chemical intuition and criteria of composition and localization for the correct determination of the frontier molecular orbital that regulates chemical reactions, can be understood as a complement to the HOMO-LUMO argument. The development of the FERMO (Frontier Effective for Reaction Molecular Orbital) concept describes the breaking and formation of new chemical bonds, providing important clues that modulate the chemical reactivity of atoms and molecules. Through this concept, it was possible to locate the frontier molecular orbitals involved in protonation reactions of substituted phenols, since protonation and deprotonation processes in aromatic molecules, such as phenols, are important in organic and biochemical chemistry. The analysis was performed using the MOLPROJ software to compare the computational results with experimental NMR data obtained from the literature. As a result, an accuracy rate of approximately 86% was achieved in the protonation sites. In another study, we analyzed the activation energies of the organic reaction between ethylene and nitrosoethylene, a Diels-Alder reaction, catalyzed by different types of catalysts: Lewis acid, oriented electric field, and electron-donating and electron-withdrawing substituents. All calculations were performed using Gaussian09 software. The compounds were fully optimized using the restricted Hartree-Fock method with the 6-31G basis set. Single-point energies were determined using the MP3 method and 6-31G basis set. It was observed that the lowest activation barrier was found when the electric field was applied, followed by the use of Lewis acid. It is worth noting that the field-catalysis field is still relatively new, and research is ongoing to explore its full potential and applicability in different chemical reactions. We can perceive that the FERMO idea is an innovative concept that has been pointed out as quite promising in the study of the importance of molecular orbitals for chemical reactivity and has been successfully applied to describe acid-base behavior, chemical reactions of organic compounds and inorganic complexes, pericyclic reactions, and biological systems. Understanding the behavior of molecular orbitals is essential for a better understanding of chemistry. Therefore, these investigations lead to new perspectives and new ideas about the reactivity of molecules.

Keywords: FERMO. Reactivity. Molecular orbitals. DA reaction. Eletric field.

LISTA DE FIGURAS

LISTA DE SIGLAS E ABREVIATURAS

DFT - *Density Functional Theory* (Teoria do Funcional de Densidade).

EEF - *External Electric Field* (campo elétrico externo).

FERMO - *Frontier Effective for Reaction Molecular Orbital* (orbital molecular de fronteira efetivo para a reação).

FMO - *Frontier Molecular Orbital* (orbital molecular de fronteira).

GGA - *Generalized Gradient Approximation* (aproximação generalizada do gradiente).

HF - *Hartree-Fock*

HOMO - *Highest Occupied Molecular Orbital* (orbital molecular de mais alta energia ocupado por um elétron).

IV - Infravermelho.

LDA - *Local Density Approximation* (aproximação da densidade local).

LUMO - *Lowest Unoccupied Molecular Orbital* (orbital molecular de mais baixa energia não ocupado por elétrons).

OMs - Orbitais Moleculares.

PA - Afinidade Protônica

RHO - *Reactive Hybrid Orbital* (orbital híbrido reativo).

RMN - Ressonância magnética nuclear.

TLV - Teoria da Ligação de Valência.

TOM - Teoria dos Orbitais Moleculares.

SUMÁRIO

PRIMEIRA PARTE

1 INTRODUÇÃO

As reações químicas podem ser descritas segundo o modelo dos orbitais moleculares,os quais explicam a reatividade química em nível atômico. Foi Lewis quem estabeleceu o primeiro conceito de reatividade, a qual está relacionada com a disponibilidade de elétronsde uma molécula. Em 1926, Erwin Schrödinger determinou, por meio de várias operações matemáticas, as regiões no espaço que apresentariam máxima probabilidade de se encontrarum elétron (os chamados orbitais), cujo principal resultado é a equação de órbitas estacionárias dos elétrons do átomo de hidrogênio, conhecida como Equação de Schrödinger (CARLTON, 1999).

Graças a Max Born, os orbitais moleculares constituíram a base do entendimento das propriedades das moléculas como um todo, como a energia de ligação e o comprimento de ligação. As funções de onda dos orbitais atômicos são combinadas matematicamente para produzir as funções de onda dos orbitais moleculares resultantes, isto é, um novo conjunto de níveis energéticos que correspondem a novas distribuições da nuvem eletrônica (densidade de probabilidade) (ATKINS; FRIEDMAN, 1997; RAUK, 2001).

Na busca de uma relação quantitativa entre reatividade e configuração eletrônica, surgiu o conceito de orbitais de fronteira. Em uma reação química, o eletrófilo, ou aceptor de elétrons, e o nucleófilo (doador de elétrons) estão associados respectivamente a uma espécie contendo um orbital molecular vazio que acomoda o par de elétrons doado oriundo de um orbital molecular ocupado da outra espécie, sendo que o orbital mais acessível é o que apresenta menor energia entre os orbitais desocupados (LUMO), e o mais propenso a perder seus elétrons é naturalmente o orbital de mais alta energia ocupado (HOMO). Quando moléculas se aproximam uma das outras, a configuração mais favorecida é a sobreposição HOMO-LUMO. Porém, segundo Fukui (FUKUI, 1982), o HOMO e o LUMO podem não ser adequados para a compreensão do mecanismo de uma dada reação, mas pode ser o próximo orbital ou qualquer orbital que tenha energia muito próxima do HOMO ou do LUMO.

O conceito de Orbital Molecular de Fronteira Efetivo para a Reação (FERMO) surgiu diante das limitações impostas pelos mencionados argumentos de HOMO e LUMO. Tal conceito, proposto por da Silva e Ramalho, 2006 (DA SILVA *et al.*, 2006), pode ser entendido como um complemento ao HOMO-LUMO, segundo o qual o HOMO só será o orbital de reação caso cumpra os requisitos para ser o FERMO. Essa ideia vem sido bem aplicada na descriçãodo comportamento ácido-base, em complexos orgânicos e inorgânicos, em reações pericíclicas e no estudo de sistemas biológicos (LA PORTA *et al.*, 2014).

O uso da energia do FERMO foi sugerido e utilizado com sucesso por da Silva e colaboradores (DA SILVA; RAMALHO; et al., 2006), para correlacioná-la com os valores de pKa de ácidos carboxílicos, álcoois e fenóis. Foi proposto que qualquer orbital molecular ocupado próximo do orbital HOMO ou mesmo este pode ser o responsável pela interação de uma determinada molécula, com tendência a doar elétrons, com outra espécie predisposta a receber elétrons, por meio da interação entre o orbital HOMO – X (X: 0, 1, 2 etc.) do nucleófilo com o orbital LUMO do eletrófilo.

O conceito do FERMO também pode ser aplicado na regiosseletividade de compostos. Ela ocorre quando qualquer processo favorece a formação de ligações em um átomo particular em relação a outros átomos possíveis.

Seguindo essa linha, as reações pericíclicas também podem ser racionalizadas por meio da Teoria dos Orbitais Moleculares de Fronteira e, portanto, do FERMO. Em 1965, B. Woodward e R. Hoffmann desenvolveram a Teoria de Conservação de Simetria, que foi um grande marco para o desenvolvimento e a utilização de modelos teóricos para a racionalização de mecanismos de reações orgânicas como, por exemplo, a reação de cicloadição de Diels-Alder (DA) (PAULING, 1931; RAUK, 2001). Segundo a teoria FMO, uma simplificação desenvolvida por Fukui a partir do método de Woodward e Hoffmann, ao ocorrer a aproximação dos dois componentes, dieno e dienófilo, ocorre a combinação de todos os orbitais moleculares destas espécies. A combinação entre HOMO de uma espécie com o LUMO, de acordo com esta teoria, é a mais significativa para a estabilização do sistema (MORAES, 2014).

Por causa da sua imensa relevância na química e do seu impacto no pensamento mecanicista, a reação de Diels-Alder tornou-se um ícone químico. Possui uma aplicabilidade incomparável e profundas implicações conceituais (MEIR *et al.*, 2010). Sendo assim, realizar-se catálise em tal reação tornou-se interessante graças à sua importância na síntese química.

A catálise de uma reação de Diels-Alder pode acontecer por meio de um ácido de Lewis, cujo aumento na velocidade da reação pode ser explicado segundo a teoria da FMO. Outro fator também aumenta a taxa de velocidade de uma reação DA. Sabe- se que a reatividade, a regioquímica e a estereoquímica dessas reações são controladas pela interação suprafacial em fase do HOMO de um componente (o FERMO da reação) e o LUMO do outro (FRINGUELLI; TATICCHI, 1988). Quanto menor for a diferença de energia entre esses orbitais moleculares de fronteira, menor é a diferença de energia no estado de transição da reação. O que pode contribuir para a diminuição ou elevação dessa energia são os substituintes no dieno e/ou dienófilo. Os substituintes que retiram elétrons diminuem a energia do LUMO, enquanto os grupos doadores de elétrons aumentam a energia do HOMO. Consequentemente, a diferença de energia entre os dois orbitais diminui (FERNÁNDEZ; FRENKING, 2019).

Entretanto, como as reações químicas são descritas pelo movimento de elétrons e/ou núcleos, a cinética e a termodinâmica desse tipo de reação também podem ser influenciadas por campos elétricos externos (STUYVER *et al.*, 2020). Assim, os efeitos eletrostáticos podem modificar a estabilidade das espécies químicas, estabilizando ou desestabilizando contribuintes de ressonância separados por carga e, assim, influenciar a energia de ligação (MEIR *et al.*, 2010). Um campo elétrico externo (EEF) orientado na direção do "eixo da reação",ao longo do qual a reorganização eletrônica ocorre, pode afetar a taxa de reação por ordens de grandeza, tornando-se mais rápida ou mais lenta, dependendo da mudança de direção do campo.

2 OBJETIVO GERAL

Estudar a reatividade de compostos por meio do conceito de orbitais de fronteira, com ênfase na regiosseletividade de fenóis e na avaliação do efeito de campos elétricos sobre como catalisadores em reação de Diels-Alder entre etileno e nitrosoetileno e revisar algumas considerações sobre as contribuições da abordagem dos orbitais moleculares de fronteira para o entendimento da reatividade química.

2.1 OBJETIVOS ESPECÍFICOS

- Revisar conceitos de reatividade química e orbitais moleculares;
- Analisar a regiosseletividade na protonação de fenóis à luz dos orbitais molecularesde fronteira, especificamente o orbital molecular de fronteira efetivo da reação (FERMO);
- Identificar sítios de protonação em grupos definidos de fenóis.
- Quantificar os coeficientes orbitais dos átomos de carbono e oxigênio envolvidos para comparar com resultados experimentais obtidos por meio da técnica de RMN.
- Avaliar computacionalmente os efeitos estereoeletrônicos que governam reações de substituição eletrofílica aromática com base em um estudo experimental escolhido como exemplo.
- Comparar as energias de ativação da reação de Diels-Alder entre etileno e nitrosoetileno, usando um campo elétrico e um ácido de Lewis como catalisadores.
- Investigar a influência de substituintes no dieno e no dienófilo da reação de Diels-Alder.

3 REFERENCIAL TEÓRICO

3.1 Reatividade

A teoria da reatividade química surgiu a partir das tentativas de entender e classificar muitas interações químicas e reações com o objetivo final de prevê-las antes das observaçõesde laboratório (MINEVA, 2006). Dentre os principais conceitos dessa teoria, os chamados "índices de reatividade" podem derivar do número de elétrons, eletronegatividade, dureza e moleza, entre outros (MALEK; BALAWENDER, 2015).

Os primeiros trabalhos sobre reatividade surgiram com Lewis (LEWIS, 1913, 1916). Foi ele quem estabeleceu alguns fundamentos essenciais para se entender hoje o que é a reatividade. Segundo Lewis, a reatividade é resultante da disponibilidade de elétrons e as propriedades presentes nas substâncias estão diretamente correlacionadas com a mobilidade desses elétrons na molécula (LEWIS, 1913, 1916).

A estrutura eletrônica ainda é o foco para a representação de modelos estáticos de reatividade desde o começo das aplicações da teoria dos orbitais de Mulliken (MULLIKEN, 1934). Utilizou-se muitas vezes desse modelo de reatividade na análise da população de elétrons, sendo feita em cada centro atômico do sistema molecular, bem como na população de elétrons nas regiões internucleares, nos índices de ordem das ligações (POPLE, 1999).

Por meio da teoria do orbital molecular de Hückel (HMO), foi possível descrevervários índices de reatividade local e não local e explicar a estrutura eletrônica de sistemas conjugados. Estes eram definidos na forma de funções deresposta à densidade estática, polarizabilidade atômica e de ligação (COULSON *et al.*, 1947). Tal generalização foi inserida na teoria da reatividade química, inicialmente por Klopman e Salem (KLOPMAN *et al.*, 1982; SALEM, 1968) e, depois, por Fukui (FUKUI, 1975; PARR; YANG, 1984), tornando-se conhecida como teoria do Orbital Molecular de Fronteira (FMO).

Muitas propriedades atômicas e moleculares ligadas à reatividade, à forma e ao modode ligação de fragmentos e substituintes moleculares podem ser definidas segundo métodosde Química Quântica e modelagem molecular. Uma destas propriedades corresponde à categoria dos descritores químico-quânticos. Ela se relaciona à energia dos orbitais de fronteira, utilizando as energias do HOMO e do LUMO (ARROIO; HONÓRIO; DA SILVA, 2010). Tais energias fornecem conhecimento sobre o caráter doador ou aceptor de elétrons de um composto e, consequentemente, à formação de um complexo de transferência de carga (HONÓRIO; DA SILVA, 2003).

São também correlacionadas com outros índices, tais como afinidade eletrônica e potencial de ionização (ARROIO, HONÓRIO, DA SILVA, 2010; HEATON, MILLER, POWELL, 2001). Do ponto de vista teórico, os índices de reatividade foram introduzidos como descritores de seletividade e reatividade (MINEVA, 2006).

3.2 Orbital Molecular de Fronteira

A mecânica quântica surgiu um pouco depois dos trabalhos pioneiros de Lewis. Segundo Schrödinger, uma funçãode onda (Ψ) é uma representação matemática abstrata de um sistema, um elemento essencial para definir as propriedades moleculares (RAUK, 2001). Uma dessas propriedades é a energia do sistema, a qual pode ser determinada a partir da função de onda por meio da equação de Schrödinger, que é resolvida para átomos e sistemas monoeletrônicos (Equação 1) (CARLTON, 1999):

$$\widehat{H}\Psi = E\Psi \underset{(r)}{\rightarrow}$$

Ou

$$\left\{\frac{-\hbar^2}{2m}\left(\frac{\partial^2}{\partial_x^2}+\frac{\partial^2}{\partial_y^2}+\frac{\partial^2}{\partial_z^2}\right)+V\left(\underset{r}{\rightarrow}\right)\right\}\Psi\left(\underset{r}{\rightarrow},t\right) = i\hbar\frac{\partial\Psi\left(\underset{r}{\rightarrow},t\right)}{\partial t} \qquad \text{(Eq.1)}$$

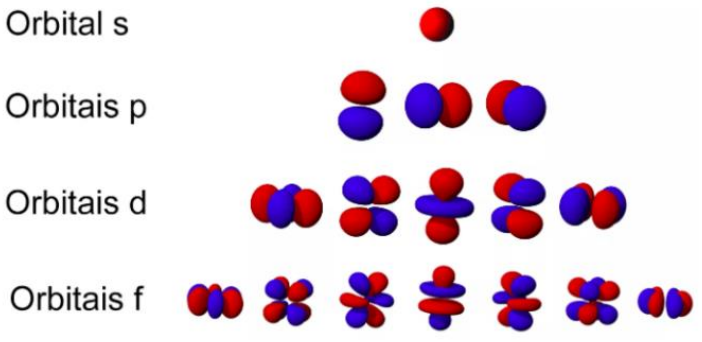
em que Ψ é a função de onda que descreve o sistema, o qual está sujeita a um potencial externo V. $\widehat{H}$ é o operador Hamiltoniano, que fornece a energia do sistema ao ser aplicado à função de onda.

Por meio dos conceitos contruídos por Schrödinger, Max Born propôs que poderia ser dado um significado físico preciso ao quadrado de Ψ (Ψ^2), para um elétron com uma localização particular definida por x, y e z. De acordo com Eq. 2, Ψ^2 exprime a probabilidade de se encontrar um elétron numa posição x, y e z do espaço, sendo que esta região de probabilidade fornece a forma dos familiares orbitais atômicos s, p, d e f, como mostrado na

Figura *1* (RAUK, 2001).

$$p(x,\mathrm{t}) = (\Psi(x,\mathrm{t}))^2 \qquad \text{(Eq. 2)}$$

Figura 1- Forma dos orbitais s, p, d e f para o átomo de hidrogênio.



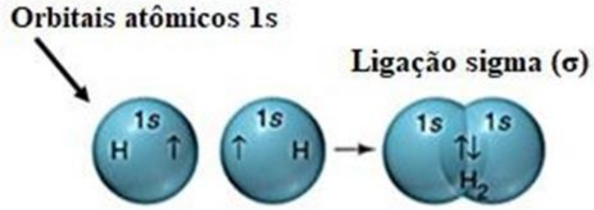
FONTE: (AUTOR).

O modelo de hibridização utiliza os orbitais atômicos para explicar a formação das ligações químicas, considerando a reorganização dos orbitais atômicos para formação dos orbitais híbridos com a finalidade de reduzir a energia do sistema. Isso é alcançado ao se distanciar grupos na molécula, o que consequentemente diminui a repulsão entre eles (MAKSIĆ, 1986). É um modelo útil para representar ligações químicas e geometria molecular, porém possui algumas limitações, como por exemplo não ser capaz de explicar oestado excitado das moléculas (FREITAS, RAMALHO, 2013).

Um modelo moderno que é capaz de explicar alguns fenômenos usualmente de difícil compreensão por meio de outras abordagens é o modelo de orbitais moleculares. Ele combina a tendência dos átomos de preencher seus octetos, isto é, compartilhando elétronstal como o modelo de Lewis, com as propriedades ondulatórias, conforme as quais os elétrons ocupam determinados volumes do espaço, os chamados orbitais. Nestes, as ligações covalentes originam-se da combinação de orbitais atômicos para formar orbitais moleculares.

Esses orbitais pertencem à molécula inteira, e não a um único átomo, como mostrado na Figura 2 (FREITAS, RAMALHO, 2013). Da mesma forma que um orbital atômico descreve o volume do espaço ao redor do núcleo de um átomo, onde é provável que um elétron seja encontrado, um orbital molecular descreve o volume do espaço em torno de uma molécula onde um elétron provavelmente será encontrado. Os orbitais moleculares possuem tamanhos, formas e energias específicas.

Figura 2- Formação de um orbital molecular de uma molécula de hidrogênio.



Fonte: (FREITAS, RAMALHO, 2013).

Como já mencionado anteriormente, os orbitais moleculares são formados a partir dos orbitais atômicos. Especificamente dos orbitais atômicos que pertencem à camada de valência dos átomos da molécula. Assim, um orbital molecular de uma molécula é descrito como na Eq. 3:

$$T_1=c_1\phi_a + c_2\phi_b$$
$$T_2=c_1\phi_{\mathrm{b}} - c_2\phi_b \qquad \text{(Eq. 3)}$$

Aqui, c_i representa os coeficientes dos orbitais, enquanto ϕ_a e ϕ_b representam as funções de onda dos orbitais atômicos a e b, respectivamente. A soma da equação 3 indica uma interação construtiva das funções de onda que descrevem os orbitais (interação ligante, em fase), já a subtração indica uma interação antiligante ou fora de fase.

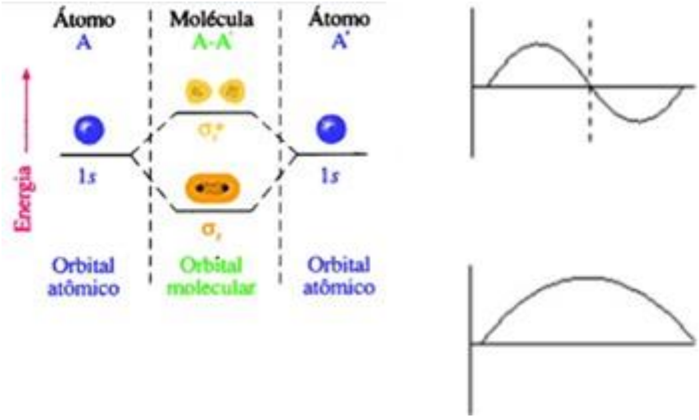
Por meio de combinações lineares dos orbitais atômicos envolvidos, pode sermontada a função de onda aproximada para a molécula estudada e determinada por um cálculo de campo autoconsistente. Uma das maiores utilidades dos orbitais atômicos está na compreensão de como os átomos se combinam formando moléculas (FREITAS, RAMALHO, 2013).

Os orbitais moleculares podem ser definidos qualitativamente a partir das combinações lineares de orbitais atômicos. Isto é, cada orbital atômico que compõe um orbital molecular possui um coeficiente (peso) que representa sua contribuição para um orbital molecular

(FREITAS, RAMALHO, 2013). Essa combinação pode ocorrer de duas formas: em fase (ligante) ou fora de fase (antiligante). Elas podem ser representadas de diferentes maneiras: por meio de ilustrações, gráficos e diagramas.

A Figura 3 mostra a combinação da formação da molécula de H_2. A interação ligante é representada pela interação entre lóbulos da mesma cor, enquanto que a interação antiligante é representada por lóbulos de cores diferentes e separados por um plano nodal, também chamado de nó.A representação gráfica apresenta a forma do orbitale suas fases. Já o diagrama de orbitais indica a interação dos orbitais atômicos para a formação dos orbitais moleculares de mais baixa ($\boldsymbol{\phi}$) e mais alta energia ($\boldsymbol{\phi}$*) (FREITAS, RAMALHO, 2013).

Figura 3- Esquema de combinação de orbitais atômicos para formar orbitais moleculares para a molécula de H_2.



Legenda: Desenhos, gráficos (os sinais das fases são arbitrários) e diagrama de orbitais.
Fonte: (FREITAS, RAMALHO, 2013).

Assim como os orbitais atômicos, o orbital molecular é uma função matemática bem definida, que pode ser determinada em qualquer ponto do espaço e desenhada em três dimensões (ATKINS; FRIEDMAN, 1997). A combinação linear de orbitais atômicos sempre retorna o mesmo número de orbitais moleculares.

Qualquer elétron que ocupa um orbital molecular é atraído por ambos os núcleos e tem energia menor do que quando está confinado ao orbital atômico de um átomo. Além disso, como o elétron pode ocupar agora um volume maior do que quando está confinado a um único átomo, ele também tem energia cinética mais baixa. O orbital resultante da combinação de orbitais que tem menor energia total é chamado de orbital ligante. Já a combinação de orbitais atômicos que tem a maior energia total é chamada de orbital antiligante (HOFFMANN, 1963).

Em princípio, precisamos resolver a equação de Schrödinger para todos os orbitais em uma molécula e, em seguida, preenchê-los com pares de elétrons como fazemos para os orbitais nos átomos. Mas na prática, estamos realmente interessados apenas nos orbitais moleculares que derivam dos orbitais de valência dos átomosconstituintes, porque esses são os orbitais que estão envolvidos na ligação.

Estamos especialmente interessados nos orbitais de fronteira, ou seja, o orbital molecular mais alto ocupado (HOMO) e o orbital molecular mais baixo não ocupado (LUMO) (NAUMOV; HEMLEY, 2014). Orbitais preenchidos com energias muito menores (ou seja, orbitais centrais) não contribuem tanto para a ligação, assim como orbitais vazios com energia mais alta também não contribuem. Esses orbitais são, no entanto, importantes em fotoquímica e espectroscopia, nas quais as transições eletrônicas de orbitais ocupados para vazios possuem maior importância (HOFFMANN, 1982).

Kenichi Fukui e coloboradores introduziram o conceito de HOMO e LUMO, o qual tornou-se muito importante para a definição de reatividade. O HOMO corresponde aos elétrons que estão menos “presos” à molécula, sendo mais suscetíveis a serem doados. Ele então, determina a capacidade doadora de elétrons. Já o LUMO corresponde à rota mais fácil para se adicionarem novos elétrons ao sistema (FREITAS, RAMALHO, 2013). Esses orbitais, também conhecidos como orbitais de fronteira, são utilizados para determinar a maneira pela qual a molécula interage com outras espécies (RESMI et al., 2016).

De acordo com a teoria dos orbitais moleculares de fronteira (FMO), a formação de um estado de transição é devida a uma interação entre os orbitais de fronteira (HOMO e LUMO) dos reagentes (LATHA et al., 2017) e uma pequena diferença de energia (gap) entre esses orbitais é associada a uma alta reatividade química (ŞAHIN *et al.*, 2016). Essa reatividade química pode ser explicada pelos descritores de reatividade global como o potencial de ionização, a afinidade eletrônica, a eletronegatividade e o potencial químico (RESMI *et al.*, 2016).

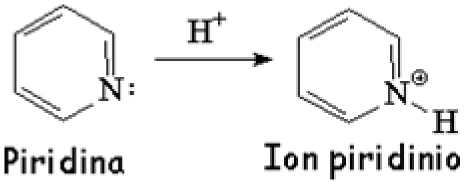
Reunindo-se os fundamentos de Lewis com respeito à reatividade ao conhecimento dos orbitais moleculares, a reatividade dos compostos químicos tornou-se mais compreensiva e qualitativa (LIANG *et al.*, 2017). Os orbitais moleculares tornaram-se então importantes descritores para a reatividade dos compostos (DA SILVA; SANTOS; *et al.*, 2006; PEREIRA *et al.*, 2016).

3.3 Orbital Molecular de Fronteira Efetivo para Reação-FERMO

Mesmo com o sucesso do argumento HOMO-LUMO, muitos pesquisadores se perguntaram se esses dois orbitais seriam os únicos responsáveis pela reatividade das moléculas (BRAGA *et al.*, 2019; PEREIRA *et al.*, 2016). Fukui expôs essa preocupação em um artigo que escreveu em comemoração ao Prêmio Nobel (FUKUI, 1982).

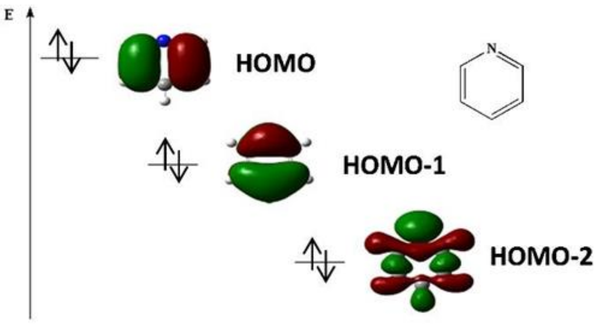
Para exemplificar, Fukui apresentou o caso da protonação da piridina, como pode ser visto na Figura 4. No processo de protonação, o HOMO da reação é um orbital do sistema π do anel piridínico (Figura 5) (FUKUI, 1982). Porém, o átomo de hidrogênio se liga ao par de elétrons do nitrogênio, portanto, o HOMO não teria ligação com essa reação na piridina. O orbital que realmente estaria envolvido na reação seria o terceiro HOMO (ou HOMO– 2), o qual possui a característica do par de elétrons não ligante do nitrogênio (PEREIRA et al., 2016), como mostrado na Figura 5.

Figura 4- Protonação da piridina.



Fonte: (PEREIRA *et al.*, 2016)

Figura 5- Forma dos orbitais moleculares de maior energia da piridina.



Fonte: (FUKUI, 1982a; BRAGA *et al.*, 2020)

Por meio da protonação da piridina, foi possível demonstrar que, mesmo com os avanços, a teoria dos orbitais de fronteira possuía algumas limitações, abrindo assim, a possibilidade para novas teorias, dentre elas o FERMO (Orbital Molecular de Fronteira Efetiva para Reação) (BRAGA *et al.*, 2020; BRAGA *et al.*, 2019; PEREIRA *et al.*, 2016).

O conceito FERMO emergiu como um instrumento para investigar o papel dos orbitais moleculares aplicados à descrição da quebra e formação de ligações químicas. Como observado por Fukui, o HOMO e o LUMO podem não ser adequados para uma dada reação, mas certamente o próximo orbital ou qualquer orbital que tenha energia muito próxima do HOMO poderia ser usado. É uma ferramenta simples, mas bastante útil. Com ele, as reações que não eram compreendidas com base nas propriedades HOMO-LUMO deixaram de ser exceções (BRAGA *et al.*, 2020).

Dentre essas reações, destacam-se comportamento ácido-base, complexos orgânicos e inorgânicos, reações pericíclicas e estudo de sistemas biológicos (LA PORTA *et al.*, 2010b; LA PORTA *et al.*, 2011; LA PORTA *et al.*, 2012; BRAGA *et al.*, 2019).

Segundo da Silva (DA SILVA *et al.*, 2006), para uma determinada molécula, a escolha do orbital FERMO é feita de acordo com as seguintes etapas:

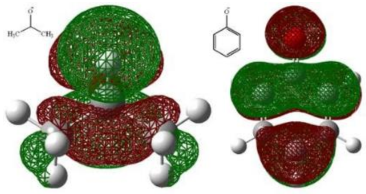
I. Verificação da forma dos orbitais moleculares.

II. Verificação das energias dos orbitais moleculares.

III. Avaliação de qual dos orbitais moleculares apresenta maior contribuição do átomo ou grupo de átomos que é ou são o centro da reação. Isto é feito analisando o valor da composição dos orbitais moleculares em função dos coeficientes de expansão dos orbitais atômicos.

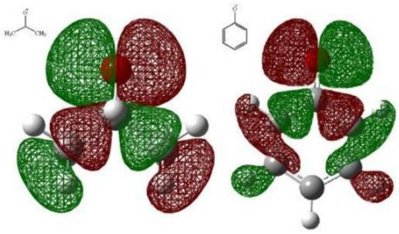
Por exemplo, em algumas reações ácido-base, as energias do HOMO podem não descrever seu comportamento ácido-base. Em compostos como álcoois e fenóis, observa-se que o melhor orbital que descreve o comportamento ácido-base na reação de protonação das bases conjugadas aniônicas para esses compostos não é o HOMO (Figura 6), mas sim o orbital P_xP_y (Figura 7), que é o FERMO para esta reação em cada molécula, conforme ilustrado nas Figuras 6 e 7 (DA SILVA *et al*, 2006; BRAGA *et al.*, 2020).

Figura 6- Orbitais HOMO para os ânions isopropóxido (esquerda) e fenóxido (direita).



Fonte: (FUKUI, 1982b; BRAGA *et al.*, 2020).

Figura 7- Orbitais FERMO p_xp_y para os ânions isopropóxido (esquerda) e fenóxido (direita) em suas reações de protonação.

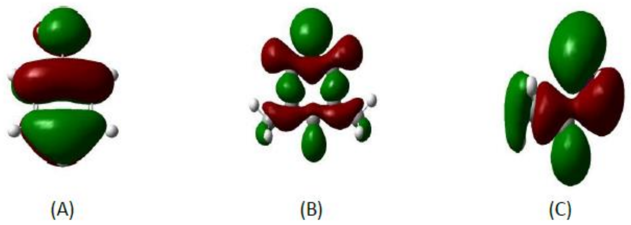


Fonte: (FUKUI, 1982b; BRAGA *et al*., 2020).

Por meio do conceito de FERMO, é possível analisar cada forma, energia e composição dos orbitais moleculares para assim determinar qual destes orbitais irá descrever a reação (PEREIRA *et al.*, 2016). Este conceito também foi aplicado a uma série de aminas para observar o comportamento ácido-base (LA PORTA *et al.*, 2010). La Porta e colaboradores investigaram quais orbitais moleculares descreveriam melhor o comportamento ácido-base de um conjunto de 18 aminas em que a abordagem FERMO também poderia ser aplicada. Como resultado, o conceito do FERMO foi aplicado com sucesso para descrever o comportamento ácido-base da série de aminas estudadas, apresentando melhor correlação com o pK_b do que o HOMO.

Nesse sentido, o conceito FERMO levou em consideração cada forma e composição atômica dos orbitais moleculares para determinar qual deles seria o orbital que descreve a reação (Figura 8). Foi observado que o FERMO possuía uma alta contribuição do orbital atômico do nitrogênio no plano 'xy' (plano do anel aromático) do grupo amina.

Figura 8- Superfície para o FERMO no nível de HF para as aminas aromáticas (A), heterocíclicas (B) e alifáticas (C).



Fonte: (LA PORTA *et al.*, 2010)

O FERMO também apresentou bons resultados em relação a complexos orgânicos e inorgânicos quando empregado para certos tipos de ligantes ambidentados correlacionando com o princípio de dureza e moleza de Pearson. No trabalho de da Silva e colaboradores (DA SILVA *et al.*, 2006), seguindo o princípio de Pearson, que afirma que moléculas moles têm menor valor de energia para a barreira HOMO-LUMO quando comparados com sítios duros, foi encontrado que, por meio do FERMO, os sítios de reação mole em uma molécula teriam uma menor barreira de energia FERMO-LUMO do que os mais duros. Sendo assim, a barreira de energia HOMO-LUMO não poderia descrever a diferença de dureza entre os dois sítios de ligação na mesma molécula.

As reações pericíclicas também foram estudadas com base nesse conceito. Estas reações podem ser definidas como uma reorganização concertada de ligações químicas, por meio de um arranjo cíclico de átomos continuamente interligados. Os principais tipos de reações pericíclicas são: reações eletrocíclicas, reações de cicloadição, reações de rearranjo sigmatrópico e as reações do tipo Ene.

Em um trabalho de La Porta e colaboradores (LA PORTA *et al.*, 2011), o conceito de FERMO foi aplicado com sucesso no estudo de quatro reações de cicloadição 1,3-dipolar. Cálculos teóricos foram realizados para obter o mínimo de energia dos sistemas estudados e alguns substituintes foram escolhidos a fim de abordar a influência de grupos pequenos e grandes, bem como grupos com efeito retirador e doador de elétrons nos reagentes. Por meio de cálculos simples foi possível identificar o orbital molecular efetivo para a reação para todos os casos estudados. Baseado na composição e localização dos orbitais moleculares, o FERMO foi identificado como o HOMO para 3 dos modelos das reações.

Esses resultados, no entanto, ainda tinham um caráter qualitativo. Em um trabalho recente

(BRAGA *et al.*, 2019), buscou-se investigar quantitativamente a localização dos orbitais moleculares correspondentes em cada centro de reação, utilizando o grau de localização do FERMO.

3.4 Grau de localização do FERMO

Para quantificar a localização do FERMO foi desenvolvido o software MOLPROJ® (BRAGA et al., 2019), o qual foi baseado no uso de operadores de projeção para construir os orbitais moleculares por combinação linear de orbitais atômicos (a abordagem CLOA). Nesse mesmo estudo, foi possível determinar o sítio de reação de uma série de aminas e descrever seu comportamento ácido-base. Dessa forma, a localização do FERMO indicaria o orbital em que ocorre a reação e, consequentemente, apontaria o local mais favorável para a protonação.

Pode-se utilizar a base de orbitais atômicos para criar operadores de projeção em um determinado subespaço do sistema. Um operador de projeção pode ser conceituado como a projeção de um subespaço vetorial em outro (ou de um vetor em particular sobre um subespaço), correspondendo à componente que cada vetor do primeiro teria sobre o segundo (a sombra de um em outro) (AZEVEDO, 2013).

Como já comentado, a localização do FERMO foi baseada no uso de operadores de projeção, como se observa na Eq. 4, em que os MOs, θ_μ, são construídos por uma combinação linear de orbitais atômicos (a abordagem CLOA) (BRAGA *et al.*, 2019):

$$\theta_\mu = \sum C_{l\mu}\zeta_l(x) \qquad \text{(Eq. 4)}$$

onde $C_{l\mu}$, é a matriz dos coeficientes de orbitais moleculares e $\zeta_l(x)$ são AOs gaussianos. Eles são construídos como um conjunto ortogonal de vetores com componentes em cada orbital atômico de uma determinada molécula. No entanto, o conjunto de orbitais atômicos, $\zeta_l(x)$, forma um conjunto de base não ortogonal, que define a matriz de sobreposição S_{ij}, como pode ser visto na Eq. 5 (AZEVEDO, 2013; BRAGA *et al.*, 2019):

$$S_{ij} = \int \zeta_i(x)\zeta_j(x)dx \qquad \text{(Eq. 5).}$$

A matriz de sobreposição pode ser usada para construir um operador de projeção P_G, observando que, para um conjunto de orbitais atômicos G (Eq. 6):

$${}_{ij}P_G = \sum_{i\in G}\sum_{j\in G}\zeta_i\, S^{-1}\zeta_j \qquad \text{(Eq. 6)}$$

P_G é um projetor e, ou seja, é idempotente ($P_G P_G = P_G$).

Observe que um operador de projeção pode ser intuitivamente entendido como a projeção de uma "sombra" de um orbital molecular selecionado no subespaço de um conjunto arbitrário ou orbital atômico (AZEVEDO, 2013) enquanto sua formulação matemática torna-se complicada devido ao caráter não ortogonal dos orbitais atômicos. Esta propriedade é precisamente uma caracterização quantitativa da forma de um dado orbital molecular em um conjunto de orbitais atômicos e, consequentemente, um conjunto de átomos (BRAGA *et al*., 2019).

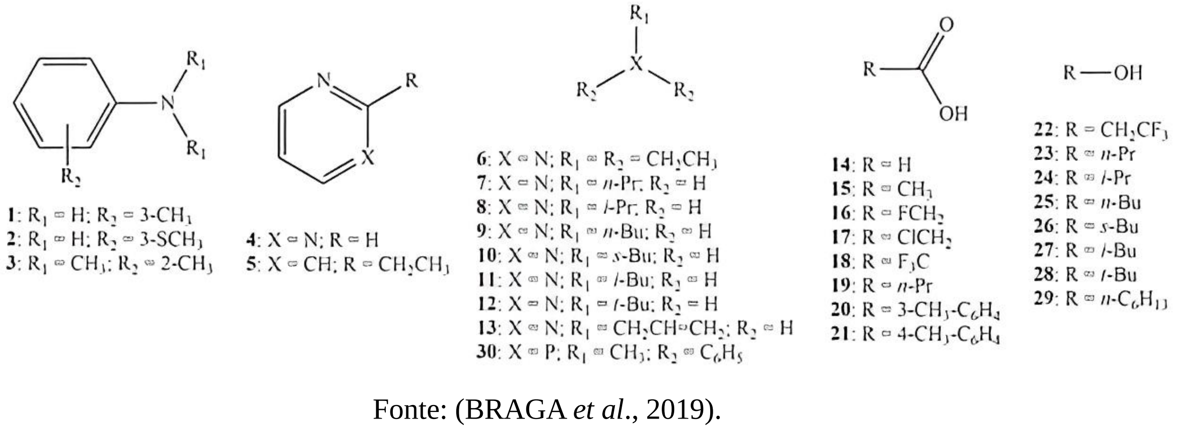
O grau de localização Γ_{FERMO} de um orbital molecular, θ_{μ}, foi definido como a normal de um orbital molecular projetado no conjunto esperado de orbitais atômicos que são relevantes para o centro de reação de um determinado composto. Assim, é possível calcular a localização de orbitais moleculares em grupos de átomos por um critério matemático bem definido usando a Eq.7 (AZEVEDO, 2013):

$$\Gamma_{FERMO} = \sqrt{\sum_{l} \sum_{i \in G} \sum_{j \in G} \sum_{k} C_{l\mu} S_{li} S_{ij}^{-1} S_{jk} C_{k\mu}} \qquad \text{(Eq. 7)}$$

Os orbitais espacialmente localizados são formados a partir das rotações dos orbitais moleculares, segundo critérios variados (AZEVEDO, 2013). O operador de projeção permite construir qualquer subespaço de orbitais atômicos, e não necessariamente o de um único átomo (AZEVEDO, DA SILVA, 2013; BRAGA *et al*., 2019).

Essa abordagem foi aplicada no estudo de 30 de compostos orgânicos diferentes, como mostrado na Figura 9 (BRAGA et al., 2019). Eles foram classificados em anilinas (1–3), pirimidinas/piridinas (4–5), aminas alifáticas (6–13), ácidos carboxílicos (14-21), álcoois (22-29) e fosfinas (30).

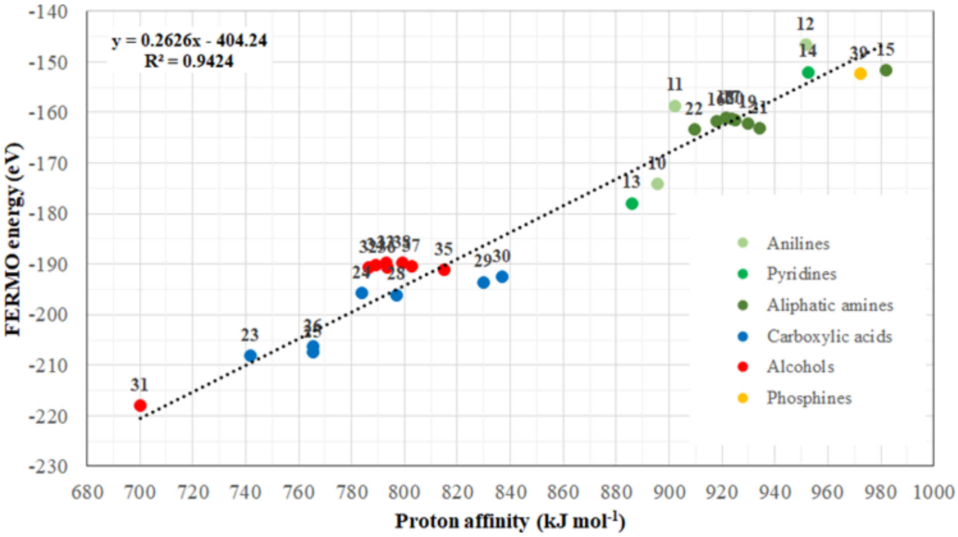
Figura 9- Estruturas dos compostos usados nas reações de protonação consideradas no estudo.



Fonte: (BRAGA *et al*., 2019).

Sabe-se que, embora as energias do HOMO para famílias de compostos possam ser correlacionadas com seus valores de afinidade protônica (PA), há muitos casos para os quais essa correlação não é boa, exigindo outros parâmetros para análise de regressão linear. Foi utilizada então a abordagem do FERMO. Com a utilização das energias do FERMO em vez das energias do HOMO, obteve-se uma correlação com um valor de R2 igual a 0,92, como mostrado na Figura 10, indicando uma tendência de redução da energia do FERMO com o aumento da PA e, consequentemente, da basicidade das aminas na fase gasosa.

Figura 10- Correlação entre valores de PA e energias do FERMO para os 30 compostos selecionados para o estudo da acidez.

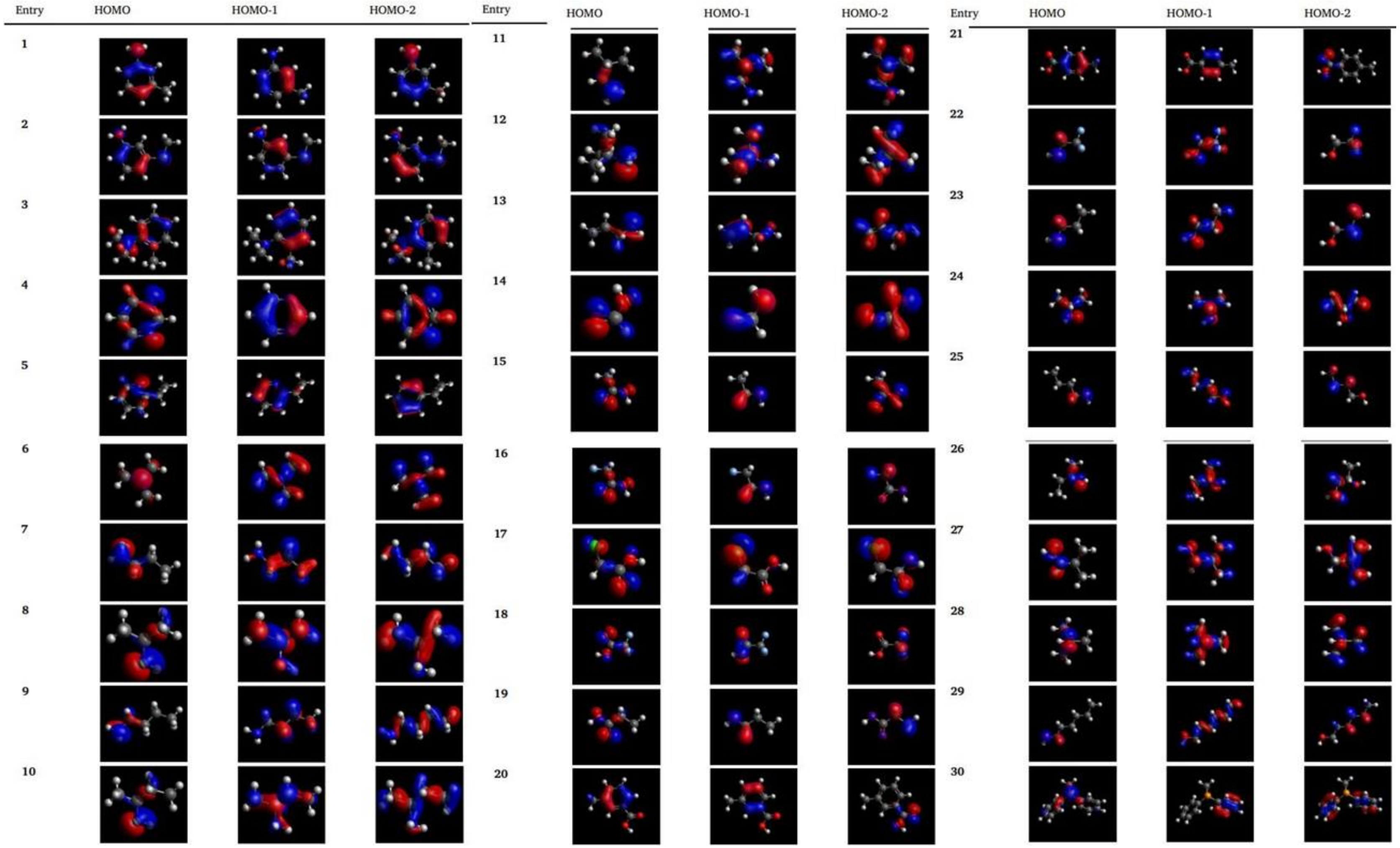


Legenda: A linha pontilhada corresponde ao ajuste linear.

Fonte: (BRAGA et al., 2019).

Com base no grau de localização de cada orbital molecular, foi possível inferir que o orbital que rege a reação ácido/base correspondia aos apontados pelo novo algoritmo como o FERMO, mostrando que a composição de orbital molecular também era um indicador importante para determinar quais eram os orbitais apropriados. Na Figura 11 é possível observar a forma dos orbitais moleculares HOMO a HOMO-2 dos 30 compostos.

Figura 11- Formas de orbitais moleculares de HOMO a HOMO−2 para os compostos estudados.



Fonte: (BRAGA *et al*., 2019).

3.5 Regiosseletividade

A regiosseletividade ocorre quando qualquer processo favorece a formação de ligações entre determinados átomos em relação a outros átomos possíveis. A descrição da regiosseletividade de uma reação (ou ausência de regiosseletividade) é chamada de regioquímica da reação.

Podemos racionalizar a regiosseletividade em termos da protonação de moléculas. A protonação é um ato químico simples, mas importante (TISHCHENKO *et al.*, 2001). As moléculas protonadas são de interesse para os químicos, uma vez que frequentemente são intermediários importantes nos mecanismos de reação (MAYER *et al.*, 1997). Muitos sítios básicos podem estar presentes em um sistema molecular. Assim, a protonação acaba sendo regiosseletiva, a qual produz predominantemente uma espécie protonada. O conhecimento do sítio de protonação preferencial de um composto polifuncional é de interesse fundamental no estudo da reatividade química (TISHCHENKO *et al.*, 2001).

Um desses grupos de compostos polifuncionais estudados são os fenois. Os locais de protonação preferidos para fenóis foram discutidos de um ponto de vista experimental (CHILDS; PARRINGTON, 1974; CHILDS; GEORGE, 1988; ILCZYSZYN; RATAJCZAK, 1995; WOOD *et al.*, 1983) e teórico (CATALÁN *et al.*, 1983; VOETS *et al.*, 1990). Em soluções superacídicas, os fenóis são protonados nos átomos de oxigênio, para formar íons oxônio (*O*-PhH^+), ou nos carbonos do anel aromático nas posições *orto* (*o*- PhH^+), *meta* (*m*-PhH^+) ou *para* (*p*-PhH^+) (OLAH; MO, 1973; OLAH; WHITE; O'BRIEN, 1970; SOLCÀ; DOPFER, 2001). A extensão relativa da protonação nos átomos de oxigênio e carbono e a posição da protonação nos carbonos dependem de vários fatores, como estrutura eletrônica da base, acidez e propriedades de solvatação do meio e temperatura (ECKERT-MAKSIC, 1982).

Além de estudos computacionais, estudos experimentais de espectroscopia de fase líquida, principalmente espectroscopia de ressonância magnética nuclear (RMN) e espectroscopia no infravermelho (IV), foram amplamente utilizados para localizar os locais de protonação preferidos das moléculas de fenois e benzeno substituídos em função do solvente e da temperatura (BIRCHALL; GILLESPIE, 1964; DEFREES *et al.*, 1977; MARTINSEN; BUTTRILL, 1976). Para produzir informações sobre a protonação competitiva nos substituintes em compostos aromáticos substituídos, além da protonação no próprio anel, é necessário separar os efeitos do solvente das propriedades eletrônicas moleculares, cujas investigações devem ser feitas na fase gasosa (BIRCHALL; GILLESPIE, 1965).

Os dados espectroscópicos, particularmente aqueles de RMN, são suficientemente exatos para identificar de forma inequívoca os locais de protonação em compostos aromáticos. Informações experimentais sobre a protonação na fase gasosa também vêm de estudos de espectrometria de massa envolvendo reações de transferência de prótons (BIRCHALL; GILLESPIE, 1964; SOLCÀ; DOPFER, 2001; VOETS *et al.*, 1990).

Embora esses estudos tenham mostrado a existência de vários isômeros protonados de muitos íons aromáticos e, em alguns casos, também as localizações específicas dos prótons, os detalhes de suas estruturas permaneciam constantemente confusos. Para esses casos, a atribuição estrutural dos vários isômeros às vezes depende de cálculos químicos computacionais (VAN LAU; KEBARLE, 1976; VIANELLO; PERAN; MAKSIĆ, 2006).

3.6 Reações Concertadas: reações pericíclicas

A história dos estudos sobre reações pericíclicas é longa e repleta de contraditórios e achados (DOMINGO *et al.*, 2018; LENNARD-JONES, 1929). Em 1923, Lewis propôs o conceito de "reação concertada". Considerava-se que, durante uma "reação concertada", o custo de energia associado à ruptura de ligações fosse compensado pela energia liberada durante a formação de novas ligações (DOMINGO et al., 2018a; LOWRY, 1924).

Por meio século, os químicos orgânicos reconheceram a possibilidade de que certas reações e rearranjos moleculares poderiam ocorrer por um mecanismo que envolvia a permutação cíclica concertada de ligações em torno de um anel de átomos (DEWAR *et al.*, 1971). Lapworth, Robinson e IngoId (INGOLD, 1934) propuseram mecanismos para várias reações usando o atual simbolismo da seta curva para representar o deslocamento das ligações dos pares de elétrons na era da Teoria Eletrônica Clássica (DEWAR *et al*, 1971).

No ano de 1965, apareceu uma série de comunicações que abalaram o mundo químico (WOODWARD; HOFFMANN, 1965). As descobertas relatadas por R.B. Woodward e Roald Hoffmann culminaram em um artigo de revisão intulado "*The Conservation of Orbital Symmetry"* (WOODWARD; HOFFMANN, 1969). Tal trabalhocapturou a imaginação dos químicos, revelando princípios teóricos simples que influenciamprofundamente a química das reações. Nesse mesmo ano, eles formularam as regras de "conservação de simetria orbital" para reações concertadas e isso se tornou o triunfo da teoria dos orbitais moleculares.

As regras de Woodward e Hoffmann tornaram-se particularmente vívidas para reações pericíclicas, isto é, processos concertados procedendo por estados de transição cíclicos. As reações concertadas ocorrem sem um intermediário. A estrutura de transição envolve quebra e formação de ligações, embora não necessariamente no mesmo grau. Além disso, o estado de transição cíclico deve corresponder a um arranjo dos orbitais participantes que podem manter uma interação de ligação entre os átomos que reagem ao longo da reação (HOFFMANN, WOODWARD, 1969).

A chave para entender os mecanismos das reações pericíclicas concertadas foi o reconhecimento por Woodward e Hoffmann de que o caminho de tais reações é determinado pelas propriedades de simetria dos orbitais diretamente envolvidos. A idéia de que a simetria de cada orbital participante deve ser conservada durante o processo de reação transformou dramaticamente o entendimento de reações pericíclicas e estimulou muitos trabalhos experimentais para testar e estender sua teoria (WOODWARD, HOFFMANN, 1969). Esse conceito levou a outras interpretações relacionadas das propriedades orbitais que também são bem-sucedidos em prever e interpretar o curso de reações pericíclicas concertadas.

Segundo estas interpretações, estados de transição com certos alinhamentos orbitais são energeticamente favoráveis (permitidos), enquanto outros levam a estados de transição de alta energia (proibidos). Os estados de transição estabilizados compartilham certos recursos eletrônicos com os sistemas aromáticos, enquanto os de alta energia são mais semelhantes aos sistemas antiaromáticos (DEWAR, 1952; DEWAR *et al*, 1971). Como essas reações prosseguem através de estruturas de transição cíclicas altamente ordenadas com alinhamentos de orbitais específicos, as reações pericíclicas geralmente apresentam estereosseletividade característica e previsível (CAREY, SUNDBERG, 2007).

Em muitos casos, as reações exibem regiosseletividade que pode estar diretamente relacionada ao efeito das interações dos orbitais na estrutura de transição. Da mesma forma, os efeitos dos substituintes na reatividade podem ser interpretados em termos do efeito dos substituintes nos orbitais em interação (CAREY, SUNDBERG, 2007).

Em uma reação pericíclica, o evento da formação da ligação σ é crucial, pois determina o resultado geral da reação em termos de ciclização, abertura de anel ou migração de grupo. As reações pericíclicas são geralmente unimoleculares ou bimoleculares e, dentro dessa categoria geral, é conveniente dividir as reações pericíclicas em quatro classes principais. Elas são: cicloadições, rearranjos sigmatrópicos, reações eletrocíclicas e rearranjos de transferência de grupo.

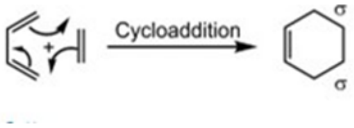
Os aspectos fundamentais dessas reações podem ser analisados em termos de características de simetria orbital associadas ao estado de transição. Para cada grupo principal de reações, a regio- e a estereosseletividade são determinadas pelo estado de transição cíclico (CAREY, SUNDBERG, 2007). Como as reações de cicloadição estão no foco do presente trabalho, elas serão melhor abordadas e aprofundadas.

3.7 Reações de Cicloadição

As reações de cicloadição consistem na combinação de duas moléculas para formar um novo anel. As cicloadições 1,3-dipolares entre azidas e alquinos ou nitrilas, levando a 1,2,3-triazois e a tetrazóis, são muito usadas em síntese orgânica, fazendo parte dos métodos do tipo click chemistry (HUISGEN, 1963; MOSES; MOORHOUSE, 2007; NANDIVADA; JIANG; LAHANN, 2007).

Cicloadições pericíclicas concertadas envolvem a reorganização dos sistemas de elétrons π dos reagentes para formar duas novas ligações σ, como mostrado na Figura 12. Os principais exemplos podem incluir a ciclodimerização de alcenos, cicloadição de cátion alil a um alceno e a reação de adição entre alcenos e dienos (reação de Diels-Alder) (CAREY; SUNDBERG, 2007).

Figura 12- Formação das novas ligações σ em uma cicloadição.



Fonte: (MANDAL, 2018).

Essas reações podem ser caracterizadas especificando o número de elétrons π envolvidos para cada espécie. Nos exemplos citados acima, elas seriam do tipo [2+2], [2+2] e [4+2], respectivamente. Algumas dessas reações de cicloadição ocorrem rapidamente, enquanto outras não são observadas. Isso pode ser entendido de acordo com o padrão de reatividade, por meio da aplicação do princípio de conservação da simetria orbital (CAREY, SUNDBERG, 2007). Elas são reversíveis e é possível realizar a reação reversa por uma escolha adequada de substratos e condições da reação. A cicloadição reversa é denominada retro-cicloadição ou ciclorreversão.

As reações de cicloadição são designadas por convenções de elétrons e átomos:

- Convenção de elétrons: Por convenção de elétrons, uma cicloadição é designada como [l+m] cicloadição, onde l e m denotam o número de elétrons π envolvidos nos dois componentes.
- Convenção de átomos: Por convenção de átomos, uma cicloadição é designada como (l+m), cicloadição em que l e m indicam o número de átomos envolvidos nos dois componentes.

A designação [l+m] descreve o número de elétrons que participam da cicloadição, enquanto (l+m) indica o número de átomos. A convenção de elétrons é mais importante no que se refere ao mecanismo da reação. A convenção de átomos, no entanto, identifica o tamanho do anel do produto.

3.8 Simetria dos orbitais em uma cicloadição

Para entender e explicar os resultados das várias reações pericíclicas com base em diferentes modelos teóricos, é necessária uma compreensão básica dos orbitais moleculares das moléculas, em especial dos alcenos e dos sistemas de polienos conjugados e suas propriedades de simetria.

Como já dito anteriormente, os orbitais moleculares são formados pela combinação linear de orbitais atômicos (CLOA) e depois preenchidos pelos pares de elétrons. Na CLOA, quando dois orbitais atômicos de mesma energia interagem, produzem-se dois novos orbitais moleculares (um orbital ligante e um orbital antiligante). O orbital molecular ligante é o resultado de uma sobreposição positiva(construtiva), e a densidade de elétrons fica na região entre dois núcleos. Um orbital antiligante é formado pelo resultado da sobreposição negativa (destrutiva), e exibe um plano nodal na região entre os dois núcleos (MANDAL, 2018).

Os orbitais moleculares degenerados adequados participam das reações para fornecer produtos através de estados de transição cíclicos em um processo concertado. As formas dos orbitais moleculares formadas pela combinação linear de orbitais atômicos estão relacionadas às formas dos orbitais atômicos (DINDA, 2017).

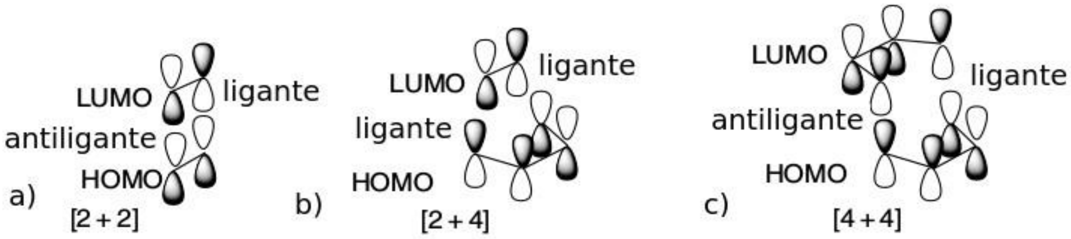
Todos os orbitais moleculares de um componente podem interagir com todos os orbitais moleculares do outro componente em um processo bimolecular. Em uma reação desse tipo, a interação de um orbital ocupado com um orbital desocupado leva a uma estabilização por redução de energia.

As reações de cicloadição que ocorrem através de um mecanismo concertado pericíclico podem ser escritas como um rearranjo contínuo de elétrons (KUMAR; SINGH, 2016). Pode-se limitá-las a sistemas conjugados com dois a seis elétrons π. Para entender sea reação acontece ou não, é necessário explorar como os requisitos de simetria orbital distinguem entre reações favoráveis e desfavoráveis. As observações de simetria orbital providenciam uma visão fundamental da natureza eletrônica das reações de cicloadição e assim, permitem verificar que algumas das estruturas de estado de transição são eletronicamente favoráveis, enquanto outras não (CAREY, SUNDBERG, 2007).

Como mencionado, Woodward e Hoffmann elaboraram os princípios de simetria orbital para reações de cicloadição em termos dos orbitais de fronteira. Um estado de transição energeticamente acessível demanda sobreposição dos orbitais de fronteira para permitir a formação das novas ligações sigma (CAREY, SUNDBERG, 2007).

Isto é, em termos de interações em FMO, uma reação de cicloadição é permitida quando as interações entre os orbitais nas extremidades dos componentes se dão com a sobreposição em fase (mesmo sinal). Se qualquer uma das interações estiver ocorrendo com uma sobreposição fora de fase (sinal diferente), o processo combinado será proibido, como mostrado na Figura 13.

Figura 13- Interação dos orbitais: princípios de simetria orbital para reações de cicloadição.



Legenda: (a) Desfavorável, proibido, (b) favorável, permitido, (c) desfavorável, proibido.

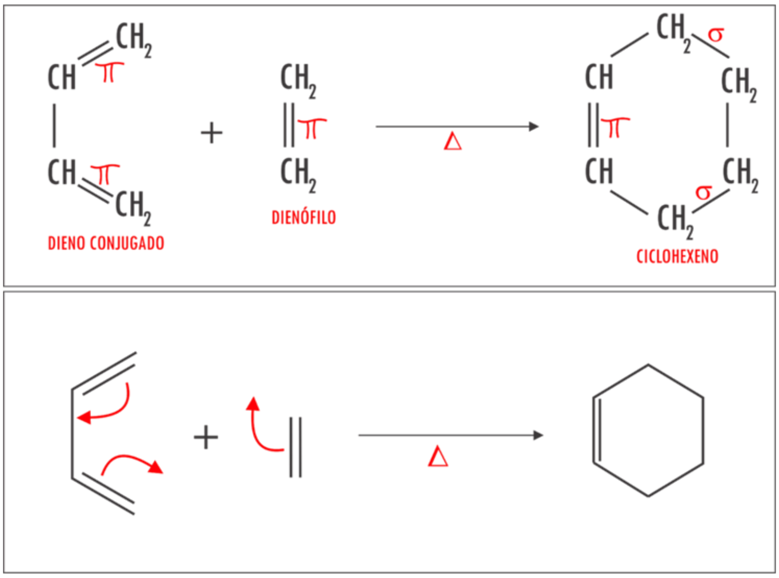
Fonte: (CAREY, SUNDBERG, 2007).

3.9 Reação de Diels-Alder

A reação de Diels-Alder foi formulada por Otto Diels e Kurt Alder em 1928 (DIELS; ALDER, 1928) e intensamente pesquisada por eles. Tornou-se então uma das principais reações, já que era útil no arsenal do químico orgânico sintético (DOMINGO, 2016). Ganhou reconhecimento de sua importância e seus descobridores receberam o Prêmio Nobel de Química em 1950 (MARTIN; HILL, 1961).

Tal reação é uma reação pericíclica de cicloadição [4+2] que ocorre entre um dieno conjugado com quatro elétrons π e um segundo composto insaturado que possui dois elétrons π, o qual é chamado de dienófilo (FERNÁNDEZ; BICKELHAUPT, 2014) (Figura 14). É também uma reação concertada, que opera em uma única etapa, sem intermediários, por um único estado de transição (BROCKSOM *et al.*, 2001).

Figura 14- Reação de cicloadição de Diels-Alder entre um dieno conjugado e um dienófilo.



Fonte:(HERAVI; VAVSARI, 2015).

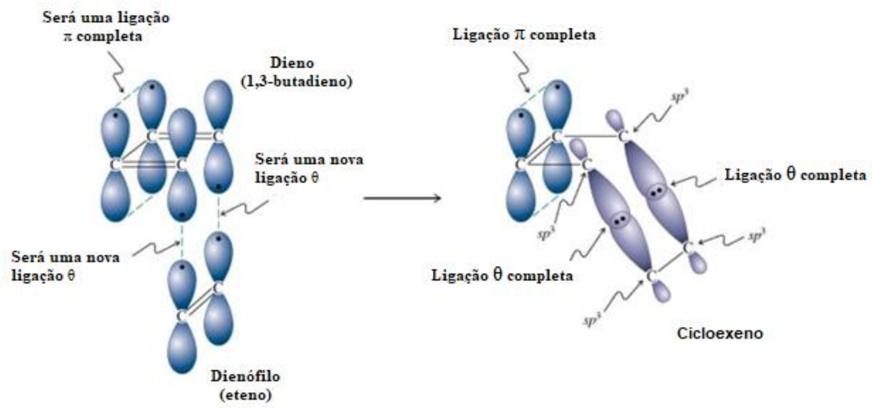
A reação pode ser realizada em condições moderadamente simples, aquecendo-se juntos o dieno e o dienófilo, em solventes não polares, seguidos de evaporação, o que normalmente leva a elevados rendimentos do(s) produto(s) (BROCKSOM *et al.*, 2001).

A reatividade dos componentes de uma reação de Diels-Alder depende da diferençade energia dos orbitais HOMO e LUMO: quanto menor a diferença de energia, menor será a energia do estado de transição da reação em relação aos materiais de partida e mais rápida será a reação. Substituintes retiradores de elétrons diminuem as energias do LUMO, enquanto os grupos doadores de elétrons aumentam a energia do HOMO (FRINGUELLI, TATICCHI, 1988a) .

A regiosseletividade da reação de Diels-Alder depende da natureza e do número de substituintes no dieno e no dienófilo, bem como das condições reacionais (catalisador, temperatura, pressão, solvente etc.). A regiosseletividade da reação é explicada pela TOM com base nos coeficientes dos orbitais dos átomos que formam a ligação σ. A regioquímica é determinada pela sobreposição dos orbitais que possuem os maiores coeficientes. Quanto maior a diferença entre os coeficientes orbitalares dos átomos do dieno e do dienófilo que participam da reação, mais regiosseletiva será a reação (FRINGUELLI, TATICCHI, 1988ª).

A representação dos orbitais na Figura 15 mostra a formação das ligações pela sobreposição dos orbitais p terminais do dieno. Enquanto estes quatro átomos de carbono se re-hibridizam a sp_2, os dois orbitais p internos restantes do dieno dão origem a uma nova ligação π.

Figura 15- Representação dos orbitais mostrando a formação das ligações pela sobreposição dos orbitaistais p terminais do dieno.



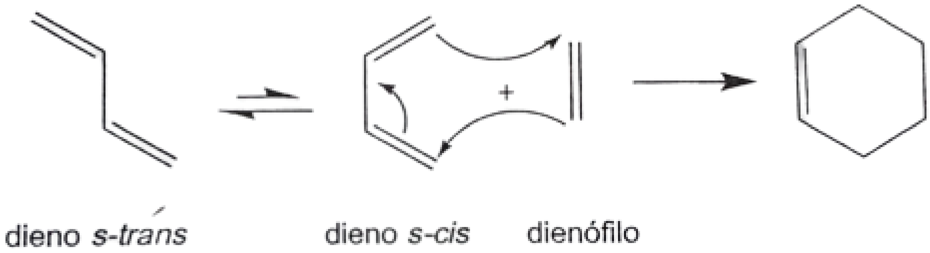
Fonte: (Adaptado: VOLLHARDT; SCHORE, 2013).

3.10 Estereoquímica e o efeito dos substituintes na aceleração da reação DA

A reação de Diels-Alder é muito útil na formação de ciclo-hexenos. Geralmente, o HOMO do dieno, o qual é mais rico em elétrons, e o LUMO dodienófilo interagem, já que há simetria de orbitais para que ocorra a formação da ligação e, consequentemente, a ciclização. Isso explica a necessidade de o dieno estar na conformação*s-cis*, como mostrado na Figura 16 , para que a reação aconteça (DOMINGO *et al.*, 2018).

O mecanismo da reação de Diels-Alder requer que ambas as extremidades do dieno fiquem no mesmo sentido para que possam reagir simultaneamente com os carbonos do dienófilo. Isso significa que o dieno deve adotar a conformação s-cis, energeticamente menos favorecida em relação à forma mais estável, s-trans (VOLLHARDT, SCHORE, 2013).

Figura 16- Conformações s-cis e s-trans do dieno.



Fonte: (FREITAS, RAMALHO, 2013).

Esssa reação é uma adição estereoespecífica sin (suprafacial) em relação ao alceno e ao dieno. Tal estereoespecificidade foi mostrada com muitos dienos e alcenos substituídos e também é o exemplo mais simples possível da reação entre eteno e 1,3-butadieno, como demonstrado por marcação isotópica (CAREY, SUNDBERG, 2007; HOUK; LIN; BROWN, 1986).

O motivo pelo qual as reações de Diels-Alder são quase sempre estereoespecíficas se dá pelo fato de um intermediário não existir, já que ele demonstra não ter vida útil suficiente para aderir a uma rotação ou inversão. Por isso, grande parte dos pesquisadores concordam que a maior parte das reações de Diels-Alder são reações concertadas, o que estáde acordo com a maioria das análises teóricas que seguem com essa visão (CAREY, SUNDBERG, 2007; (BRANCHADELL, 1997; GAIEWSKI; PETERSON; KAGEL, 1987; HOUK; LIN; BROWN, 1986).

Dependendo da abordagem suprafacial entre os grupos funcionais do dieno e do dienófilo, dois cicloadutos estereoisoméricos podem ser formados. Isto é, para um dienófilo substituído, existem dois tipos de orientações estereoquímicas possíveis em relação ao dieno: endo e exo (CUVELLIER et al., 2019).

O modo preferido de adição em muitas vezes é o modo *endo* quando um substituinte retirador de elétrons está presente (por exemplo, quando um grupo carbonila está presente no dienófilo). Essa preferência é chamada de regra de Alder. A preferência pela cicloadição endo tem origem em várias influências estéricas e eletrônicas sobre o estado de transição da reação (VOLLHARDT; SCHORE, 2013). A TOM explica que a adição *endo* é cineticamente favorável, pois considera uma interação adicional não-ligante. Essa interação secundária dos orbitais não dá origem a uma ligação, mas contribui para diminuição da energia do estado transição endo em relação ao estado de transição *exo*.

Algumas vezes, uma mistura de ambos os estereoisômeros é formada e, às vezes, o produto *exo* predomina, mas a regra de Alder é um guia inicial útil para a previsão da estereoquímica de uma reação de Diels-Alder (CAREY, SUNDBERG, 2007). A separação entre os componentes HOMO e LUMO comanda a reatividade da reação de Diels-Alder: quanto menor for a diferença de energia, menor é a diferença de energia (gap) HOMO-LUMO e menor a barreira de ativação da reação.

Quando o HOMO do dieno controla a reação, a reação pode ser acelerada por substituintes doadores de elétrons no dieno e por retiradores de elétrons no dienófilo, sendo então considerada como uma reação normal de Diels-Alder por demanda de elétrons. Já as reações de Diels-Alder controladas pelo LUMO do dieno são influenciadas pelos efeitos eletrônicos dos substituintes da maneira oposta, ou seja, é uma reação de Diels- Alder com demanda inversa de elétrons (FRINGUELLI, TATICCHI,1988b).

3.11 Catálise em reações de Diels-Alder por ácidos de Lewis

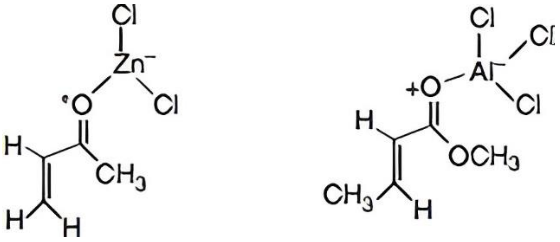
Existem diferentes maneiras de se conceituar os termos ácido e base (MOURA SOUZA; ARICÓ, 2017). Esses diferentes conceitos surgem devido à forma de se analisar as propriedades da acidez e da basicidade. A primeira definição surgiu por Arrhenius (BOCHTLER, 2020). Ele definiu ácidos como compostos que ionizam em solução aquosa para produzir íons hidrônio e bases como compostos que ionizam para produzir íons hidróxido. Já para Brönsted-Lowry, um ácido é um doador de prótons e uma base é um aceitador de prótons (KIM *et al.*, 2017).

De acordo com a definição de Lewis, ácidos são moléculas ou íons capazes de coordenar com pares de elétrons não compartilhados, e bases são moléculas ou íons com pares de elétrons não compartilhados disponíveis para serem compartilhados com ácidos (HOUK; STROZIER, 1973). Para ser ácido no sentido dado por Lewis, uma molécula deve ser deficiente em elétrons. Este é o conceito mais geral de ácido-base. Todos os ácidos de Lowry-Brönsted são ácidos de Lewis (GARCÍA *et al.*, 1998).

A descoberta de que ácidos de Lewis podem promover a reação de Diels-Alder se tornou uma ferramenta importante na química orgânica sintética. A presença de catalisadores ácidos de Lewis permite que as cicloadições sejam realizadas em condições brandas, reações com dienos e/ou dienófilos pouco reativos são possíveis e a régio e estereosseletividade das reações podem ser modificadas (FRINGUELLI, TATICCHI, 1988). Alguns exemplos desses ácidos são: $SnCl_4$, $ZnCl_2$, $AlCl_3$, e derivados do $AlCl_3$, tais como $(CH_3)_2AlCl$ e $(C_2H_5)_2AlCl$.

Os ácidos de Lewis formam por exemplo, complexos com o oxigênio da carbonila dienófilo (Figura 17) e isso aumenta o efeito retirador de elétrons do grupo carbonila, os quais podem acelerar bastante a cicloadição (KANG; REBEK, 1997; CAREY, SUNDBERG, 2007).

Figura 17- Complexos formados pelos ácidos de Lewis com $ZnCl_2$ e $AlCl_3$, respectivamente.



Fonte: (CAREY, SUNDBERG, 2007)

O aumento na velocidade da reação de Diels-Alder é explicado pela teoria dos FMO, considerando que a coordenação do ácido de Lewis com um grupo retirador de elétrons no dienófilo aumenta o efeito retirador na ligação dupla ou tripla e diminui a energia do LUMOdo dienófilo (FRINGUELLI, TATICCHI, 1988).

A complexação com ácidos de Lewis ou a protonação influenciam tanto a energia quanto os coeficientes dos átomos de carbono do orbital LUMO do dienófilo segundo a qual a coordenação do oxigênio da carbonila pelo ácido de Lewis aumenta o efeito retirador de elétrons do grupo carbonila na ligação dupla carbono-carbono e diminui a energia dienófila do LUMO (FRINGUELLI, TATICCHI, 1988).

3.12 Catálise das reações de Diels-Alder por campo elétrico

Os movimentos de elétrons e/ou núcleos descrevem todas as reações químicas e, portanto, a cinética e a termodinâmica podem ser influenciadas por campos elétricos externos. Sendo a reação redox ou não redox, alguns estudos teóricos (ARAGONÈS *et al.*, 2016; ARRANG; GARBARG; SCHWARTZ, 1985; CHE *et al.*, 2018; MEIR *et al.*, 2010; STUYVER *et al.*, 2020; WANG *et al.*, 2018) indicam que os efeitos eletrostáticos podem influenciar as estabilidades de espécies químicas: estabilizando ou desestabilizando contribuintes de ressonância separadospor carga (MEIR *et al.*, 2010).

Esse fato foi anunciado há algum tempo por Shaik e colaboradores para a reação de Diels-Alder (SHAIK, KUMAR, 2004) e em um outro trabalho para reações simples de transferência de halogênio e hidrogênio por Bertrán e colaboradores (ANDRÉS *et al.*, 1988; CARBONELL *et al.*, 1991). Houve um grande interesse na catálise isenta de metal e especificamente em catálise por modelos de ligação de hidrogênio (MEIR *et al.*, 2010).

Nesse cenário, a existência de um campo elétrico externo, o qual deve estar orientado adequadamente, possui o potencial de estabilizar ou desestabilizar ainda mais esses contribuidores de transferência de carga e, assim, influenciar a energia de ligação (ARAGONÈS et al., 2016). É necessário então que o campo elétrico esteja alinhado de modo a atenuar ou fortalecer o dipolo ao longo do eixo de reação (MEIR *et al.*, 2010; AITKEN; COOTE, 2018). Além disso, no estudo da reação de Diels-Alder, Shaik e colaboradores sugeriram ainda que o campo elétrico pudesse ser alinhado ao longo do dipolo do fragmento de dieno para influenciar a regioquímica da reação (AITKEN, COOTE, 2018).

Um outro grupo de pesquisadores de Jerusalém (SHAIK, KUMAR, 2004) mostrou que campos elétricos externos (EEFs) orientados podem controlar a regiosseletividade da oxidação de propeno por uma espécie modelo ativa do citocromo P_{450}. A análise dessas reações levou à conclusão de que os EEFs orientados oferecem uma nova estratégia pela qual o EEF atua como um "catalisador" ou um "reagente" acessório (MEIR *et al.*, 2010).

Um EEF orientado na direção do "eixo da reação", ao longo do qual a reorganização eletrônica ocorre, pode afetar a taxa de reação por ordens de grandeza, tornando-se mais rápido ou mais lento, dependendo da mudança de direção do campo. Ao mesmo tempo, a estereosseletividade *endo/exo* da reação de Diels-Alder pode ser manipulada à vontade com EEFs orientados perpendicularmente ao eixo de reação (MEIR *et al*., 2010).

As previsões teóricas foram confirmadas experimentalmente em 2016 por meio de experimentos intermitentes de microscopia de varredura por tunelamento (STM) (ARAGONÈS *et al.*, 2016). Em resumo, o experimento foi realizado da seguinte forma: moléculas do dieno e do dienófilo foram “presas” à ponta e placa do STM, respectivamente, restringindo sua orientação e fornecendo meios de controlar o estímulo do campo elétrico e medir seu efeito na taxa de reação (AITKEN, COOTE, 2018). Obtiveram como resultados, que, na faixa de forças de campo testadas, a taxa de reação era independente da polaridade positivado campo, mas foi catalisada pelo aumento da intensidade do campo para polarização negativa. Foram realizados ainda cálculos quântico-químicos paralelos do mesmo sistema nas condições experimentais, os quais confirmaram que esses resultados se deviam ao efeito do campo nas barreiras de reação (AITKEN, COOTE, 2018).

Porém, a catálise eletrostática é a forma menos desenvolvida de catálise na química sintética (ARAGONÈS *et al.*, 2016). Tal problema está relacionado com os efeitos eletrostáticos que são fortemente direcionais e são efetivamente extintos em meios polares. Essa dificuldade é superada pelas enzimas usando um sítio ativo de baixa polaridade, no qual o substrato se liga de maneira precisa e onde um ou mais resíduos carregados dentro deste sítio podem criar um campo elétrico local orientado que pode catalisar a reação. Já a química sintética consegue imitar esse processo até certo ponto pela utilização de grupos funcionais carregados no substrato ou catalisador. Mas a partir daí surge a dificuldade de equilibrar a precisão de baixa polaridade do solvente com a solubilidade limitada de resíduos carregados em solventes não polares, o que pode levar ao enfraquecimento do efeito catalítico (ARAGONÈS *et al.*, 2016).

Campos elétricos externos em vez de espécies químicas carregadas como o “catalisador” podem manipular uma gama muito mais ampla de reações, alterando convenientemente a reatividade e a seletividade de uma maneira sintonizável que pode ser prevista pela teoria (MEIR et al., 2010). Desse modo, a partir das previsões teóricas de Shaik e colegas (MEIR et al., 2010), as barreiras de ativação para certas reações de Diels-Alder podem ser reduzidas substancialmente quando um campo elétrico é orientado adequadamente.

3.13 Cálculos teóricos

A Química Computacional atraiu muita atenção nos últimos anos devido ao grande e crescente interesse em empregar métodos teóricos para análises em geral, bem como para a investigação de relações estruturais e complementação de dados experimentais (HEHRE, 1976; LEWARS, 2016). As abordagens teóricas para calcular parâmetros estruturais e eletrônicos agora são implementadas em pacotes de programas muito eficientes que podem ser usados na computação com um desempenho cada vez maior (LEWARS, 2016).

O termo Química Computacional só se tornou popular graças a fatores científicos, históricos, tecnológicos e culturais, e seu desenvolvimento ocorreu devido ao maior poder de processamento de computadores modernos, softwares avançados e da compreensão de princípios básicos da ciência (LEWARS, 2016; McARDLE *et al.*, 2020).

A manipulação e o domínio em escala nanométrica são atualmente indispensáveis, já que apresentam aplicações úteis em diversos campos do conhecimento. E para que isso ocorra, isto é, simular o comportamento da matéria em escala atômica, são aplicados os métodos da Química Computacional baseados no formalismo da Mecânica Quântica.

Uma das maneiras utilizadas para representar a matéria em escala nano ou macro é a formulação em termos de função de onda representada por Schrödinger, o qual foi responsável pela equação que descreve corretamente o movimento dos sistemas quânticos. Conforme explicado anteriormente, a solução dessa equação é uma função denominada função de onda, que é uma representação de um vetor no espaço de Hilbert (SILVA, 2013). Essa função pode ser complexa, de variável real e só pode ser obtida para um conjunto restrito de casos. Para sistemas que contém mais de um elétron, um tratamento sofisticado é necessário.

Por esse motivo, diversos métodos de aproximação foram propostos com o intuito de se encontrar os orbitais eletrônicos para átomos de muitos elétrons. Dentre eles, estão o método Hartree-Fock e a Teoria do Funcional de Densidade (DFT), o quais estão em constante desenvolvimento.

Cálculos teóricos refinados, no entanto, em fase gasosa, habilitaram importantes informações sobre as interações moleculares. Graças ao desenvolvimento notável da química computacional, os cálculos na fase gasosa podem ter uma boa exatidão quando comparados aos dados experimentais. Além disso, alguns estudos anteriores mostraram que os cálculos na fase gasosa têm a mesma confiabilidade que a fase líquida no estudo de orbitais moleculares, quando se baseia no conceito de FERMO (LA PORTA *et al.*, 2010a).

Os cálculos para o FERMO são baseados na Teoria dos Orbitais Moleculares (TOM), segundo a qual os dados são interpretados com a Teoria da Ligação de Valência (TLV) (PEREIRA et al., 2016; BRAGA et al., 2020). Na TOM, os elétrons em uma molécula ocupam orbitais deslocalizados obtidos a partir da combinação linear de orbitais atômicos (FLOR, DAVOLOS, CORREA, 2007). Contudo, deve-se ter em mente que a abordagem da TLV é bastante útil para analisar a reatividade enzimática (NAKAMURA, TRUHLAR, 2001), fotoquímica (BRYNDA et al., 2006), dinâmica química e as teorias de condutividade, em que a representação localizada é indispensável.

3.14 Hartree-Fock

O método Hartree-Fock (HF) foi introduzido pela primeira vez por Douglas Hartree em 1928 e posteriormente melhorado por Vladimir Fock em 1930 (FOCK, 1930). O método é baseado na aproximação de que a função de onda total de um sistema de muitos elétrons pode ser aproximada como um único determinante de Slater, que é um produto de funções de onda de um elétron (FOCK, 1930). Envolve a solução da equação de Schrödinger para o sistema, sujeito à restrição de que a função de onda é um único determinante de Slater. Isso leva a um conjunto de equações não lineares acopladas, conhecidas como equações HF, que devem ser resolvidas de forma autoconsistente (FOCK, 1930). As equações HF são geralmente resolvidas usando uma abordagem iterativa, como o Roothaan-Hall ou os métodos SCF diretos (JENSEN, 2007).

A ideia básica é que cada elétron em um átomo ou molécula interage com o campo médio de todos os outros elétrons. Isso leva a um conjunto de equações integrais-diferenciais simultâneas para os spin-orbitais do elétron, que podem ser resolvidas iterativamente, até que um campo auto-consistente seja alcançado (BLINDER, 2019). O método pode ser usado para resolver a função de onda otimizada de um único elétron (ou seja, o orbital molecular), sob a condição de que a dinâmica desse único elétron seja suscetível ao núcleo e ao potencial efetivo formado pelos elétrons circundantes. Portanto, este método pode ser considerado como a aproximação que desconsidera a correlação eletrônica ao resolver o problema da estrutura eletrônica (SHIKANO *et al.*, 2021).

Uma das principais limitações do método HF é que ele não leva em conta a correlação de elétrons, que é a interação entre os elétrons que surge de sua repulsão Coulomb mútua. Isso leva a imprecisões nas energias calculadas e nas propriedades das moléculas, especialmente para sistemas com elétrons fortemente correlacionados (BARTLETT; MUSIAŁ, 2007). Apesar disso, o método Hartree-Fock é um método computacional amplamente utilizado em química quântica, que fornece uma aproximação útil para a estrutura eletrônica de átomos e moléculas (AI QUANTUM, 2020; JONES et al., 2022). Continua sendo uma ferramenta valiosa para entender sistemas químicos e projetar novos materiais.

3.15 Teoria do Funcional de Densidade

A equação de Schrödinger possui solução exata apenas para o átomo de hidrogênio (SCHRÖDINGER, 1926a) e para o íon da molécula de hidrogênio H_2^+, com a ressalva de se considerar os núcleos fixos (BURRAU, 1927). Porém, quando o número de partículas dinâmicas é maior que dois, o problema de elétrons interagentes ainda é intratável de forma exata, como ocorre com os casos do sistema molecular de dois elétrons do átomo de Hélio (He) e da molécula de hidrogênio H_2, para os quais pode-se obter apenas soluções analíticas aproximadas. Portanto, o caso de muitos corpos interagentes ainda não possui uma solução exata (SILVA, 2013).

Vários métodos foram propostos para tratar esse problema, como os métodos Hartree-Fock, pós Hartree-Fock (*Coupled Cluster* e *Configuration Interaction*), a Teoria doFuncional de Densidade (DFT), entre outros.

A DFT é uma das técnicas mais utilizadas atualmente para tratar o problema de muitos elétrons interagentes em sistemas moleculares (SILVA, 2013). As primeiras ideias desta técnica surgiram por meio de Thomas e Fermi, os quais utilizaram os conceitos de mecânica estatística para simplificar o problema de muitos corpos com alguns postulados que partem do pressuposto de que os elétrons estão distribuídos uniformemente no espaço. Surgiu como uma alternativa aos tradicionais métodos *ab initio* e semi-empíricos no estudo das propriedades do estado fundamental dos sistemas moleculares.

A grande vantagem da DFT em relação aos métodos ab initio tradicionais (por exemplo, Hartree-Fock ou pós- Hartree-Fock) reside no ganho de velocidade computacional e espaço de memória (ALCÁCER, 2007; CRAMER, TRUHLAR, 2009). Construiu-se assim uma teoria atômica baseada na densidade eletrônica ρ(r), diferentemente da teoria proposta por Schrödinger em 1926, que utilizava a função de onda como objeto de descrição dos átomos (SCHRÖDINGER, 1926b). Como consequência, a integral de repulsão de Coulomb necessita ser calculada apenas para a densidade eletrônica, que é uma função tridimensional com N^3 , em que N é o número de funções de base. Por outro lado, os métodos ab initio lidam com funções que envolvem mais dimensões, com N^4 ou maior (ALCÁCER, 2007).

Portanto, a entidade básica da DFT é a densidade eletrônica ρ(r), que descreve a distribuição de cargas presentes em uma dada molécula. Os conceitos modernos desta teoria foram formulados por Khon e Sham em 1965 e são baseados em dois teoremas:

1. A função de onda do estado fundamental e, portanto, todas as propriedades desse estado são funcionais da densidade eletrônica, ρ(r). Assim, a densidade eletrônica de um sistema determinará o potencial externo v(r) e o número de elétrons N e, portanto, o Hamiltoniano do próprio sistema.
2. A energia do estado fundamental de um sistema multieletrônico sob um determinado potencial externo v(r) pode ser escrita como:

$$E_v(\rho(r) = \int v(r)\rho(r)dr + F(p) \quad \text{(Eq. 8)}$$

em que F é chamado de funcional universal de ρ, que é independente do potencial *v(r)*(ALCÁCER, 2007; JENSEN, 2007).

Logo, para um átomo arbitrário, a energia do estado fundamental depende somente da densidade eletrônica, que descreve a distribuição de carga em uma molécula, como mostrado na Equação 9:

$$E = K(\rho) - Z\int d^3r\frac{\rho(r)}{r} + \frac{1}{2}\int d^3r\int d^3r'{}'\frac{\rho(r)\rho(r')}{(r-r')} \qquad \text{(Eq. 9)}$$

sendo K[ρ] o funcional da densidade, o qual é responsável pela contribuição da energia cinética dos elétrons para a energia total. O segundo termo refere-se à parcela de energia devido à atração dos elétrons pelo núcleo, e o último termo corresponde à energia devido à repulsão elétron-elétron (SILVA, 2013). O modelo de Fermi foi baseado na divisão do espaço real em pequenas caixas cúbicas contendo elétrons, os quais não interagem uns com os outros em caixas diferentes e nem nas mesmas caixas.

Em 1962, Edward Teller mostrou que, devido à aproximação do funcional da energia cinética utilizado no modelo de Thomas-Fermi, não existiam ligações estáveis entre átomos, ou seja, a soma das energias dos átomos isolados é sempre menor que a energia da molécula (TELLER, 1962). Dirac também percebeu um outro problema: a ausência da energia de troca (exchange). Ele propôs então um termo adicional, apresentando um novo modelo, o modelo de Thomas-Fermi-Dirac. Porém, o problema relativo à forma do funcional da energia cinética ainda existia (SILVA, 2013).

O modelo de Thomas-Fermi-Dirac também sofreu uma correção, realizada por Weizsäcker em 1935, utilizando o gradiente da densidade eletrônica para descrever a energia cinética, na forma $\left(\frac{1}{8}\int d^3rV\frac{\nabla\rho(r)V^2}{\rho(r)}\right)$ (WEIZSÄCKER, 1935). Essa correção possibilitou um cálculo muito mais preciso da energia total do átomo de hidrogênio, chamando a atenção novamente para a teoria do funcional da densidade (SILVA, 2013).

A resolução exata da equação de Schrödinger (equação 3) apresenta um nível muito alto de complexidade. Assim, aproximações são necessárias para permitir seu uso em sistemas reais. Uma das aproximações mais importantes é a chamada aproximação de Born- Oppenheimer. Basicamente, esta desconsidera o movimento dos núcleos na molécula, já que a massa nuclear é várias vezes maior que a massa dos elétrons. Assim, a equação de Schrödinger é resolvida apenas para os elétrons, que são descritos por uma função de onda puramente eletrônica na presença de um potencial produzido pelos núcleos que assumem posições fixas no espaço (ALCÁCER, 2007; JENSEN, 2007).

Foi em 1964 que Walter Kohn e o seu aluno Pierre Hohenberg demostraram uma reformulação da mecânica quântica que não utilizava funções de onda e sim funcionais da densidade (KOHN, SHAM, 1965). Um funcional é algo mais genérico, e mapeia uma função em um número. De outra forma, um funcional é uma função cuja variável é outra função. Então, para conhecer qualquer propriedade de um átomo, de uma molécula ou de um sólido, era preciso saber qual é a sua densidade eletrônica. E, para se encontrar o estado fundamental do sistema, bastava apenas minimizar a energia total em função da densidade.

Este princípio é equivalente ao princípio variacional de Rayleigh-Ritz (SILVA, 2013). O primeiro funcional de troca e correlação foi nomeado como aproximação da densidade local (LDA), proposto por Konh-Shan (KOHN, SHAM, 1965), no qual a densidade não homogênea de elétrons é aproximada como se cada ponto do espaço fosse resultado de uma densidade homogênea (SZABÓ, 1996). Os subsequentes foram referidos como aproximação generalizada do gradiente (GGA) (THOMAS, 1927) e meta GGA (TAO et al., 2003). Posteriormente, ocorreu a combinação entre os funcionais de troca e de correlação, formando os chamados funcionais híbridos. Tais funcionais utilizam o termo de troca exato do método de HF com os funcionais de troca e correlação GGAs.

O B3LYP é atualmente um dos funcionais de DFT mais utilizados e citados na literatura (NAZARPARVAR, ZAHEDI, KLEIN, 2012; HUANG, LEE, 2012). Ele é um funcional híbrido, isto é, a combinação dos funcionais de troca e de correlação, que contém em sua formulação funcionais GGA, de troca e correlação e que inclui uma contribuição vinda do método de HF. Ele foi desenvolvido por Becke (indicado pela letra B) e possui um termo de correlação desenvolvido por Lee, Yang e Parr (sigla LYP), e ainda possui três parâmetros empíricos escolhidos para otimizar sua performance (indicado pelo número 3) (PEREIRA, 2008).

Um conjunto de bases é um conjunto de funções cuja finalidade é a criação de orbitais moleculares. Pode ser entendido como uma função primitiva que é utilizada para representar cada um dos orbitais na teoria de valência para o tratamento da molécula, ou seja, é disponibilizada uma função para cada átomo de hidrogênio, H, e de hélio, He (para simular o orbital 1s), cinco funções para cada átomo de lítio, Li, ou de neônio, Ne (para os orbitais 1s, 2s e três orbitais 2) e assim por diante (ATKINS *et al*., 2009).

Existem dois tipos de conjunto de base usados em cálculos de estrutura eletrônica: orbitais atômicos do tipo Slater (STOs) e orbitais atômicos do tipo Gauss (GTOs). Slater propôs as primeiras funções de base a serem utilizadas, as quais apresentavam semelhança com os orbitais atômicos do átomo de hidrogênio (ARRUDA, 2009). Essas funções são apropriadas para o cálculo de propriedades físicas de sistemas atômicos ou moleculares, mas, no entanto, não permitem uma resolução analítica e computacionalmente rápida das integrais de dois elétrons de mais de um centro ou, ainda, integrais de atração nuclear de três centros (ARRUDA, 2009). Elas são dadas pela Eq. 10 (equação de Slater):

$\chi_{\varsigma,n,l,m}(r,\theta,\varphi) = NY_{l,m}(\theta,\varphi)r^{n-1}e^{-\varsigma r}$ (Eq. 10)

em que N é uma constante de normalização, *Y l*, *m* são as funções harmônicas esféricas usuais e $\varsigma = \frac{Z-W}{n}$ é uma constante. O termo Z–W representa a carga nuclear efetiva, com W sendo uma constante de blindagem. Os expoentes ς são números positivos e determinam as características das funções (ARRUDA, 2009).

Foi Boys (BOYS, EGERTON, 1950) que apresentou as funções tipo Gaussiana (GTF), por meio das quais conseguiu-se a simplificação dos cálculos computacionais de integrais multicêntricas. Elas podem ser escritas em termos de coordenadas polares ou cartesianas, respectivamente, como:

$$\chi_{\varsigma,n,l,m}(r,\theta,\varphi) = NY_{l,m}(\theta,\varphi)r^{2(n-1)}e^{-\varsigma r^2}$$

(Eq. 11)

Ou

$$\chi_{\varsigma,l_x,l_y,l_z}(r,\theta,\varphi) = Nx_x^l y_y^l z_z^l e^{-\varsigma r^2}$$

(Eq. 12)

sendo que a soma de $L = l_x + l_y + l_z$ determina a simetria orbital, já que, quando L for 0,a Gaussiana Cartesiana é do tipo s; quando L for 1, esta é do tipo p; quando L for 2, a Gaussiana é do tipo d, e assim por diante (JENSEN, 2007).

Devido à eficiência computacional obtida por meio do uso de GTOs, eles são normalmente preferidos e amplamente utilizados como funções básicas nos cálculos de estrutura eletrônica (JENSEN, 2007).

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SEGUNDA PARTE: ARTIGOS

ARTIGO 1- Perspectives on the Role of Frontier Molecular Orbitals in the Study of Chemical Reactivity: An Updated Review

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Perspectives on the Role of Frontier Molecular Orbitals in the Study of Chemical Reactivity: An Updated Review

Abstract

Molecular orbitals are critical in the rationalization of several chemical reactions. Thus, the Frontier molecular orbital theory, proposed by Fukui's group, postulated the importance of the highest occupied molecular orbital (HOMO) and the unoccupied molecular orbital of lowest energy (LUMO) for chemical reactions. It should be kept in mind, however, that there are limitations of this theory and new perspectives about the chemical reactivity have recently been arisen based on composition and location of other frontier molecular orbitals. In this review, we have reported the development of the Frontier Effective-for-Reaction Molecular (FERMO) concept, which describes the breaking and formation of new chemical bonds and can be in turn provide important clues that modulate chemical reactivity of atoms and molecules.

Introduction

In 1916, the famous chemist Gilbert N. Lewis set some fundamentals for what is known about chemical bonding today (LEWIS, 1913, 1916). According to Lewis, with a brilliant intuition, the reactivity was due to availability of electrons, being that the difference of the properties presented by substances was directly correlated to the mobility of the electrons of their molecules.

On the other hand, quantum mechanics emerged shortly after Lewis's pioneering work and played a crucial role in this study (ALLINGER, 1976; ATKINS; FRIEDMAN, 1997; HOFFMANN; SHAIK; HIBERTY, 2003; JENSEN, 1382; SCHRÖDINGER, 1926). For a while, following Schrödinger's proposal in 1926, a precise physical interpretation for the wave function (Ψ) challenged the early enthusiasts of quantum mechanics. It was up to Max Born to show, a few months later, that the square of Ψ had a precisephysical meaning. According to Born, $|\Psi|^2$ for a position x, y, z expresses the probability of finding an electron in that space location. This region of probability generates, for example, theform of the atomic orbitals s, p, d and f (RAUK, 2001). Since the importance of electron pairs for the chemical reactivity of molecules had already been discussed previously by Lewis et al., the molecular orbitals rapidlyaroused great interest throughout the scientific community, because they could now be calculated by approximate quantum mechanics methods, presenting a more quantitative understanding. Therefore, for chemists in general, a great utility of atomic orbitals is related to the understanding of how atoms combine to form molecules (Da Silva, 2006).

The great scientific interest in the subject can be easily verified by the expressive number of publications that deals with the subject (Figure 1): a simple search in the ISI Web of Knowledge(Web of Science), using the term “molecular orbital” as keyword, returns 2,000-

2,500 papers by year from 2005 to 2010. Since 2011, even more papers were annually published (reaching about 3,500 in 2018), showing the increasing importance of this theme. In this respect, the importance of molecular orbitals for chemistry is undeniable. Understanding why reactions follow one path or another enables greater planning and control of chemical phenomena at a more fundamental level. In this way, molecular orbitals are important electronic parameters for description of the chemical reactivity of compounds, since chemical reactions are modulated by electrons.

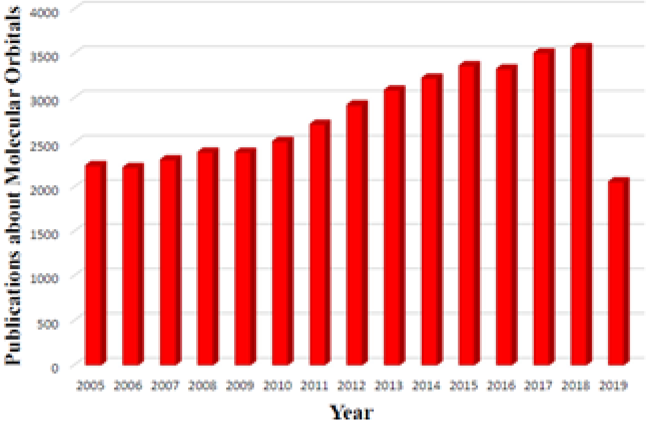


Figure 1. Number of papers retrieved with the keyword “molecular orbitals” in the ISI Web ofKnowledge database from 2005 to the middle of July 2019.

Understanding the processes involving breaking and formation of new chemical bonds is essential to the rationalization of reaction mechanisms and represents a challenge that still intrigues and generates many discussions. Furthermore, the knowledge about these processes also depends on understanding the nature of chemical bonds. It is important to keep in mind that, since the early work of Linus Pauling, the concept of chemical bonding has been changing substantially over the years (Pauling, 1931,1960). Thus, issues related to chemical bonding and molecular orbitals are always at the forefront of chemistry research.

When a concept is solid enough, predictions can be made and tested, which will inevitably lead to new discoveries. Molecular orbitals still pose a great challenge to chemists, holding some secrets that can, nowadays, contribute significantly to advancements across all frontiers of chemistry. Thus, attempting to understand chemical reactions, researchers turned their attention to the analysis of the orbital molecules (BRUICE, 2004; FUKUI *et al.*, 1954; FUKUI; YONEZAWA; SHINGU, 1952; HOFFMANN; WOODWARD, 1965c, a, b; LA PORTA, FELIPE A. *et al.*, 2010a; WOODWARD; HOFFMANN, 1965). So, in an update of a previous paper (PEREIRA *et al.*, 2016), we present in the present review some considerations about the contributions of the frontier molecular orbitals approach to the understanding of chemical reactivity.

Discussion

The Frontier Molecular Orbital Theory

The HOMO-LUMO (HOMO: Highest Occupied Molecular Orbital; LUMO: Lowest Unoccupied Molecular Orbital) approach for the interpretation of chemical reactivity came up with a Japanese research group headed by Kenichi Fukui, who was researching on the reactivity of aromatic compounds (FUKUI; YONEZAWA; SHINGU, 1952). The great difference between theirs and previous works from other researchers was the attention given to the molecular orbitals from Fukui and colleagues. Instead of interpreting only the energy or performing population analyzes, they analyzed the electron density over each atom participating in the frontier orbitals. Fukui and his collaborators realized that the HOMO electron density was very important for the reactivity of these compounds.

The HOMO electronic density was the strategy used by Fukui and his group to predict which the reaction site for electrophilic substitutions in aromatic hydrocarbons. So, soon the concept of frontier electrons became wider, leading to the Frontier Molecular Orbital Theory (FMO) (FUKUI *et al.*, 1954). With a series of intuitive postulates, they proposed rules for the interactions between frontier orbitals. Just as Lewis put the pair of electrons as a determinant of countless reactions, Fukui's group established that certain chemical reactions, for instance Lewis acids and bases, would be governed by the frontier orbitals. It was as if Lewis's pair of electrons occupied Fukui's frontier orbital. The two concepts were equally simple and powerful in the interpretation of chemical reactions. Since then, molecular orbitals have assumed a determining role in chemistry and the HOMO-LUMO approach has been applied in several reactions with great success (FUKUI, 1982; FUKUI et al., 1954).

But it was by solving some challenges such as predicting the stereochemistry of electrocyclic reactions that the molecular orbitals were confirmed as the great rulers of reactivity of several compounds. Two very talented chemists, each with their own experience, explained the intriguing behavior of pericyclic reactions. In 1965, Hoffmann and Woodward developed the theory of conservation of orbital symmetry to explain the relationship between the structure and the configuration of substrates and formation of the product under thermal and/or photochemical conditions, in which the reactions occur (BRUICE, 2004; HOFFMANN; WOODWARD, 1965c, a, b; WOODWARD; HOFFMANN, 1965).

In these works, the authors postulated that, for a system like the formation of 1,3-cyclohexadiene from 1,3,5-hexatriene, a disrotatory motion would be observed for thermal processes, as in Figure 2 (a), while a conrotatory motion would be observed for photochemical processes like Figure 2 (b). The mystery about the exclusivity of one or another type of movement, depending on the process involved, was intimately related to the HOMO symmetry. In this sense, the creation of a new chemical bond would involve the superposition of different phases of the frontier molecular orbitals. The conrotatory or disrotatory movement would be only a result of the orbitals seeking a constructive overlap, which, in other words, would be the overlapping of equal phases. Another important aspect about the contribution of the work of Hoffmann and Woodward, based on calculations using Hückel's Extended Theory, is that they have obtained extremely useful results for the understanding of fundamental aspects of the chemistry involved. Thus, the concept of conservation of orbitals symmetry is a determinant of many chemical reactions.

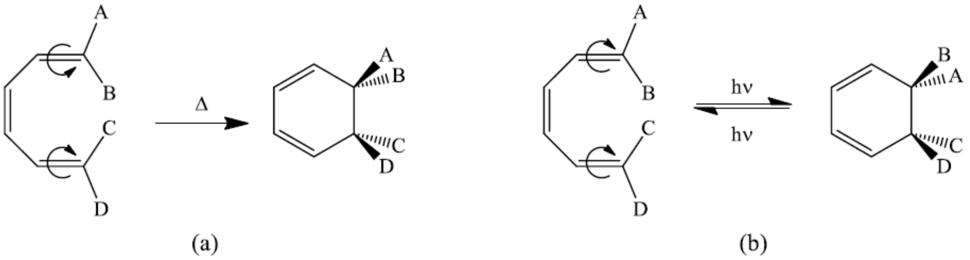


Figure 2. Thermal and photochemical conversion of hexatriene to cyclohexadiene. Disrotatory (a) and conrotatory (b) movement (adapted from reference (PEREIRA *et al.*, 2016).

Over the years, chemists have developed several processes in which molecular orbitals symmetry is responsible for controlling the reaction course (BERSKI et al., 2006; BIRNEY; HOUK, 1990; DEWAR, 1971; DOMINGO; ARNO; ANDRES, 1998; HARNETT et al., 2004; KLOPMAN, 1968; PEARSON, 1986; POLO et al., 2004; RHYMAN et al., 2011; ROQUE et al., 2002; SVERGUN et al., 2000). The recognition of the impact brought to science by the concept of molecular orbitals occurred in 1981, when the Nobel Prize in Chemistry was awarded to Kenichi Fukui and Roald Hoffmann. It could be said that, at that time, chemists were living the age of HOMO-LUMO, and molecular orbitals had already been accepted as a determinant of chemical reactions and sacred those who began to study the subject. However, despite the great success, the HOMO-LUMO approach was not unanimously accepted. Some wondered if only two orbitals would be responsible for the reactivity of molecules. Was it all dependent on HOMO and LUMO alone? Fukui exposed this concern in an article he wrote in commemoration of his Nobel Prize (FUKUI, 1982).

According to Fukui, the HOMO or LUMO orbitals could not be suitable for a given reaction, but, according to him, surely the next orbital or any orbital with energy very close to HOMO or LUMO could be used (FUKUI, 1982). As an example of his argument, Fukui cited the case of pyridine protonation. In pyridine, the HOMO is clearly an orbital of the π-system of pyridine ring (Figure 3). Since the proton binds to the nitrogen electron pair, the HOMO would not be related to this reaction in pyridine. The orbital involved in the reaction would be the third highest occupied orbital or HOMO-2, which in fact has the typical shape of the nitrogen non-bonding pair, as seen in Figure 3. As it can be seen, the HOMO-LUMO approach has certain limitations, thus leaving a gap for the emergence of new theories.

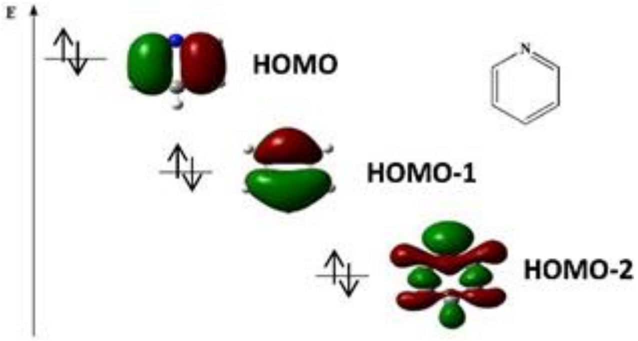


Figure 3. Shapes of the three highest occupied molecular orbitals for pyridine (adapted from reference (PEREIRA *et al.*, 2016).

The Concept of Localized Reactive Orbital

One of the most intriguing theories involving molecular orbitals was developed by Hiroshi Fujimoto, who worked with Fukui (FUJIMOTO, 1987; FUJIMOTO; MIZUTANI; IWASE, 1986; FUJIMOTO; SATOH, 1994; ROQUE et al., 2002). The main argument of Fujimoto and colleagues was that molecular orbitals were too delocalized and thus it was difficult to deal with certain reactions that were entirely localized. Their strategy was to recombine some molecular orbitals chosen according to certain criteria and locate their maximum at the reaction site. The procedure was called Localized Reactive Orbital (LRO) approach (FUJIMOTO, 1987; FUJIMOTO; MIZUTANI; IWASE, 1986; FUJIMOTO; SATOH, 1994).

The Concept of Reactive Hybrid Orbital

The same kind of argument used by Fujimoto, according to which localized orbitals would be better to describe the reactivity of molecules, was employed by Hirao and Ohwada to formulate the concept of Reactive Hybrid Orbital (RHO) (HIRAO; OHWADA, 2003, 2005; NAKAMURA, SATOSHI; HIRAO; OHWADA, 2004; OHWADA; HIRAO; OGAWA, 2004).

So, according to these authors, when an electron-donor orbital ϕoc is represented by a linear combination of canonical occupied molecular orbitals (Equation 1):

$$\phi_{oc} = \left(\sum_{i}^{oc} d_i \psi_i\right) / \left(\sum_{i}^{oc} d_i^2\right)^{\frac{1}{2}} \qquad (1)$$

the energy level λoc can be identified according to Equation 2:

$$\lambda_{oc} = \left(\sum_{i}^{oc} d_i^2 \varepsilon_i\right) / \left(\sum_{i}^{oc} d_i^2\right) \qquad (2)$$

where ε_i is the energy level of the canonical molecular orbital ψ_i obtained by solving a Hartree-Fock-Roothaan equation. The orbital ϕ_{oc} is represented by a linear combination of atomic orbitals like (Equation 3):

$$\phi_{oc} = \sum_{\mu} C_\mu \chi_\mu \qquad (3)$$

By extracting from Equation 3 only the terms containing the atomic orbitals ϕ'_{oc} on the atom of the reaction center (named A), the Equation 4 can be defined:

$$\phi'_{oc} = \sum_{\mu \in A} C_\mu \chi_\mu \qquad (4)$$

Then, similar functions can be defined for the frontier electron density f_{oc} and for an index ρ_{oc}, respectively according to Equations 5 and 6:

$$f_{oc} = \langle \phi_{oc} / \phi'_{oc} \rangle \qquad (5)$$

$$\rho_{oc} = -f_{oc} / \lambda_{oc} \qquad (6)$$

The value $2f_{oc}$ corresponds to the electrons in the orbital ϕ_{oc} for the atom A. The formula for ρoc is similar to the superdelocalizability based on Hückel approximation. d_i values are obtained from Equation 1, which gives the maximum value of ρ_{oc}, by minimizing $1/\rho_{oc}$ numerically according to the Davidon-Fletcher-Powell method. The ϕ_{oc} orbital represented in Equation 1 with the d_i value optimization is specifically called RHO (HIRAO; OHWADA, 2003).

The Triadic Analysis

Vianello and colleagues introduced the *triadic* formula (VIANELLO; MAKSIĆ, 2006), which also uses the concepts of frontier molecular orbitals, with the difference that such calculations are based on an equation with three terms like the Equation 7 for the interpretation of acidities:

$$PA(A^-)_\alpha = -IE(A^-)_n^{Koop} + E(ei)_{rex}^{(n)} + (BAE)_\alpha + 313.6\ kcal/mol \quad (7)$$

Equation 7 describes the protonation of the anionic conjugated base $A-$, in which $PA(A^-)^\alpha$is the proton affinity of $A-$ at the site α and $IE(A^-)_{Koop}^n$ determines the nth Koopman's ionization energy of the anion $A-$ calculated in the approximate electronic density. Since ionization is not a sudden event, a reorganization of the nuclei-electrons system occurs, denoted by the relaxation energy term $E(ei)_{rex}^{(n)}$ given by Equation 8:

$$E(ei)_{rex}^{(n)} = IE(A^-)_n^{Koop} - IE(A^-)_1^{ad} \quad (8)$$

in which $-IE(A^-)_1^{ad}$is the first adiabatic ionization energy. The term $(BAE)_\alpha$ is the effect of the bond association energy between hydrogen and a cation radical. The electron affinity of theproton is 313.6 kcal/mol. Thus, the proposal from Vianello et al. has a term related to the ionization energy, another one related to the relaxation energy and a third term related to association energy between the first ones. This methodology is currently widely used in the global description of deprotonation processes (VIANELLO; MAKSIĆ, 2006; VIANELLO; PERAN; MAKSIĆ, 2006, 2007).

The Frontier Effective-for-Reaction Molecular Orbital

In line with that, the limitations of the arguments of HOMO-LUMO approach and the new approaches proposed in the literature to understand chemical reactivity, it became necessary to extend the role of molecular orbitals in chemistry. The FERMO (Frontier Effective-for-Reaction Molecular Orbital) concept emerged as a tool to explore the role of molecular orbitals and chemical reactivity as well as breaking and formation of chemical bonds (DA SILVA; RAMALHO; et al., 2006a, b; DA SILVA; SANTOS; et al., 2006). As noted by Fukui, the HOMO and LUMO orbitals could not be suitable for a given reaction, but certainly any close orbital with energy very close to those for HOMO or LUMO. The FERMO concept was proposed by Da Silva and Ramalho (DA SILVA; RAMALHO; et al., 2006a, b; DA SILVA; SANTOS; et al., 2006) and its approach arose from composition and localization criteria, along with some chemical intuition, to correctly determine the frontier molecular orbital that regulates chemical reactions. This theoretical approach could be understood as a complement to the HOMO-LUMO approach, so the HOMO will only be the orbital that rules a reaction if it fulfills the requisite to be the FERMO.

This concept has attracted attention and has been successfully applied in the description of chemical processes as acid-base behavior, in organic and inorganic complexes, in pericyclic reactions and in the study of biological systems (Figure 4) (A. LA PORTA et al., 2012; DA COSTA; TRSIC, 2010; DA SILVA; RAMALHO; et al., 2006a, b; DA SILVA; SANTOS; et al., 2006; DE ALMEIDA et al., 2013; LA PORTA, FELIPE A. et al., 2010a, 2011; PORTA, FELIPE LA; RAMALHO; PEREIRA, 2009; SOLEYMANI, 2018; SOLEYMANI; DASHTI KHAVIDAKI, 2017; T. SANTIAGO et al., 2010). In this sense, this review will focus now in a quantitative and detailed description of the FERMO in the understanding of chemical reactivity. The following discussion is divided into five subsections. In the first one, it is described the acid-base behavior for some important classes of compounds commonly used in organic chemistry. In the second subsection, the results obtained for the understanding of some organic and inorganic compounds are presented. The third subsection shows a detailed investigation on the reactivity and selectivity of pericyclic reactions. The fourth subsection is related to the case of biological systems. Finally, the main conclusions are summarized in the fifth subsection.

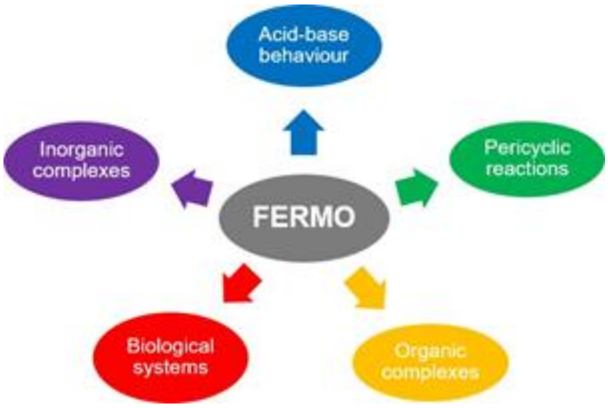


Figure 4. Some applications of the FERMO concept studied (adapted from reference (PEREIRA *et al.*, 2016).

Despite the major advances in the understanding of the role of molecular orbitals in the study of chemical reactivity, it is not easy yet to find didactic, well-founded and critical papers based on the perspective of FERMO in scientific literature. So, we took it as motivation for preparing this review, which aims to present the basic ideas of this concept as well as some of its applications in different areas of chemistry. We hope that this study will be useful to the general public, providing the readers (particularly students and researchers) interested in understanding this model.

Acid-base Behavior

Proton transfer is one of the most important processes of changing organic molecules. In this sense, the acidity of organic compounds, measured in several solvents, is fundamental for the study of reaction mechanisms in organic chemistry (LI et al., 2006). In this context, Da Silva and Ramalho have shown in their works that the molecular orbitals responsible for acid-base reactions in phenols and alcohols, in many cases, may not be rationalized in the light of the HOMO-LUMO approach (DA SILVA; RAMALHO; et al., 2006a, b). In these same works, it was observed that the molecular orbital that best described the acid-base behavior in the protonation reaction of the anionic conjugated bases for these compounds was not the HOMO (Figure 5), but rather the pxpy orbital, which was the FERMO for this reaction in each molecule, as shown in Figure 6. In this sense, it is observed that the FERMO concept take into account each shape as well as atomic composition of molecular orbitals to determine which orbitals can describe a chemical reaction.

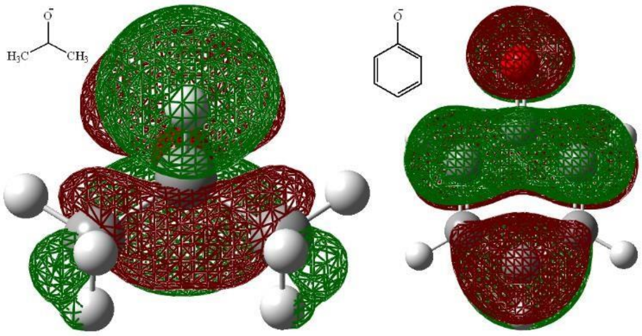


Figure 5. HOMO orbitals for the anions isopropoxide (left) and phenoxide (right) (adaptedfrom reference (DA SILVA; RAMALHO; *et al.*, 2006a).

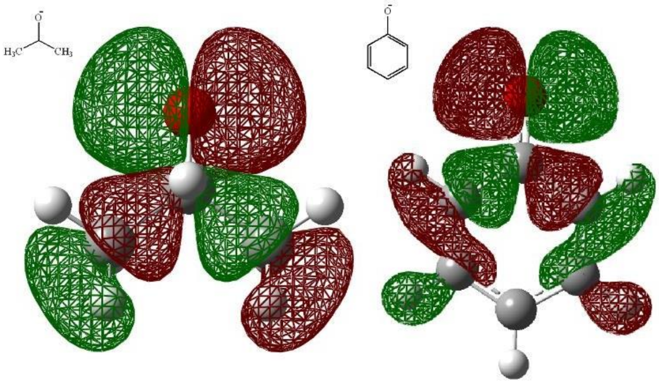


Figure 6: $p_x p_y$ orbitals for the anions isopropoxide (left) and phenoxide (right) (adapted from reference (DA SILVA; RAMALHO; *etal*., 2006a).

The orbitals of Figures 5 and 6 indicate that the HOMO-LUMO orbitals are not always responsible for all chemical reactions, as previously quoted by Fukui (FUKUI; YONEZAWA; SHINGU, 1952). Another important consideration for employing the FERMO concept is that both Hartree-Fock (HF) or Kohn-Sham (KS) orbitals lead to the same conclusions about chemical reactivity. This brings us back to the discussion about the validity of the interpretation of KS orbitals. In Figures 7 and 8, there are two representations of the HF and KS molecular orbitals for the p-cyanophenoxide and p-methylphenoxide anions (RAMALHO; PEREIRA, 2009). Moreover: based on these results, we can observe that both calculation methodologies used (MP2 and DFT) point to the same molecular orbital as the FERMO in the protonation reaction of these anions (HOMO-2 and HOMO-1 with MP2 and DFT, respectively). Thus, this is a very intuitive concept, presenting the same molecular orbital shape for the same reactive site or class of compounds.

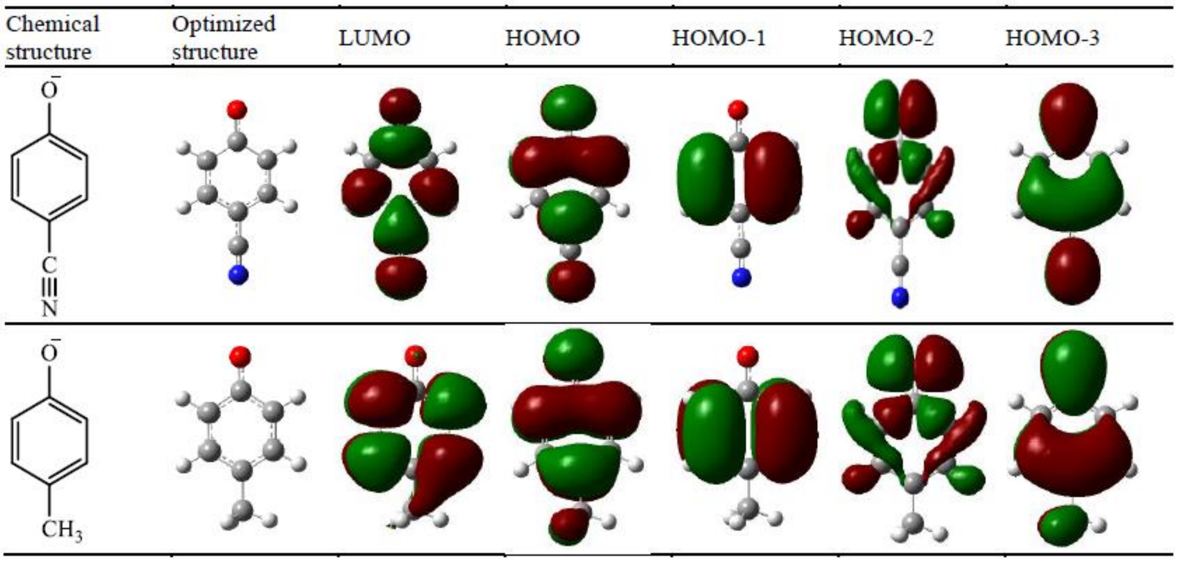


Figure 7. Representation of molecular orbitals of the anions p-cyanophenoxide and p-methylphenoxide calculated at MP2 level (adapted from reference (RAMALHO; PEREIRA, 2009).

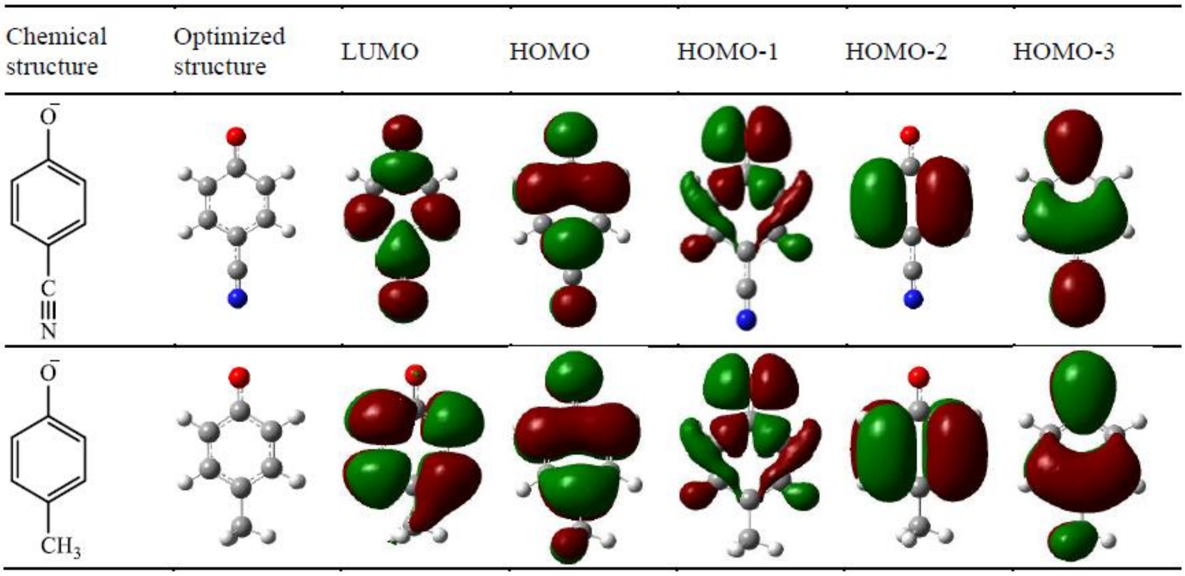


Figure 8. Representation of molecular orbitals of the anions *p*-cyanophenoxide and *p*-methylphenoxide calculated at DFT level (adapted from reference (RAMALHO; PEREIRA, 2009).

It is important to keep in mind that, in spite of the physical and chemical meanings of some virtual orbitals being very dependent on the calculation method employed, the variation in the HOMO-LUMO or FERMO-LUMO energy barriers can be used as a reactivity index. For example, following Pearson's principle, it is well-known that soft molecules will have lower energy values for the HOMO-LUMO gap when compared to hard sites. In this way, the HOMO-LUMO energy can be used.

Thus, once again looking at the shape of molecular orbitals, based on the composition and location criteria, the HOMO problem can be better understood.

The FERMO concept was also successfully applied in describing the acid-base behavior for a series of amines, being pointed out the HOMO as the FERMO for aromatic and aliphatic amines but not for heterocyclic amines, whose FERMO corresponded to the HOMO-2 (Figure 9) (LA PORTA, FELIPE A. et al., 2010b). It is known that amines have great importance and play an essential role in organic chemistry, and its basicity is directly related to the availability of the nitrogen electron pairs. In this context, molecular orbitals and their properties, such as energy and symmetry, are very important to better understand their reactivity and represent a fundamental step in the rational planning of some important synthesis routes.

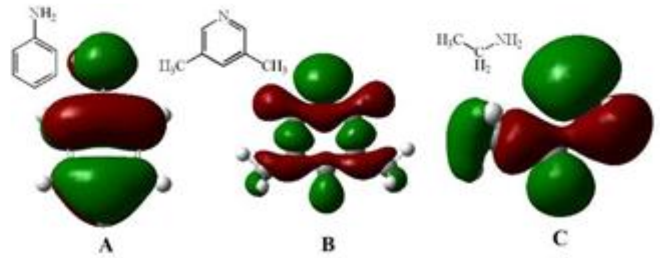


Figure 9. FERMO shapes for aromatic (A: aniline), heterocyclic (B: 3,5-dimethylpyridine) andaliphatic (C: ethylamine) amines (adapted from reference (LA PORTA, FELIPE A. *et al.*, 2010a).

Another important contribution of this work was the use of Chemometrics which, through an exploratory analysis using PCA and regression analysis using PLS, along with the FERMO approach, allowed a more detailed analysis of data. So, in this quantitative description based on chemometric methods and *ab initio* calculations, it was possible to correlate the energies of frontier orbitals with pK_b values for the compounds classified into aliphatic, aromatic and heterocyclic amines (Figure 10) (LA PORTA, FELIPE A. *et al.*, 2010a). For this study, it was verified that the energy of the FERMO shows a better correlation with basicity and acidity constants when compared to the HOMO energy. In addition, this work showed that the B3LYP functional produces good results for the description of the acid-base behavior, when the FERMO concept is used in the study of organic compounds.

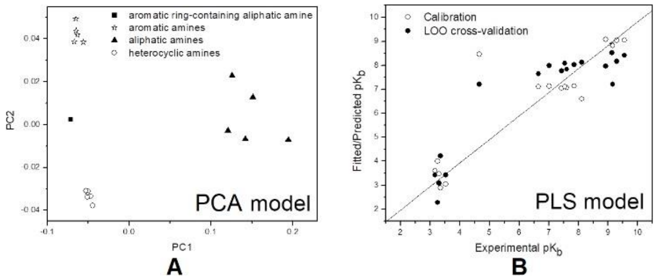


Figure 10. PCA (A) and PLS (B) models employed in the study of aromatic, heterocyclic and aliphatic amines (adapted from reference (LA PORTA, FELIPE A. *et al.*, 2010a).

In this same line of thought, the FERMO approach was applied with great success in describing the acid-base behavior for a series of phosphines (T. SANTIAGO *et al.*, 2010). The HOMO-*n* and LUMO+*n* (*n* = 0-4) energies were obtained from MP2 calculations in the form of an $a \times b$ matrix with *a* lines for phosphines and *b* columns for the energy of frontier molecular orbitals. It is remarkable that these results can be used to investigate the effect of the solvent on acid-base processes, using parameters from theoretical calculations of orbital energies. By analyzing more deeply the location and composition of the molecular orbitals of phosphines, it can be observed that the FERMO has great contribution of the phosphorus atom (above 54%; see Table 1). Thus, this orbital, shown in Figure 11 for the compound trimethylphosphine, describes better the acid-base behavior.

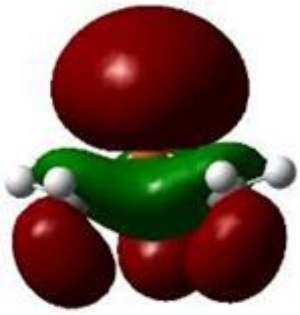
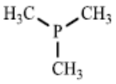
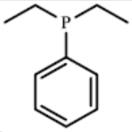
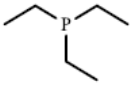
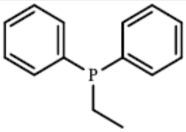
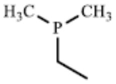
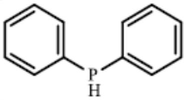
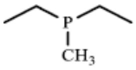
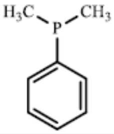
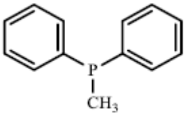


Figure 11. The FERMO shape of trimethylphosphine (adapted from reference (T. SANTIAGO *et al.*, 2010)

Table 1. Percentual contribution of the phosphorus atom for the FERMO and its orbital energyin studied phosphines through MP2/6-311G (d, p) in solution (adapted from reference (T. SANTIAGO *et al.*, 2010).

Entry	Compounds	Contribution (%)	FERMO (Hartree)	Entry	Compounds	Contribution (%)	FERMO (Hartree)
1		81.25	-0.33033	6		71.68	-0.29692
2		80.87	-0.32209	7		67.90	-0.29729
3		81.62	-0.32574	8		53.90	-0.31453
4		81.17	-0.32392	9		81.38	-0.33617
5		64.96	-0.30515	-	-	-	-

In these works, the FERMO argument was used in a qualitative manner. However, in a very recent paper (BRAGA, LETÍCIA SANTOS *et al.*, 2019), Braga and colleagues investigated, in a quantitative way, which molecular orbital would be better for the description of acidity in amines, carboxylic acids, alcohols and phosphines. For so, they developed a more quantitative methodology for the characterization of FERMO orbitals in chemical reactions based on projection operators. A projection operator could, in principle, be understood as the projection of a "shadow" of a selected molecular orbital in the subspace of an arbitrary set of atomic orbitals (AZEVEDO, 2013). This parameter is precisely a quantitative characterization of the shapes of molecular orbitals given in a set of atomic orbitals and, consequently, a set of atoms.

In this work, 30 different organic compounds were selected for studying their chemical reactivity, considering their protonation reactions to the corresponding cathionic conjugated acids. They were grouped in anilines, pyridines, aliphatic amines, carboxylic acids, alcohols and phosphines, as shown in Figure 12.

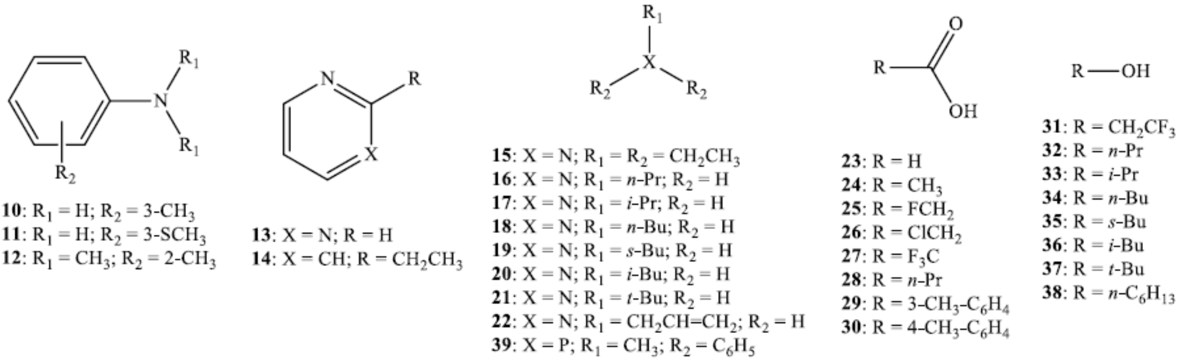


Figure 12. Structures of the organic compounds selected for the study from Braga and colleagues (adapted from reference (BRAGA, LETÍCIA SANTOS *et al.*, 2019).

Employing the FERMO energies instead of those for their HOMO orbitals, a correlation with a R^2 value equal to 0.94 was obtained. This result indicates that the energy of the FERMO is proportional the proton affinity and, consequently, the basicity of the neutral forms of amines, carboxylic acids, alcohols and phosphines in the gas phase, as shown in Figure 13. Based on the localization degree of each molecular orbital, it was possible to infer that the orbital which governs the protonation reaction corresponded to that pointed out by the new quantitative algorithm proposed by the authors as the FERMO, showing again that the molecular orbital composition is also a critical parameter to investigate the appropriate orbital (BRAGA, LETÍCIA SANTOS et al., 2019). So, both shapes and atomic composition of molecular orbitals were essential parameters for the determination and analysis of the FERMO.

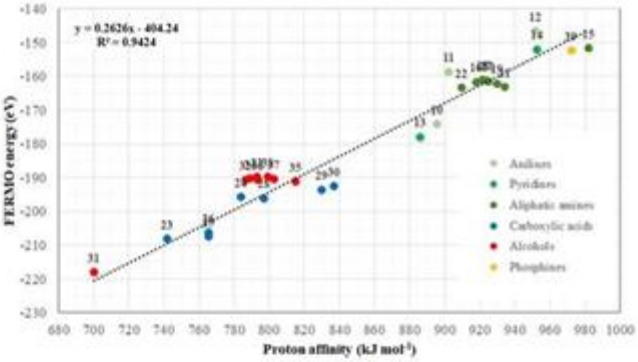


Figure 13. PA values as well as FERMO energies for the selected compounds. The dotted linecorresponds to the linear fit (adapted from reference (BRAGA, LETÍCIA SANTOS *et al.*, 2019).

Organic and Inorganic Complexes

The FERMO concept and Pearson's principle of hardness and softness were also successfully employed on four ambidentate ligands (that can bind to metals in two distinct ways). In this work, Da Silva and Ramalho (DA SILVA et al., 2006), following Pearson's principle which states that soft molecules have lower energy values for the HOMO- LUMO barrier when compared to hard sites, reported that, in the light of the FERMO approach, it can be observed that a soft reaction site in a molecule will have a lower FERMO-LUMO energy barrier than a harder. Clearly, the HOMO-LUMO energy barrier cannot describe the hardness difference between these two binding sites on the same molecule. Thus, a molecule can have as many FERMO orbitals as there are reaction sites, which, in this case, could be the HOMO or any other frontier molecular orbital.

For this study, the authors used as ambidentate ligands the anions SCN^-, NO_2^- and $CH_3COCH_2^-$ and the neutral molecule dimethylsulfoxide (DMSO). These ligands were chosen due to the great amount of theoretical and experimental work reported in the literature. Thus, based on the location as well as composition of molecular orbitals, it was possible to find the shape of the FERMO for these ligands (Figures 14 and 15).

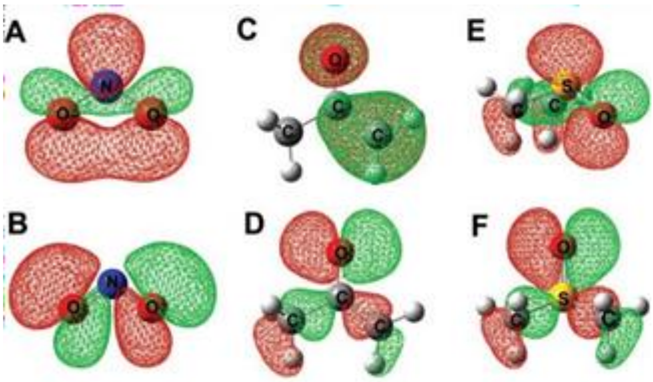


Figure 14. The FERMO shapes for NO_2^-, $CH_3COCH_2^-$ and DMSO. NO_2^- nitrogen-FERMO (A)and oxygen-FERMO (B); $CH_3COCH_2^-$ carbon-FERMO (C) and oxygen-FERMO (D); DMSO sulfur-FERMO (E) and oxygen-FERMO (F) (adapted from reference (DA SILVA *et al*., 2006).

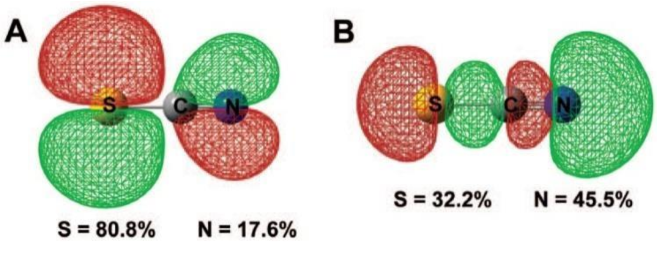


Figure 15. FERMO orbitals for the anion SCN^- at HF level. Sulfur-FERMO (A) and nitrogen- FERMO (B) (adapted from reference (DA SILVA *et al.*, 2006).

The results obtained through the FERMO concept also explained the bond formation angle, because a proper orbital orientation is required for the formation of a new bond. All results of this work are in agree with experimental X-ray results.

Another interesting study involves the application of the FERMO concept to the description of Pearson's principle of hardness and softness for four tridentate ligands (once they can bind metals in three different ways). The shapes of the frontier orbitals that govern reactions of these ligands are shown in Figure 16 (A. LA PORTA *et al.*, 2012).

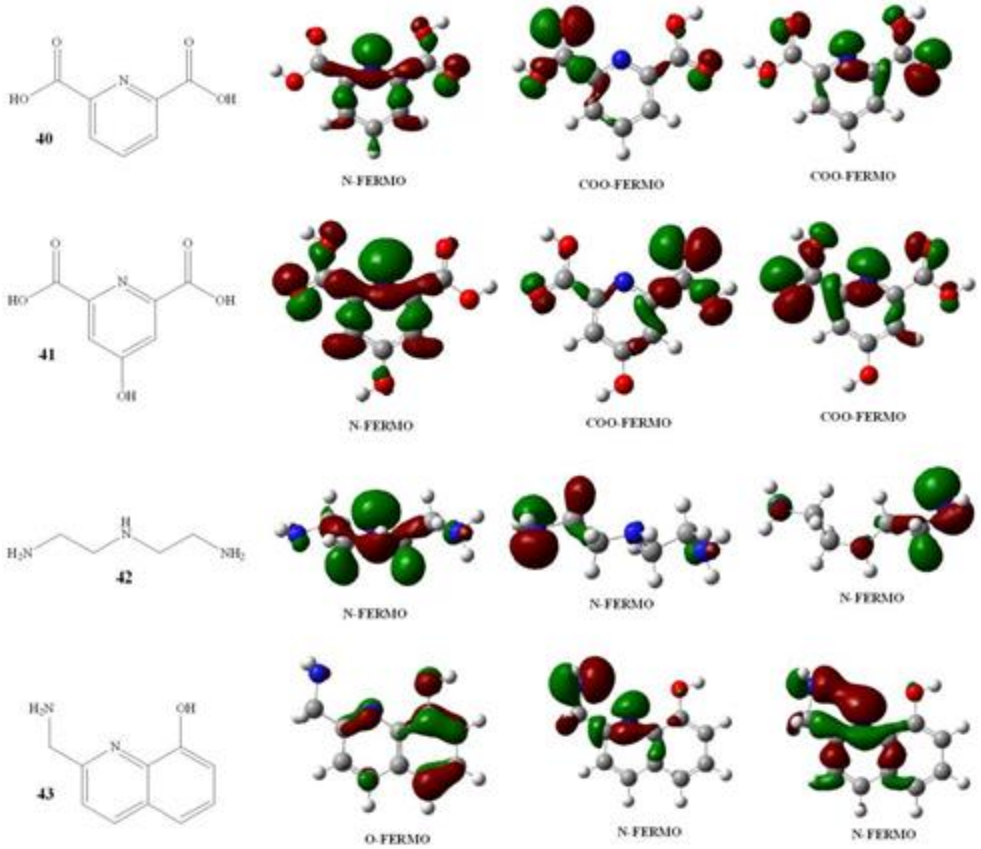


Figure 16. FERMO shapes for the studied tridentate ligands (adapted from reference (A. LA PORTA *et al.*, 2012).

The complexation of metal ions with 2,6-pyridinedicarboxylic acid (PDC), corresponding to compound 40 in Figure 16, has been extensively studied (CHATTERJEE et al., 1998; GONZALEZ-BARÓ et al., 2005; LAINÉ; GOURDON; LAUNAY, 1995; LIMA; MALTA; ALVES, 2005; WANG et al., 2004), since PDC is a very versatile chelating agent, which acts as a bidentate, tridentate or bridged-bond ligand with different metal ions (HSEU et al., 1991; LA PORTA, FELIPE A. et al., 2014). In addition, PDC has also other features such as low toxicity and a biologically diversified activity, present in many natural products, such as oxidative degradation products of vitamins, coenzymes and alkaloids (CRANS et al., 2000; KHAN et al., 2009). In this way, we performed chemical reactivity studies between iron(III) ions and the ligand PDC in the light of the FERMO concept.

The theoretical results indicated that the chemical bond between oxygen and iron atoms in the Fe-PDC complex is predominantly electrostatic, and a small variation along the C-N-N-C dihedral is favored (Figure 17) (LA PORTA, FELIPE A. et al., 2014). The use of iron complexes in catalysis has been considered promising due to stabilization of iron in a wider pH range compared to the free ion in solution. Another promising characteristic is that most chelating agents can be easily degraded by microorganisms. This finding makes this organometallic complex an interesting material for catalytic applications.

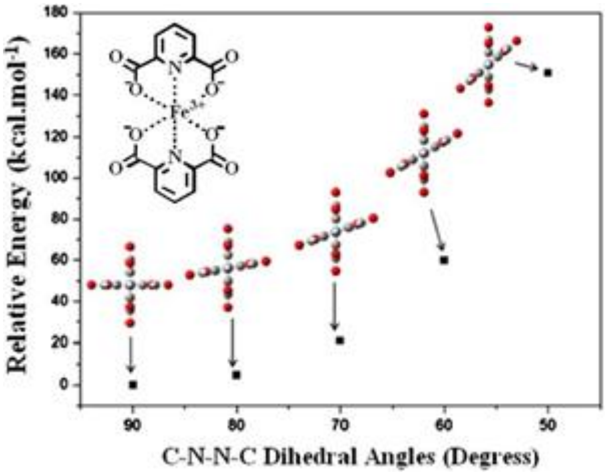


Figure 17. Potential energy surface for the C-N-N-C dihedral angles of the Fe-PDC complex (structures visualized along the N-Fe-N bond) (adapted from reference (LA PORTA, FELIPE A. *et al.*, 2014).

Most of the complexes between Fe^{3+} and tridentate ligands are also octahedral, and the complex with d^9 configuration can generate Jahn-Teller distortion. This observation is in very good agreement with experimental studies (DANIELE *et al.*, 1997).

Molecular modeling of transition metal complexes is complicated because of the partially filled d orbitals of metal ions which are responsible for both structures and multiplicity of coordination compounds with a wide variety of coordination numbers and possible geometries. In this case, the coordination geometry of a coordination compound always presents a relation between size and electronic structure of the metal ion, and type, size, geometry and rigidity of coordinated ligands. Thus, the structure of a coordination compound is strongly influenced by the linker structure (COMBA; HAMBLEY; MARTIN, 2008; NAKAMURA, EIICHI; YAMAGO, 2002).

In a recent study on methane dehydrogenation reactions with niobium ions (Nb^+ and Nb^{2+}) (DE ALMEIDA *et al.*, 2013), the FERMO concept was used to evaluate the process of charge transfer in the reaction mechanisms involved. In this work, it was possible to observe that the FERMO of Nb^{2+} ion has a higher contribution of C and Nb atoms (Figure 18), besides having lower energy than the FERMO of Nb^+ ion. This can be evidenced by a factor that corresponds to the variation between the energy values of FERMO for molecular precursor (MP) and transition state (TS1) structures in each of the cases, due to Equation 9 below:

$$\Delta E_{FERMO} = |E_{FERMO} - E_{FERMO}(TS1)| \quad \text{(Equation 9)}$$

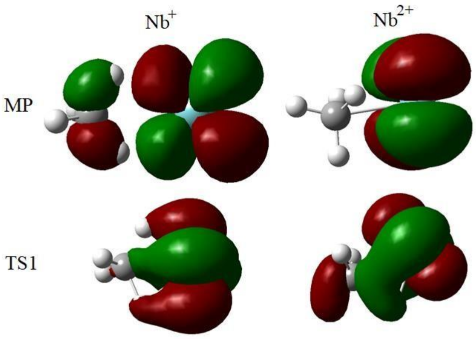


Figure 18. FERMO orbitals for molecular precursors (MP) and transition state (TS1) structures of the studied methane dehydrogenation reactions by niobium ions (adapted from reference (DEALMEIDA *et al.*, 2013).

The obtained values were 0.03427 and 0.00424 a.u. (atomic units) for Nb^+ and Nb^{2+}, respectively. These values showed a good correlation with Gibbs free energy values. Finally, it is worth to mention that these results of molecular orbital analysis are in agreement with other analyzes also carried out during the study involving structural and energetic parts and dehydrogenation mechanisms (DE ALMEIDA et al., 2013).

Niobium compounds were again investigated in a related work (ALMEIDA et al., 2016), in which Almeida and collaborators reported the use of the HOMO-LUMO and FERMO-LUMO energy differences to provide information about the methane C-H bond activation by niobium oxides (NbO, NbO+, NbO2+, NbO2, NbO2+ and NbO22+). The calculations for HOMO, LUMO and FERMO orbitals were performed for all niobium oxides. The localized FERMO for the methane C-H bond activation by niobium-oxo as well as for the niobium ions (DE ALMEIDA et al., 2013) were quite similar and showed besides a major contribution of niobium d orbitals and a small participation of oxygen s orbitals.

The energy gap between HOMO and LUMO orbitals ($E_{HOMO-LUMO}$) show a rather poor linear correlation with $E_{bonding}$ and E_{act} energies for the hydrogen abstraction from methane by niobium oxides (Figure 19, left side). $E_{bonding}$ and E_{act} are respectively the energy differences between isolated structures of niobium oxides and methane and their adduct before activation (bonding energy) and between transition states and reactant adducts (activation energy). These results can be explained by the fact that in several cases, the HOMO-LUMO approach fails to rationalize the reactivity of the chemical systems. However, the results show that the $E_{FERMO\text{-}LUMO}$ values have a good and strong correlation with $E_{bonding}$ and E_{act} (Figure 19, right side) (ALMEIDA et al., 2016).

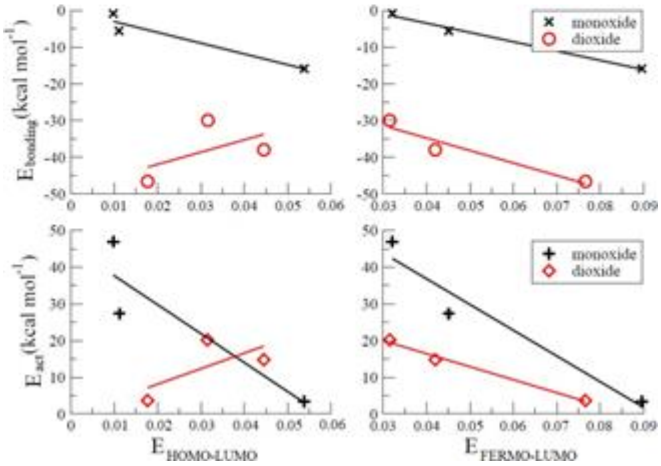


Figure 19. Correlation of the energy differences $E_{HOMO\text{-}LUMO}$ and $E_{FERMO\text{-}LUMO}$ with the $E_{bonding}$ and E_{act} values of the hydrogen abstraction from methane by niobium oxides (adapted from reference (ALMEIDA *et al.*, 2016).

There is an increase in $E_{FERMO\text{-}LUMO}$ compared to $E_{HOMO\text{-}LUMO}$, which is followed by a more favorable initial electrostatic interaction between methane and charged niobium oxides, as well as a decrease in E_{act} values. 0.08964 and 0.07661 atomic units are the highest $E_{FERMO\text{-}LUMO}$ values, calculated respectively for doubly charged monoxide and dioxide, for which the best kinetic and thermodynamic parameters were computed in the mentioned work. Methane is known to show a high $E_{HOMO\text{-}LUMO}$, a fact that has been used to explain its high chemical inertia (CRABTREE, 1995).

According to the hardness and softness acid base principles (HSAB), the inert methane is a hard acid (high $E_{HOMO\text{-}LUMO}$ and $E_{FERMO\text{-}LUMO}$) and therefore should only react to hard species (those with high $E_{HOMO\text{-}LUMO}$ or $E_{FERMO\text{-}LUMO}$). These characteristics are therefore in complete agreement with the results obtained for niobium oxides (ALMEIDA *et al.*, 2016).

Therefore, the orbital FERMO analyses showed that the reactive molecular orbital is energetically more stable in NbO^{2+} and NbO_2^{2+}, leading to the highest $E_{FERMO\text{-}LUMO}$ gaps. This feature is in agreement with the HSAB principles since, in these cases, NbO^{2+} and NbO_2^{2+} can be considered as hard species, like methane (ALMEIDA *et al.*, 2016).

Pericyclic Reactions

Another subject that is worth mentioning is the study of pericyclic reactions, which can be defined as a concerted reorganization of chemical bonds, through a cyclic arrangement of continuously interconnected atoms. In this process, the reaction occurs through a conjugate transition state with usually six atoms in the cyclic arrangement, but it may contain another number of atoms ("(BRUICE, 2004). The main kinds of pericyclic reactions are: a) electrocyclic; b) cycloaddition; c) sigmatropic rearrangement; d) queletropic; and e) "ene" reactions.

Cycloaddition reactions can be particularly considered as one of the most important and of great interest in synthetic organic chemistry. In a cycloaddition reaction, two different molecules, both containing π bonds, form a cyclic molecule by rearrangement of π electrons, in addition to creating two new σ bonds. This interaction between two different π systems is usually intermolecular. The cycloaddition reactions are classified according to the number of π electrons interacting in the reaction, taking into account only the π electrons participating in the electronic rearrangement (AURELL *et al.*, 2004; DOMINGO; ARNO; ANDRES, 1998; ESS; HOUK, 2008; GOTHELF; JØRGENSEN, 1998; JHAUMEER-LAULLOO, [S.d.]; LA PORTA, FELIPE A. *et al.*, 2011; NAKAMURA, EIICHI; YAMAGO, 2002; POLO *et al.*, 2004).

1,3-dipolar cycloaddition reactions are processed by a concerted [3+2] mechanism (AURELL et al., 2004; LA PORTA, FELIPE A. et al., 2011). Their importance is related to the ease of formation of five-membered heterocyclic compounds. Through the molecular orbital energies for each compound, we can also calculate some global properties, which gives us an idea about their reactivities. In general, the energy difference between reactants and products is not very high in 1,3-dipolar cycloaddition reactions, and their activation energies are not usually very high. This allows these reactions to proceed at room temperature. Thus, the HOMO-LUMO approach correctly describes pericyclic reactions.

In a paper from La Porta et al. (LA PORTA, FELIPE A. et al., 2011), the FERMO concept was successfully employed to the study of four different 1,3-dipolar cycloaddition reactions (named A-D) between methyl acrylate or propiolate and substituted nitrilium or azomethine ylides or nitrilimine compounds, proceeding through the corresponding TS-4-I-type or TS-5-II-type transition states (Figure 20). Initially, calculations were made to obtain the minimum energy of the A-D studied systems for fully relaxed molecules in gas phase. The H, CH_3, CF_3, and Ph substituents have been selected in order to address small and huge groups, as well as electron-withdrawing and donating effects in reactants.

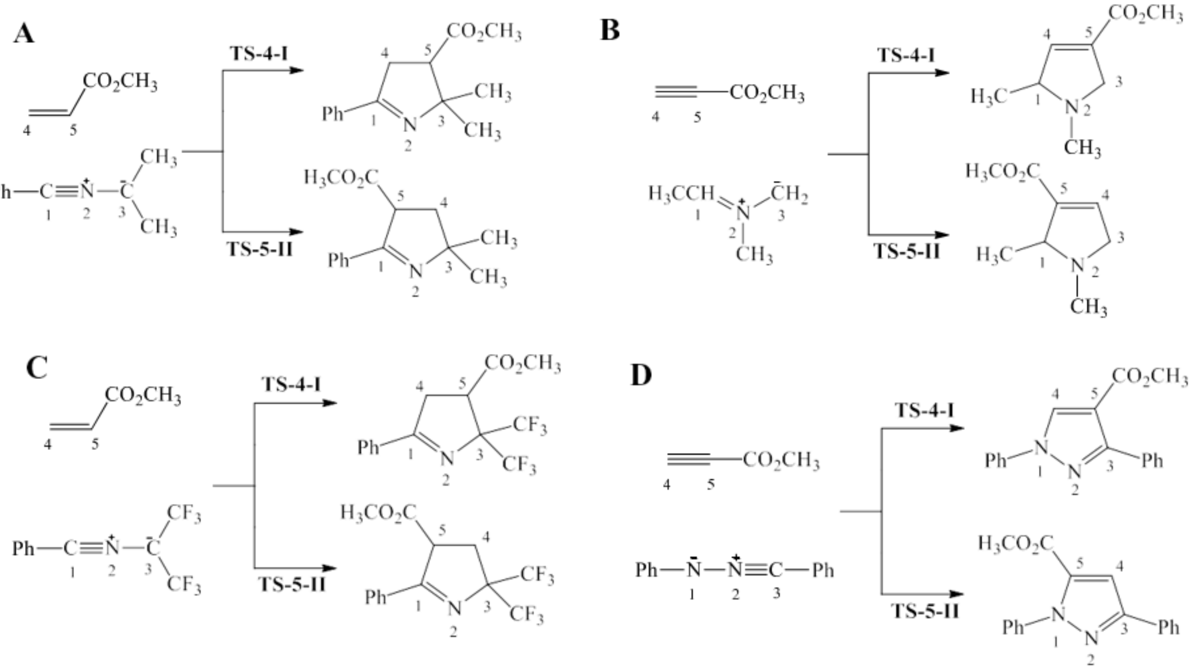


Figure 20. Investigated 1,3-dipolar cycloaddition reactions between insaturated esthers and nitrogenated ylides or nitrilimine compounds (adapted from reference (LA PORTA, FELIPE A.*et al.*, 2011).

Through simple calculations, it was possible to identify the FERMO for all the studied cases. Based on composition and location of molecular orbitals, the FERMO was identified as the HOMO for A, B and C reactions, whereas, in D reaction, the FERMO was an orbital other than HOMO but with very close energy (Figure 21).

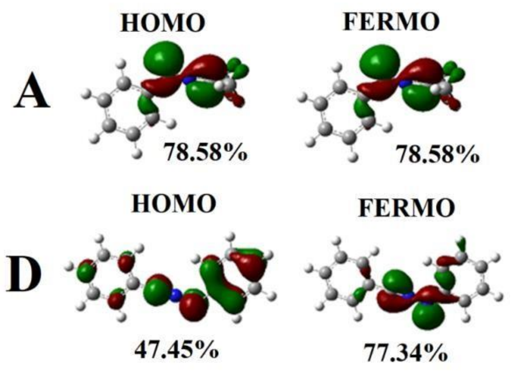
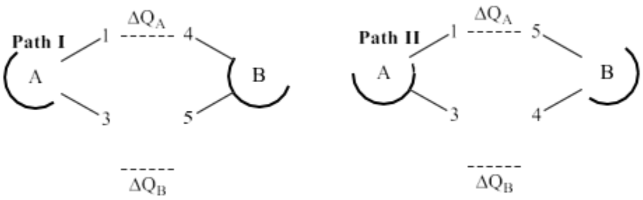


Figure 21. HOMO (left) and FERMO (right) shapes and their respective contributions in the reactive sites for the studied A (up) and D (down) system cycloaddition reactions (adapted fromreference (LA PORTA, FELIPE A. *et al.*, 2011).

Chemical reactivity can be described in terms of long-range forces through the electrostatic potential (Marcus, 1993; Oliveira and De Araújo, 2007; Williams, 1991). The ΔQ charge transfer involved in the studied reactions (LA PORTA, FELIPE A. et al., 2011) could be calculated according to Equation 10 and Scheme 1. In general, the charge transfer occurs by mean of the interaction between ligand orbitals of the charge donor molecule and anti-ligand orbitals of the proton donor species.

$$\Delta Q = \sum \Delta Q \; XY_{(Z \cdots XY)} - \sum \Delta Q \; Z \qquad (10)$$



Scheme 1. Load transfer system between atoms 1 and 3 from insaturated esthers and atoms 4 and 5 from nitrogenated ylides or nitrilimine compounds in the studied reactions (adapted fromreference (LA PORTA, FELIPE A. *et al.*, 2011).

In this case, the charge is transferred from the atom Z to the species XY and ΔQ $XY_{(Z---XY)}$ is the sum of point charges of the atoms X and Y, which represent the active site of this isolated molecule XY, ΔQ Z (Williams, 1991).

It is important to point out that there are many methods that describe the molecular electron distribution in terms of atomic charges, such as Mülliken population analysis, GAPT dipolar model, AIM molecular partition and CHELPG charges (Oliveira and De Araújo, 2007; Williams, 1991). In this context, there is an appreciable number of papers applying these methodologies to the study of charge transfer and intermolecular stabilization energy phenomena (Marcus, 1993; Oliveira and De Araújo, 2007; Cormanich and Freitas, 2009; Oliveira, 2013; Williams, 1991).

In addition, in this same work from La Porta and collaborators (LA PORTA, FELIPE A. *et al.*, 2011), it is proposed the use of the difference between the sum of the module of charge transfers in the system as a new Δ_{FERMO} reactivity index, as described in Equation 11. This new reactivity index allows us to gather information about thermodynamic properties for these reactions with good correlation mainly with free energy values. The lower its value, the more effective is the charge transfer in the system, due to a greater interaction between orbitals.

$$\Delta_{FERMO} = \sum |\Delta Q_A - \Delta Q_B| \qquad (11)$$

However, in order to calculate this electronic parameter, the implementation and interpretation of point charges is often used. An appropriate explanation for the concentration of atomic charges in donors can be demonstrated by the CHELPG charge transfer data and the Δ_{FERMO} index results, which explains very well the regioselectivity of these reactions (Table 2). A qualitative analysis of charge transfer allows us to gain important insights into the mechanism of 1,3-dipolar cycloaddition reactions (Marcus, 1993; Georgescu and Gérard, 1999; Aurell et al., 2004; Oliveira and De Araújo, 2007; Cormanich and Freitas, 2009; Oliveira, 2013;Williams, 1991).

Table 2: ΔQ charge transfer values obtained from CHELPG method and Δ_{FERMO} index obtained for the studied reactions (adapeted from reference (LA PORTA, FELIPE A. *et al.*, 2011).

Model		ΔQ^{CHELPG}		Δ_{FERMO}	
		4-regioisomer	5-regioisomer	4-regioisomer	5-regioisomer
A	ΔQ_A	0.178	0.125	0.033	0.041
	ΔQ_B	0.211	0.166	-	-
B	ΔQ_A	0.106	0.142	0.132	0.023
	ΔQ_B	0.238	0.165	-	-
C	ΔQ_A	0.022	0.008	0.106	0.168
	ΔQ_B	0.128	0.176	-	-
D	ΔQ_A	0.473	0.509	0.283	0.399
	ΔQ_B	0.190	0.110	-	-

Another important contribution from La Porta and collaborators (LA PORTA, FELIPE A. *et al.*, 2011) was the use of the ADMP direct molecular dynamics method for calculations. The results obtained through this technique, in turn, provided detailed explanations at a molecular level for experimentally observed phenomena and are extremely useful for understanding fundamental aspects of chemistry. In addition, the shapes of frontier molecular orbitals were followed for the conformations obtained along the molecular dynamics simulations, showing that the reaction mechanism occurs through a concerted process (Figure 22). It is remarkable, however, that all these trajectories involved a concerted reaction path. In Table 3, the atomic contribution of frontier orbitals is presented along the mapped reaction path.

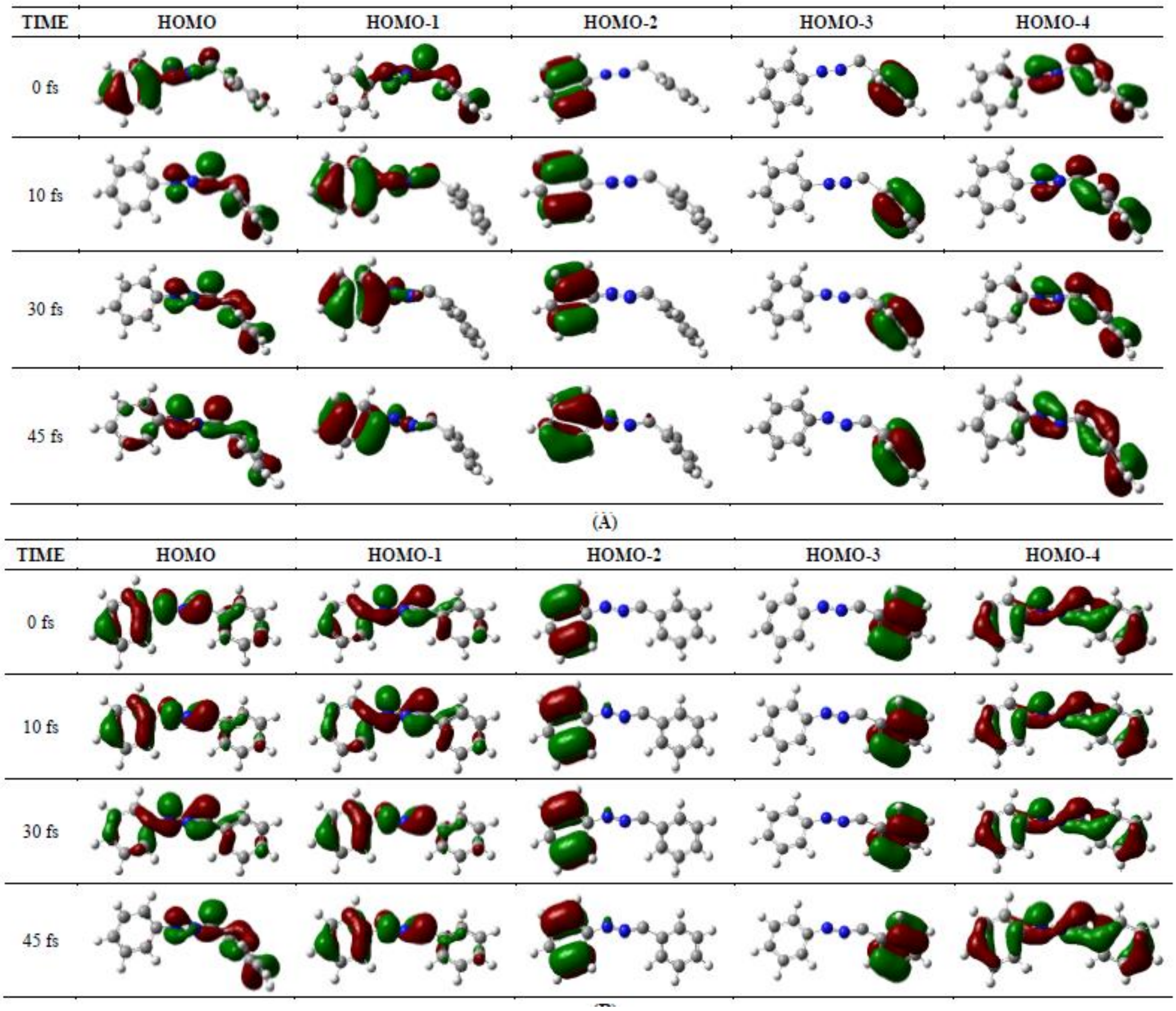


Figure 22. Representation of frontier molecular orbitals along the reaction path in the 4- (*A*) and 5-regioisomer (*B*) formation in the studied reaction D (adapted from reference (LA PORTA, FELIPE A. *et al.*, 2011).

Table 3. Percentual contribution of frontier orbitals of typical structures from trajectories for the formation of products in the reaction D (adapted from reference (LA PORTA, FELIPE A. *et al.*, 2011).

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

In these results, it was showed that the molecular orbital responsible for describing the studied D reaction, the FERMO, becomes the HOMO (Figure 22). We believe that the effective molecular orbital for the reaction is the frontier molecular orbital that has electrons with highest kinetic energy. This fact explains the increase in the energy of the FERMO orbital, which is in agreement with the Virial Theorem (GEORGESCU; GÉRARD, 1999).

Another important aspect that we can notice is that the shape of the FERMO is maintained throughout the reaction. In this way, the FERMO concept removes the limitations of the HOMO-LUMO concept arguments and the new approaches proposed in the literature, and it can be considered as an innovative tool for studying the role of frontier molecular orbitals in chemical reactions.

In another work, also involving 1,3-dipolar cycloaddition reactions, the 1,3-dipolar double cycloaddition reaction between nitrilimine and allenoate was studied. This reaction had already been investigated experimentally by Liu and collaborators (LIU et al., 2017). However, in this work, it was studied theoretically at the computational levels B3LYP/6-311G(d,p) and wB97XD/6-311G(d,p) in both gas phase and dichloromethane solution. The author intended to elucidate global and local reactivity indices of reactants (SOLEYMANI, 2018).

The mechanism was proposed, which was based on the interaction of nitrilimine with the C_α-C_β double bond of the allenoate in the first step to generate the dihydropyrazoline intermediate. There after, the second nitrilimine molecule performs the cycloaddition to the C_β-C_γ double bond of the dihydropyrazoline intermediate to produce the corresponding spirobidihydropyrazole (Figure 23) (LIU *et al.*, 2017; SOLEYMANI, 2018).

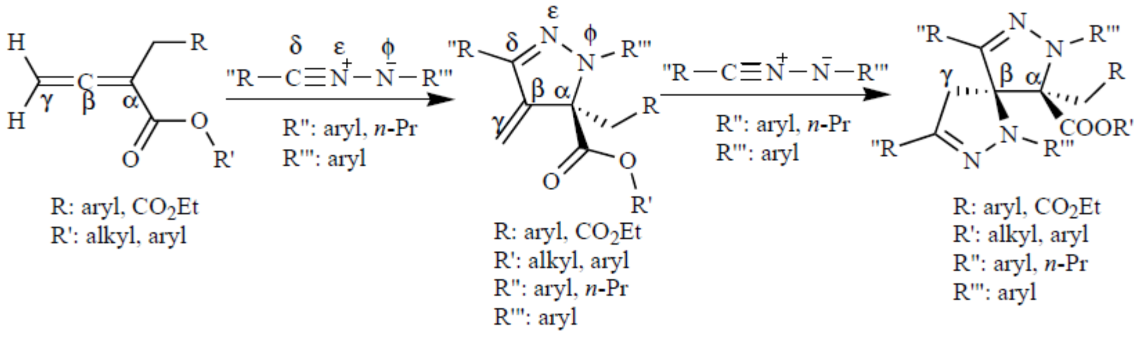


Figure 23. General scheme of the obtaining of spirobidihydropyrazoles from nitrilimines and allenoates (adapted from (LIU *et al.*, 2017; SOLEYMANI, 2018).

To determine how the molecular orbitals were interacting in this reaction, the energy differences between the frontier orbitals (HOMO / LUMO) of the electron donor (NI) and acceptor (Aln) groups were calculated. The FERMO concept was also used to describe the reactivity of pyrene active sites (SOLEYMANI, 2018). Therefore, to determine the FERMO, the relative contribution of the active sites of NI (Cδ and Nϕ atoms) in the three highest occupied molecular orbitals was calculated. Based on the composition and location of the molecular orbitals, it was found that the FERMO was once again the HOMO for the reaction, because the active sites of NI (Cδ and Nϕ atoms) have a larger contribution for to HOMO compared to the other occupied molecular orbitals (SOLEYMANI, 2018).

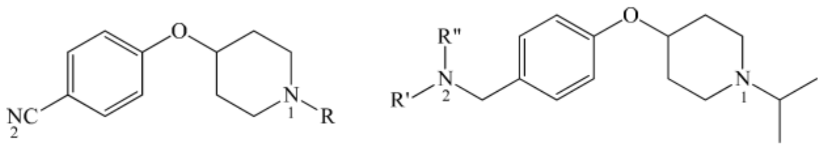
Their results showed that the formation of the experimentally described products can be clearly explained by Fukui function reactivity indices and transition states studies. Their analysis of the frontier molecular orbitals showed that the HOMO orbital of nitrilimine (acting as donor) is also the FERMO (SOLEYMANI, 2018).

Biological Systems

Heterocyclic aromatic compounds have great importance for medicinal chemistry due to their biological activities, being mainly used as anticancer, antibacterial, antidepressants, anti-inflammatories and herbicides, among other applications (Laber et al., 1999; Funakoshi et al., 2002; Maccioni et al., 2002; Holla et al., 2003; Vicini et al., 2003; Harnett et al., 2004, Ingelman et al., 2001). There are also compounds with excellent antitumor activities (BIN; PANEK, 2000; KAMATH; JORDAN, 2003; NICOLAOU; ROSCHANGAR; VOURLOUMIS, 1998; PARK *et al.*, 2003; STORER *et al.*, 2003), several compounds that catalyze decarboxylation and condensation reactions (LEONARDI *et al.*, 2003; MELNICK *et al.*, 2003; PARK *et al.*, 2003; SVERGUN *et al.*, 2000) and others used in the fight against HIV virus (DE SOUZA; DE ALMEIDA, 2003). In addition, these compounds are often used as precursors in several reactions in organic synthesis.

Arrang et al. discovered H_3 receptors in 1983 (ARRANG, JEAN MICHEL; GARBARG; SCHWARTZ, 1983). Recent studies have shown that, in human brain, H_3 receptors are located in the cognition areas in the hippocampus. In these regions, the neurotransmitter histamine is associated to other amines synthesized by human organism. Investigating the role of histamine, it has been found that it inhibits its own release and synthesis in the central nervous system (CNS) through interaction with H_3 receptors. For this reason, efforts have been directed to the development of potent non-imidazole antagonists of the H_3 receptor (which, in turn, belongs to the G-protein class), due to their potential therapeutic application in CNS disorders such as memory and learning deficit, Alzheimer's, epilepsy, sleep disorders and obesity (ARRANG, J. M.; GARBARG; SCHWARTZ, 1985; DA COSTA; TRSIC, 2010; HAAS; PANULA, 2003; MARTINEZ-MIR *et al.*, 1990).

Da Costa and Trsic have evaluated, for a set of twenty-eight H3 receptor antagonist compounds (Figure 24), which theoretical parameters together would have a significant correlation with the binding affinity to H3 receptor (pKi) (DA COSTA; TRSIC, 2010), in order to assist the design of potent H3 antagonists. In this work, they used the FERMO energy along with reactivity descriptors such as hardness, softness, electronegativity and electrophilicity indexes, chemical potential (all of them calculated by substituting the energies of HOMO orbitals with the FERMO energies), and other descriptors such as dipole moment, polarizability, hyperpolarizability, molecular volume, N1 atom charge (the nitrogen atom of piperidinic ring) and charge density in the N1 atom in the FERMO orbital ($\sum(_{FERMO})\ c2$), for the analysis of descriptors that influence the binding affinity values.



R, R' and R": alkyl, aryl

Figure 24. General structures of H_3 antagonists compounds investigated (adapted from (DA COSTA; TRSIC, 2010).

Thus, in the statistical analysis for correlation with pKi values, the FERMO energy correlated much better with these experimental values than with the use of HOMO and LUMO orbitals energies. In this research, the authors verified that four electronic descriptors, one of them being the FERMO energy, were considered more appropriate to produce a satisfactory prediction for the theoretical pKi values. For the analysis of the descriptors that influence the binding affinity values, it was observed that the FERMO energies behaved in a more pertinent way for the description of H3 binding affinity than the HOMO energies. Therefore, this result indicates that the energy value of the FERMO is a critical parameter to be considered in quantitative studies of the structure-activity relationship.

The FERMO idea uses calculations based on the molecular orbital theory and interprets this data according to the valence bond theory (DA SILVA; RAMALHO; et al., 2006a, b; DA SILVA; SANTOS; et al., 2006). In molecular orbital theory, electrons in a molecule occupy delocalized orbitals obtained from the linear combination of atomic orbitals. However, it should bear in mind that the valence bond approach is very useful for analyzing enzymatic reactivity

(NAKAMURA, HISAO; TRUHLAR, 2001; TRUHLAR, 2007), photochemistry (BRYNDA et al., 2006; TRUHLAR, 2007), chemical dynamics (BRYNDA et al., 2006) and conductivity theories where a localized representation is imperative.

CONCLUSION

The shape and atomic composition of molecular orbitals are very important indicators for discovering suitable orbitals for all reactions. Thus, in this review work, we seek to systematically present the most recent advances in the study of chemical reactivity based on a deep understanding of the physical properties of the Frontier Effective-for-Reaction Molecular Orbital, FERMO. We can notice that the FERMO idea is an innovative concept that has been identified as quite promising in the study of the importance of molecular orbitals for chemical reactivity, and which has been applied with success for descripting the acid-base behavior, chemical reactions of organic and inorganic complexes, pericyclic reactions and biological systems. In this sense, in summary, the FERMO concept is intuitive and based on simple calculations, emerging as a powerful tool that seeks to describe breaking and formation of chemical bonds. In particular, a molecule can have as many FERMOs as reaction sites. The results obtained using different approaches of theoretical calculations reinforce the idea of the FERMO concept, leading to new perspectives on the role of frontier orbitals. These evidences suggest that the molecular orbital that describes a reaction, being responsible for bond formation, has electrons with higher kinetic energy. Another interesting factor that can observed is that the FERMO shape is maintained throughout the reaction course. This evidence helps to reinforce the idea of this concept and allows us to obtain insights about the orbital responsible for describing the reaction. Thus, the FERMO concept removes the limitations of the HOMO-LUMO approach and of the new approaches proposed in the literature. It and can be considered as a powerful and innovative tool for the study of the role of frontier molecular orbitals. Maybe molecular orbitals keep a few more secrets that still need to be discovered. Understanding the behavior of molecular orbitals is fundamental to better understand chemistry. Therefore, these investigations lead to new perspectives and new ideas about the reactivity of molecules.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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ARTIGO 2- Rationalizing the regioselectivity of substituted phenols from the FERMOconcept: stereo-electronic effects on protonation and functionalization.

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Rationalizing the regioselectivity of substituted phenols from the FERMO concept: stereoelectronic effects on protonation and functionalization

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The relative extent of protonation in oxygen and carbon atoms and the position of protonation in carbons depend on several factors. We seek to locate the frontier molecular orbitals involved in the protonation reactions of substituted phenols using the FERMO concept through the MOLPROJ software, to compare the computational results with experimental NMR data obtained in the literature. We evaluate computationally the stereo-electronic effects that govern reactions of aromatic electrophilic substitution using an experimental study as an example. The MOLPROJ returned a percentage of correct answers of approximately 86% in the protonation sites. The experimental results on the protonation sites were rationalized in terms of stereoelectronic effects.

Keywords: Phenols, Protonation, molecular orbital, FERMO, MOLPROJ.

Introduction

Phenols are compounds with a hydroxyl functional group directly attached to a sp^2-hybridized carbon atom of a phenyl group. Namely, they are compounds containing one or more hydroxyl groups attached to benzene or another arene ring [1].

Many manufactured products such as dyes and oils, among others, have in their composition phenolic compounds that are of natural origin [2]. They are present in vegetables in free form or linked to sugars (glycosides) and proteins [3]. These compounds also lead to the polymerization of natural polyphenols such as lignin and melanin, besides forming an important class of antioxidants, which inhibit the oxidative degradation of organic or bio-organic molecules [2,4,5]. The antioxidant activity of phenols against free radicals comes from their elimination role, which is related to their ability to react with radicals much more quickly than other organic substrates. For example, tocopherol (vitamin E) is mentioned as an efficient capture agent that can eliminate harmful peroxide radicals in the blood plasma [5,6].

Protonation and deprotonation processes in aromatic molecules such as phenols are important in organic chemistry and biochemistry [7]. Through the deprotonation of phenol, the phenoxide or phenolate ion is formed, stabilized by resonance. In comparison with phenol, the phenoxide ion is more stable because of the high displacement of the negative charge on the aromatic ring. The resonance structures of phenol involve separation of negative and positive charges. Thus, phenol is more likely to form phenoxide, releasing the proton [6].

The preferred protonation sites for phenols have been discussed from an experimental point of view [8–12] and theoretical [13–16]. In super-acidic solutions, phenols are protonated in oxygen atoms, to form oxon ions (*O*-PhH^+), or carbon in the aromatic ring in the *ortho* (*o*-PhH^+), *meta* (*m*-PhH^+) or *para* (*p*-PhH^+)[7,17–20].

The relative extent of protonation in oxygen and carbon atoms and the position of protonation in carbons depend on several factors, such as electronic structure of the base, acidity and solvation properties of the medium and temperature [21]. Theoretical studies have been dedicated mainly to the exploration of the intrinsic basicities in the different positions in phenol molecules [15] and in the relationship between protonic affinities and ionization energies [18].

Characteristics such as spatial and electronic structure and physico-chemical and biochemical properties of phenols can be influenced by substituting groups [20]. A substituent is a minor structural subunit (atom or functional group) that disturbs the properties of a molecular system in a quantitative sense, maintaining its general character. That is, the substituent can mischaracterize the molecule in a measurable, but not dramatic, way by modifying its spatial and electronic structure and, consequently, its behavior [16,22].

The acidity of phenols can be influenced by other groups linked to the ring [21– 24]. The presence of any substituent on the aromatic ring that can stabilize the phenoxide ion will tend to increase the acidity of the phenol. On the other hand, any substituent that destabilizes the phenoxide ion, increasing its negative charge, will decrease the acidic nature of the phenol. In other words, the presence of electron withdrawing groups in phenols will increase their acidity, while electron density donor groups reduce their acidity [20,25].

To measure the basicity of organic compounds in the gas phase, the proton affinity(PA) can be used. The proton affinity is defined as the negative of the enthalpy change for the reaction $M_{(g)} + H^+_{(g)} \rightarrow MH^+_{(g)}$, being M a chemical species: molecule, radical or atom [23,25]. The higher the PA, the stronger the conjugate base and the weaker the conjugated acid in the gas phase. The PA value also illustrates the role of hydration in Brønsted acidity in the aqueous phase [26–28]. The relationships between the energies of the highest molecular orbitals (HOMO and other frontier orbitals; HOMO: Highest Occupied Molecular Orbital) and PA are often present for families of compounds, such as phenols. However, for a large number of compounds, the energies of their HOMOs do not present a good correlation with PA values [27]. Accordingly, the question arose: why are HOMO energies good acid-base descriptors for some compounds and not for others? Faced with such limitations, another approach has emerged to understand chemical reactivity: the concept of FERMO (Frontier Effective for Reaction Molecular Orbital), proposed by Silva and Ramalho [29–31].

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 [28,29].

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). In this same study [31], it was possible to determine the reaction site of a series of amines and describe their acid-base behavior. 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.

Other computational studies also look for different approaches to rationalize reactivity properties. One of these approaches is the study of the atomic charge distribution in molecules to quantify regioselectivity [42-46]. Liu and coworkers [42] proposed a method to simultaneously quantify electrophilicity and nucleophilicity using the Hirshfeld charge. This quantification is based on the Information Conservation Principle, which states that information must be conserved before and after a molecular system is formed.

It decides both where electrophilic and nucleophilic attacks will preferentially occur, but also dictates the amount of Hirshfeld charge distribution, which correlates with experimental scales of electrophilicity and nucleophilicity. In order to have the information conservation, the system that was formed is adjusted in order to have each one of the components loaded according to the contribution of its "stock" of electronic density. Therefore, the Hirshfeld charge should be a good descriptor for both electrophilicity and nucleophilicity [42-46].

Another very useful method for modeling molecule-molecule interactions are derived from a least squares fit to the electrostatic potential (ESP). ESP is one of the useful properties to acquire partial atomic charges suitable for modeling short- and long-range molecule-molecule interactions [46]. The grid-oriented CHELP (Charges from Electrostatic potentials method) was the first method of its kind to be developed, being modified to CHELPG (Charges from Electrostatic Potentials using a Grid based method) by Breneman and Wiberg. The

CHELPG method is less dependent upon molecular orientation than the original CHELP method in which partial atomic charges are fitted to reproduce the molecular ESP at a number of points around the molecule [46,48,49,50].

In addition to computational studies, experimental liquid-phase spectroscopy studies, mainly NMR and IR spectroscopy, were widely used to locate the preferred protonation site (s) of the phenol and benzene molecules substituted as a function of solvent and temperature [17,18,32–34]. To produce information about the competitive protonation in the substituents in substituted aromatic compounds, in addition to the protonation in the ring itself, it is necessary to separate the effects of the solvent from the molecular electronic properties, whose investigations must be made in the gas phase [32]. The spectroscopic data, particularly those from NMR, are sufficiently accurate to unambiguously identify the protonation sites in aromatic compounds. Experimental information on protonation in the gas phase also comes from mass spectrometry studies involving proton transfer reactions [5,7,11,12,14,23,32,35]. Even though these studies have shown the existence of several protonated isomers of many aromatic ions, and in some cases also the specific locations of the protons, the details of their structures constantly remained confused. For these cases, the structural attribution of the various isomers sometimes depended on computational chemical calculations [14,15,36,37].

In this article, we seek to locate the frontier molecular orbitals involved in the protonation reactions of substituted phenols using the FERMO concept, quantifying the orbital coefficients of the carbon and oxygen atoms involved. Once these orbitals are identified, we seek to compare the computational results with experimental NMR data obtained in the literature. In addition, we also search to computationally evaluate these stereo-electronic effects that govern reactions of aromatic electrophilic substitution using an experimental study as an example.

Methodology

Computational details

All calculations were performed with the GAMESS software for Linux, version 30 SEPT 2017 (R2). Furthermore, all studied compounds were fully optimized using the DFT method with the functional B3LYP and the basis set 6-31G(d,p) in water solution. The description of the solvent model was carried out with the Polarizable Continuum Model (PCM) using the integral equation formalism variant (IEFPCM). No symmetry restrictions were imposed during the optimization process. No imaginary frequencies were found for the optimized geometries, which were used in all subsequent calculations and had their single point energies determined with the same functional and basis set. MOs figures were prepared using Avogadro software [31] with a contour value of 0.010. The charge calculations have been performed with Gaussian 09 [47]. The Hirshfeld and CHELPG (Charges from Electrostatic Potentials using a Grid based method) charges are obtained from the population analysis with the keyword pop=hirshfeld and pop=chelpg, respectively.

Criteria for choosing the orbitals

Considering the Brönsted-Lowry acid-base concept, the MO that drives the protonation reactions of the investigated phenols must be centered on the atoms that bind to the proton. Using the software developed in our group, MOLPROJ, the investigation of these orbitals was carried out in a quantitative way from the output data generated by GAMESS.

As will be said below, MOLPROJ uses projection operators to quantify the location of FERMO in a reaction using Equation 1, in which MOs are built via LCAO [26]:

$$\theta_{\mu} = \sum C_{l\mu} \zeta_l(x)$$

(Eq. 1)

being $C_{l\mu}$the matrix of the coefficients of the molecular orbitals and the Gaussian $\zeta_l(x)$AOs. These are created as an orthogonal set of vectors, which have components in each atomic orbital of a given molecule. The S_{ij}overlay matrix is then defined by the set of AOs $\zeta_l(x)$, which forms a set of non-orthogonal bases[26]:

$$S_{ij} = \int \zeta_i(x)\zeta_j(x)dx$$

(Eq. 2)

Through the overlay matrix S_{ij}, it is possible to build a projection operator for P_Ga set of AOs G [26]:

$$P_G = \sum_{i\in G} \sum_{j\in G} \zeta_i \zeta_{ij}^{-1} \zeta_j$$

(Eq. 3)

The projector can be understood as the projection of a "shadow" of a selected MO in the subspace of a set of AOs [38], thus making it a quantitative characterization of the shape of MO in a set of AOs and, consequently, a set of atoms [26].

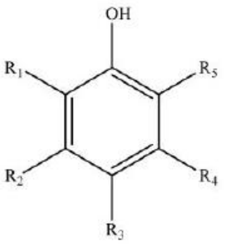
Thus, it is possible to define the degree of localization Γ_{FERMO}: it is the norm of an MO projected on the expected set of atomic orbitals, which are important and that participate in the reaction of a certain compound, as follows in Equation 4 [26]:

$$\Gamma_{FERMO} = \sqrt{\sum_{l} \sum_{i \in G} \sum_{j \in G} \sum_{k} C_{l\mu} S_{li} S_{ij}^{-1} S_{jk} C_{k\mu}}$$

(Eq. 4)

Phenols

Figure 1 shows the 13 phenols used in this work. The choice was made based on phenols that had experimentally determined protonation sites [8-10, 12].



01-13

01: R_1 = H; R_2 = H; R_3 = H; R_4 = H; R_5 = H
02: R_1 = H; R_2 = H; R_3 = CH_3; R_4 = H; R_5 = H
03: R_1 = H; R_2 = H; R_3 = F; R_4 = H; R_5 = H
04: R_1 = CH_3; R_2 = CH_3; R_3 = H; R_4 = H; R_5 = H
05: R_1 = CH_3; R_2 = H; R_3 = H; R_4 = H; R_5 = CH_3
06: R_1 = H; R_2 = CH_3; R_3 = CH_3; R_4 = H; R_5 = H
07: R_1 = H; R_2 = CH_3; R_3 = H; R_4 = CH_3; R_5 = H
08: R_1 = CH_3; R_2 = CH_3; R_3 = H; R_4 = H; R_5 = CH_3
09: R_1 = CH_3; R_2 = H; R_3 = CH_3; R_4 = CH_3; R_5 = H
10: R_1 = CH_3; R_2 = H; R_3 = CH_3; R_4 = H; R_5 = CH_3
11: R_1 = H; R_2 = CH_3; R_3 = CH_3; R_4 = CH_3; R_5 = H
12: R_1 = CH_3; R_2 = CH_3; R_3 = H; R_4 = CH_3; R_5 = CH_3
13: R_1 = CH_3; R_2 = CH_3; R_3 = CH_3; R_4 = CH_3; R_5 = CH_3

Figure 1. Structures of the 13 phenols with protonation sites experimentally determinedby NMR chosen for the work.

Results and discussion

Theory versus Experiment

Using the MOLPROJ software, optimized structures of the selected compounds were analyzed using their MOs eigenvectors and overlap matrices, both extracted from output files of single point energy calculations with GAMESS. The degree of localization for each MO and their respective energies were calculated and analyzed. For this, the $P_G$projection operators were applied to all $2p_{x-z}$ orbitals of aromatic carbon atoms as for the hydroxyl oxygen atom.

Subsequently, we calculated the coefficients of degree of localization for the HOMO and FERMO molecular orbitals (Γ_{HOMO} and Γ_{FERMO}) for comparison. These coefficients are shown in Table I, together with the corresponding MOenergies.

Table I: results from the degree of localization of phenols MOs from compounds **01** to **13** as returned by MOLPROJ along with protonation experimental data.

Phenol	**HOMO**			**Shape-based FERMO for protonation**				**Experimental protonation**
	Atom	**Γ_{HOMO}**	**Energy (eV)**	**Atom**	**Γ_{FERMO}**	**Relative Position**	**Energy (eV)**	
01	C4	0.500961	-159.704280	O	0.505728	HOMO-2	-242.406960	Solvent B; O: 100%;
02	C4	0.489308	-153.633000	C4	0.489308	HOMO	-153.633000	Solvents A, C: O: 55%; C2: 40%; C4: 5%; Solvent A^{40}; O: 19%; C2: 73,5%; C4: 7,5%;
				C2	0.499301	HOMO-1	-180.139320	
				O	0.495555	HOMO-2	-233.596200	
03	C4	0.454808	-159.482160	O	0.505810	HOMO-2	-240.185760	Solvent B; O: 100%;
04	C4	0.500184	-153.781080	C4	0.500184	HOMO	-153.781080	Solvents A, C, D; C4: 100%;
05	C4	0.480443	-152.892600	C4	0.480443	HOMO	-152.892600	Solvents A, C, D; C4: 100%;
				C5	0.496830	HOMO-1	-169.551600	
06	C4	0.500974	-151.041600	C2	0.543739	HOMO-1	-174.364200	Solvent A; C2: 90%; C4: 10%;
				C4	0.500974	HOMO	-151.041600	
07	C4	0.526782	-154.225320	C4	0.526782	HOMO	-154.225320	Solvents C, D; C4: 100%;
08	C4	0.490162	-150.301200	C4	0.490162	HOMO	-150.301200	Solvents A, C, D; C4: 100%;
				C2	0.509300	HOMO-1	-164.220720	
09	C4	0.487159	-148.080000	C4	0.487159	HOMO	-148.080000	Solvent C; C4: 85%; C6: 15%;
				C6	0.539112	HOMO-1	-168.663120	
				C3	0.492505	HOMO-1	-168.663120	
10	C4	0.473252	-147.561720	C5	0.495472	HOMO-1	-167.922720	Solvent A; C3: 100%;
11	C4	0.516664	-148.672320	C4	0.516664	HOMO	-148.672320	Solvent C; C2: 57%; C4: 43%;
				C2	0.495021	HOMO-1	-168.441000	
12	C4	0.498601	-148.598280	C4	0.498601	HOMO	-148.598280	Solvents A, C, D; C4: 100%;
13	C4	0.496808	-143.563560	C4	0.496808	HOMO	-143.563560	Solvents A, C, D; C4: 100%;

A: HSO_3F/SbF_5 [12]; **B**: H_2SO_4 [10]; **C**: HSO_3F[8]; **D**: CF_3SO_3H [9]

From these data, two doubts emerged: (1) is the reaction site pointed by the software in accordance with experimental results found in the literature, based on NMR? (2) can the software be applied to a study that has only experimental results?

We know that even simple molecules have favorable sites for protonation and thatthe preferred site depends significantly on its chemical environment. Much of the experimental information on protonation processes in gas phase came from mass spectrometry studies involving proton transfer reactions [5,7,11,12,14,23,32,35]. These studies revealed the existence of several isomers of MH^+ ions, and, in some cases, specific protonation sites. As already mentioned, this protonation can occur in the oxygen atom toform an oxonium ion (*O*-PhH^+ or $PhOH_2^+$) or in carbon atoms in *ortho* (*o*-PhH^+), *meta* (*m*-PhH^+) or *para* (*p*-PhH^+) positions in the aromatic ring [7,17–20], respectively C2, C3and C4 (Figure 2).

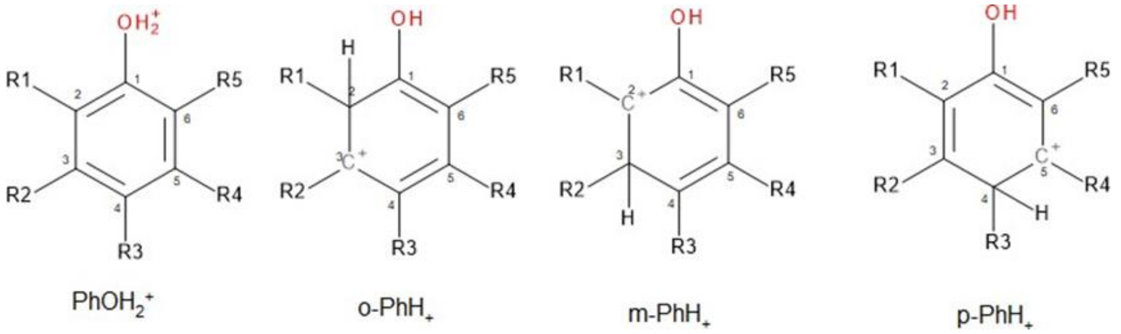
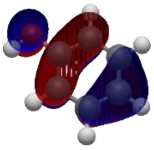
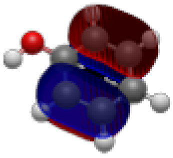
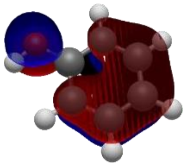
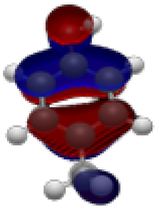
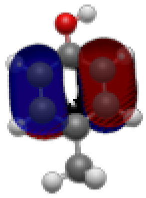
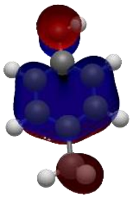
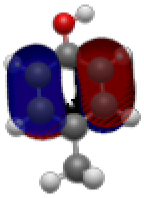
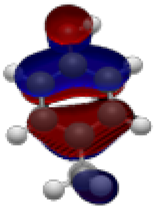
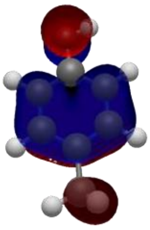
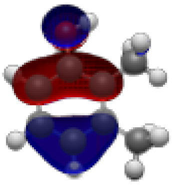
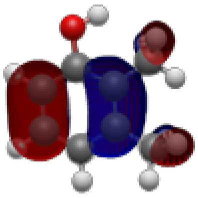
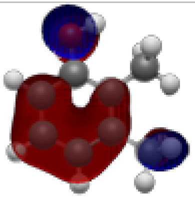
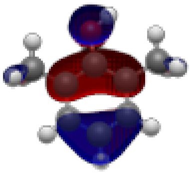
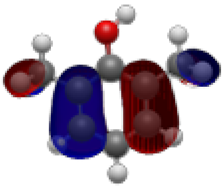
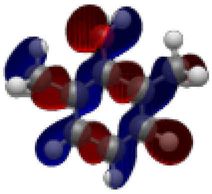


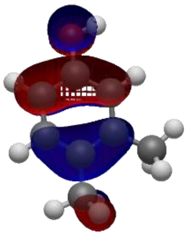
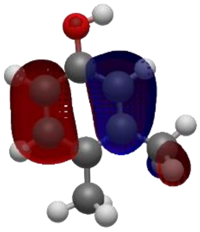
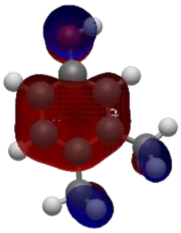
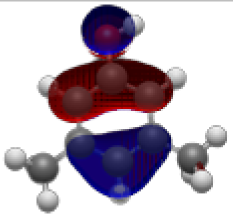
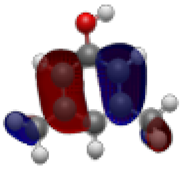
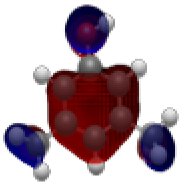
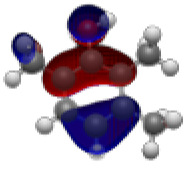
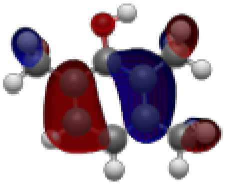
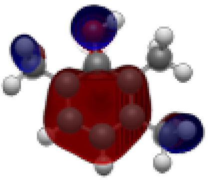
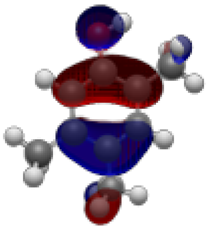
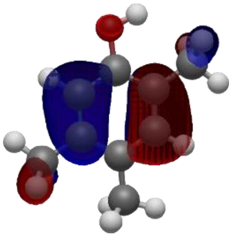
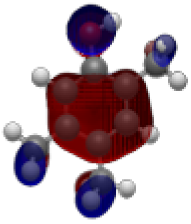
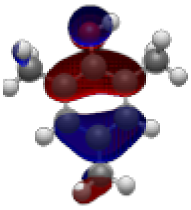
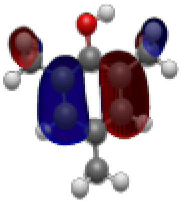
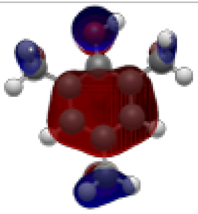
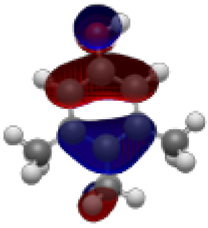
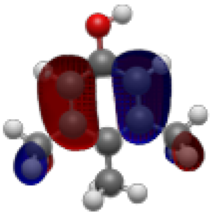
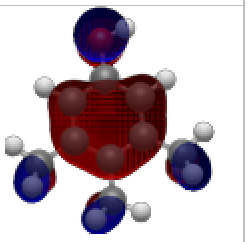
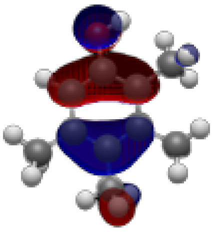
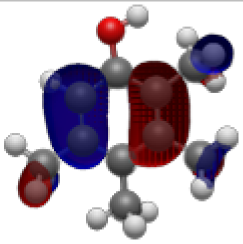
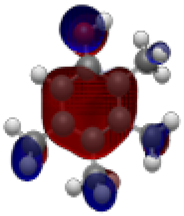
Figure 2. Nomenclature of the protonated phenols adopted in this work. Resonance structures for *o*-PhH^+, *m*-PhH^+ and *p*-PhH^+ are not represented. The numbers C1-C6 refers to the notation used in Table I.

Using data from literature about protonation of phenols based on NMR techniques, as can be seen in Table I, we performed an analysis of the protonation sites aspointed by NMR technique and by the MOLPROJ software (Table I). Literature data for protonation of phenols through NMR technique was indeed rare and, therefore, there is not a large number of samples.

As it can be seen, in some cases, and as previously discussed, the protonation sitechanges according to the chemical environment in which the compound is present. In ourcalculations, we used the water as implicit solvent and at the same temperature. Due to the scarcity of data in the literature for computational reproduction of the experimental solvation environment (i.e, H_2SO_4, HSO_3F or CF3SO3H in aqueous solution), we chose to describe the system only in implicit water, considering that, experimentally, water would already be the more abundant species. As there could be more than one protonation site, we compared the experimental reaction sites with the values of the location coefficients Γ generated by MOLPROJ for the frontier orbitals related to the atoms corresponding to these sites, checking which ones had the highest Γ values (above 0.4) between the possible protonation sites. It was done for all compounds. We start from thepremise that atoms with higher location coefficients, as returned by MOLPROJ, contribute better to the protonation sites and to the construction of the involved boundarymolecular orbitals.

Pictures of the highest MOs for each compound are shown in Figure 3. The Γ coefficients from HOMO to HOMO-3 for O and C1-C6 atoms of all compounds can be find in Supplementary Material.

Compounds	**HOMO**	**HOMO-1**	**HOMO-2**
1			
2			
3			
4			
5			

6			
7			
8			
9			
10			
11			
12			

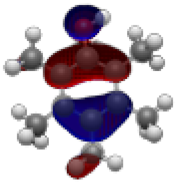
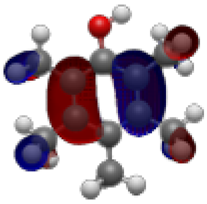
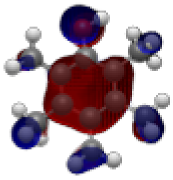
13			

Figure 3. Shapes of the four highest MOs for the protonated phenols studied in this work.

For the simplest compound, phenol (01), protonation in H2SO4 medium occurs only in the oxygen atom. An analysis performed with the MOLPROJ software returned a slightly higher Γ coefficient value for the HOMO-2 (0.505728), located at the oxygen atom, in relation to the HOMO orbital (0.500961), which is mainly located at the C4 carbon atom (the para-hydroxy carbon; Figure 3). With that, it can be understood that protonation would be more favored in this oxygen atom, which agrees with the experimental results in H2SO4 solvent, indicating that, in this case, HOMO-2 is the FERMO of the reaction. Analyzing the figure of the orbitals for compound 01, we can see that HOMO-2 describes the protonation site better than the HOMO-1 orbital.

The *p*-fluoro compound 3 shares the same 100% experimental protonation in the oxygen atom in H_2SO_4. For this compound, the MOLPROJ software returned the HOMO-2 as the FERMO of the reaction (centered at the oxygen atom). As with compound 01, HOMO-2 has a high localization coefficient Γ value in the oxygen atom (0.505810 over 0.454808 for the HOMO at C4). Thus, we understand that HOMO-2 would be the FERMO of this reaction as well. In the same way as compound 1, based on the analysis of the shape of the orbitals in Figure 3, it is possible to verify that HOMO-2 has, in fact, the characteristics of a favorable location for protonation.

For compound 10 (2,4,6-trimethylphenol), which is experimentally fully protonated at C3, our theoretical findings point out protonation at C5 (the main location of HOMO-1/FERMO). But they are chemically equivalent and can react the same way. The difference in the coefficients can only be attributed to the fact that the conformationshows the H of the hydroxyl positioned on one side or the other. In this case, an experimental protonation was conducted on HSO_3F / SbF_5 instead of H_2SO_4.

For the compounds 07, 12 and 13, experimentally protonated only at the C4 carbon atom in HSO_3F (with/without SbF_5) or CF_3SO_3H, the MOLPROJ softwarereturned sufficiently high (higher than 0.4) Γ coefficient values only for the HOMO, mainly located at the C4 carbon atom (Figure 3). In these compounds, the HOMO is the FERMO of the reaction.

The compound 11, also with a high Γ coefficient value for its HOMO at C4 carbonand for

HOMO-1 at C2 (Figure 3), was experimentally protonated at C2 and, in less extension, at C4. For the protonation of 2,4,5-trimethylphenol (09), the experimentally preferred site in the presence of HSO_3F was the C4 carbon (85% protonation), accompanied by about 15% protonation in the C6 carbon. Our MOLPROJ software returned that the three largest location coefficients were found at carbon C4, C3 and carbon C6 (0.487159, 0.492505 and 0.539112, respectively). It can be seen that, when theprotonation occurs at C4 (*para*), the reaction orbital is the HOMO. When it occurs at C6(ortho), the orbital that is describing the reaction is the HOMO-1. Therefore, both orbitalsare the FERMOs of the reaction (Figure 3).

In the case of the compound 06 (3,4-dimethyphenol), the experimentally preferred sites in the presence of the same solvent (HSO3F) were the C2 (90% protonation and a Γ coefficient of 0.531917) and C4 carbon atoms (10% protonation and a Γ coefficient of 0.502416).

Finally, for the compounds 05 and 08, it was observed that some protonation sites were different from those experimentally found. In 05, the C4 and C5 carbon atoms would be protonated according to MOLPROJ but, however, it was experimentally observed that protonation occurred at C4 and C6. We attribute this to the fact that the MOLPROJ analysis is based only on electronic effects and the fact that there is a mixture of solvent, which makes computational analysis difficult. Also because the studies used as reference are relatively old and the parameterization of implicit solvation calculations containing solvent mixtures is extremely difficult. We mean that, based on the analysis of MOs, the software helps to determine which AOs are relevant for the reaction center of a given compound.

An alternative to such approach is to apply electron density localizations at the respective atomic sites as the measure of reactivity, specifically for the protonation reactions considered. According to Liu (2014) [42], the Hirshfeld charge can determine regioselectivity. As the Hirshfeld charge is derived from the Conservation of Information Principle, which requires that atomic identity be maintained as much as possible in molecules. So, this charge can reflect the electronegativity or the electropositivity nature of atoms. Therefore, the regioselectivity can be evaluated by using Hirshfeld charges [42- 46].

Considering of comparing this method and the CHELPG charge with the MOLRPOJ, we calculated the two types of charges of the 13 compounds (charges results n the supplementary material, Table SIII).

When the direct analysis of the values of the Hirshfeld charges was performed, that is, direct analysis of the charges on the atoms involved in the protonation reaction, it was observed that the most negative values were present in the hydroxyl oxygen and in the methyl substituents and in the fluorine. Considering only the carbons of the benzene ring and oxygen and that there was at least one hit in the protonation site when compared to the experimental protonation site, 69.23% of hits were obtained (01, 02, 03, 05, 06, 08, 09, 10 and 11 compounds).

When the charge difference analysis was performed [45], with phenol being the standard of Hirshfeld charge (Δ_{Hirsh}) values compared with the insertion of substituents in phenol, 46.15% (01, 06, 08, 10, 11 and 12 compounds) of correct answers were obtained. The analysis of the CHELPG charges was done in the same way as the Hirsfeld charges, in a direct way. Reaching 61.53% hits (01, 02, 03, 06, 09, 10, 11 and 12 compounds) with a correct answer.

As the MOLPROJ it is still a code under development, we will continue to seek in future works to evaluate better the effects of solvents on molecular orbitals. However, even considering that these compounds were computationally studied in an aqueous medium, without the appropriate experimentally applied solvents and compared to experimental results in different phases, we obtained 86% of correctness of the protonation sites using the developed software. We mean that 11 compounds (01, 02, 03, 04, 06, 07, 09, 10, 11, 12, 13) presented exact results when compared to the experimental results and the Hirshfeld and CHELPG charge methods.

Therefore, from our findings, we got a much more representative answer with the FERMO approach. In fact, from the MOLPRJ software, 86% of correctness of the protonation sites using the developed software was obtained.

Stereo-electronic effects on protonation and functionalization of substituted phenols

In a second step, we validated, through a computational study using MOLPROJ, an experimental approach regarding the *ortho*-cyanation reaction of phenols to obtain aromatic nitriles by means of Lewis acids [38]. The importance of aromatic nitriles comesfrom the fact that they can be easily converted into a variety of valuable syntones, such as ketones, aldehydes, amines, among others, conferring them an important role in synthetic chemistry [38–41].

According to Zhang, Yang and Zhao [38], authors of the study under consideration, the control of regioselectivity with 3,4-disubstituted phenols is still a significant and challenging work, which remains unsolved. So, they proposed to developa selective method for C−H *ortho*-cyanation promoted by Lewis acid in 3-substituted and3,4-disubstituted phenols in two different *ortho* positions, as can be seen in Figure 4. Afteran initial step for optimizing reaction conditions, in which it was stablished that the reaction would be best conducted under a combination of both $AlCl_3$ and $BF_3 \cdot OEt_2$ as Lewis acid catalysts and CH_3SCN as cyan donor, they explored the scope of its reaction through the cyanation of 3-substituted and 3,4-disubstituted phenols to afford a wide range of the corresponding 2-hydroxybenzonitriles in good or excellent yields and with enhanced regioselectivity.

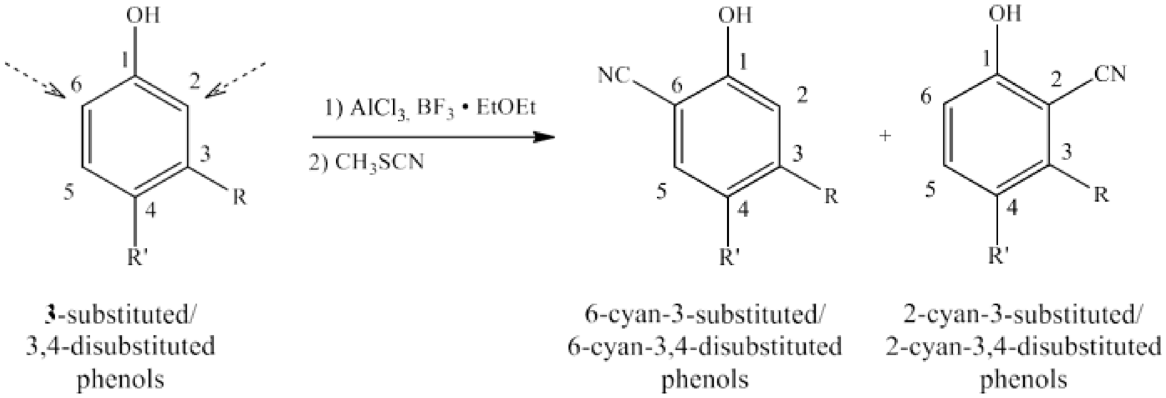


Figure 4. General structure of the two possible ortho-cyan phenols obtained through electrophilic cyanation of 3-substituted or 3,4-disubstituted phenols from Zhang, Yang and Zhao [38].

In order to explain their results, the authors proposed a mechanism in which the intermediate **I** (Figure 5) is generated from the 3-substituted phenol and $BF_3 \cdot OEt_2$ (activated by $AlCl_3$). Then, the methyl thiocyanate couples with the intermediate **I** through the transition state **TS1** to form the intermediate **II**. Another possible transition state in this step would be **TS2**, but its formation would be unfavored because of steric hindrance due to the *meta* substituent. The intermediate **II**, through tautomerization, givesthe key intermediate **III** which, after treating with aqueous NaOH solution (leading to **IV**) followed by acid treatment, leads to the desired 4-substituted 2-hydroxybenzonitriles.These steps are shown in Figure 5 [38]. To validate the mechanism proposed by the authors, we again use MOLPROJ to find the cyanation site in the model molecule **I**.

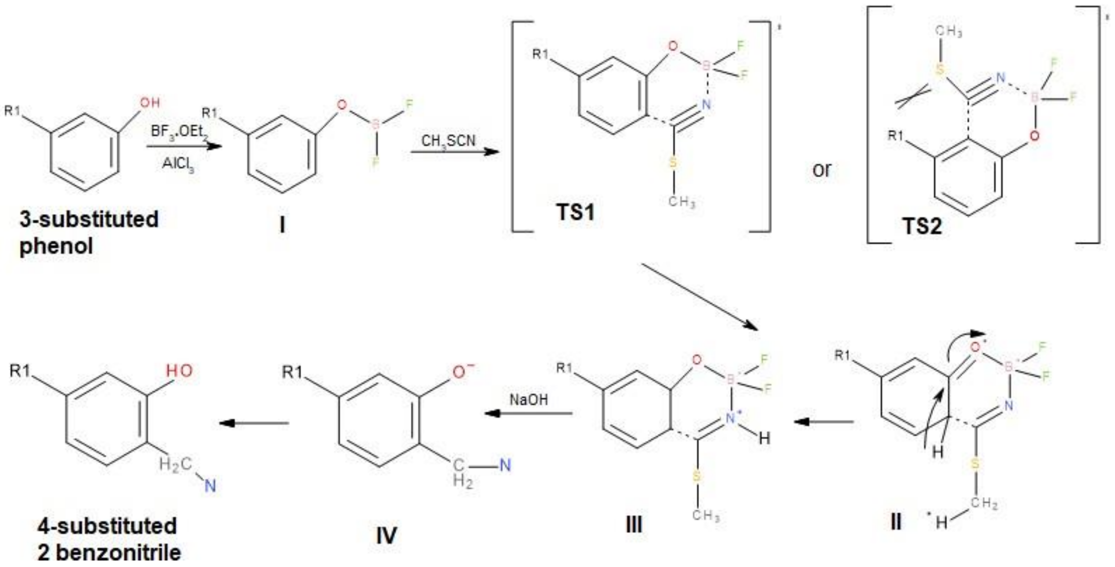


Figure 5. Reaction mechanism for the regioselective electrophilic cyanation of 3- substituted and 3,4-disubstituted phenols as proposed by Zhang, Yang and Zhao [38].

In order to find out what carbon atom would be the site for the cyanation reaction,we started from two different conformations of the first intermediate **I** which could lead the two possible transition state structures **TS1** and **TS2**, respectively named as **A** and **B**as it can be seen in Figure 6. For this step, the compound *meta*-cresol was chosen as model. These two structures were generated through optimization with B3LYP/6- 31G(d,p). According to the authors, C2 and C6 would be the ring carbons favorable for cyanation but the reaction in C6 would happen in a major way. Their explanation for thepreference of **TS1** formation is related to the steric hindrance at the C3 *meta*-substituent,therefore unfavoring the formation of **TS2**. Based on this assumption, we obtained the values of the coefficients Γ over C2 and C6 for both structures **A** and **B** in Figure 6. The data returned by the MOLPROJ software and the experimental cyanation site are shown in Table II.

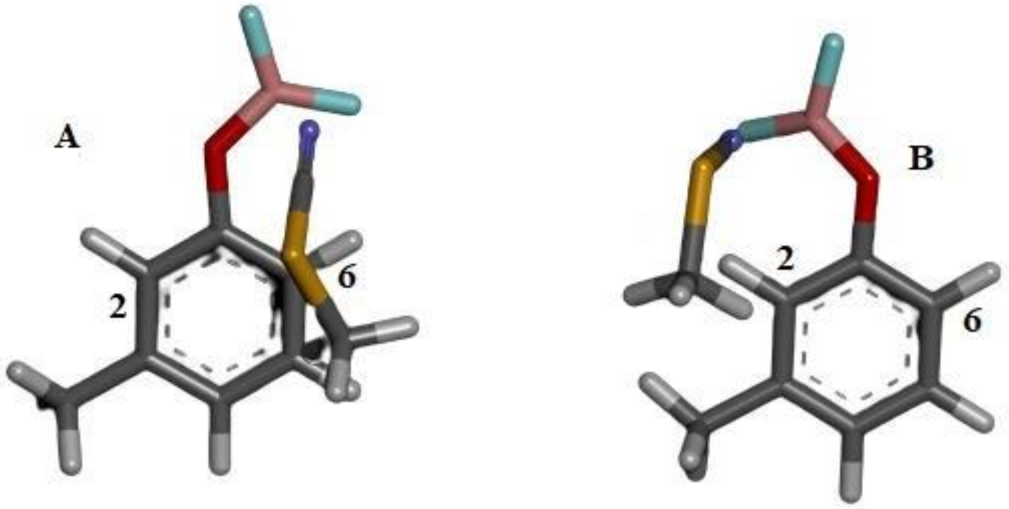


Figure 6. Structures of the two optimized conformations of intermediate **I** chosen for prediction of cyanation sites. **A**: structure of **I** with methyl thiocyanate close to C6, relatedto **TS1**. **B**: structure of **I** with methyl thiocyanate close to C2, related to **TS2**. Only the C2 and C6 carbon atoms are highlighted in both structures. Conformations were obtained through B3LYP/6-31G(d,p) calculations.

Table II: results for the degree of localization of MOs from structures **A** and **B** (derived from *meta*-cresol) as returned by MOLPROJ.

Structure	**HOMO**			**Shape-based FERMO**				**Experimental cyanation site**
	Átomo	**Γ_{HOMO}**	**Energy (eV)**	**Átomo**	**Γ_{FERMO}**	**Relative position**	**Energy (eV)**	
A	C2	0.247323	-169.847760	**C2**	**0.543365**	**HOMO-1**	-181.027800	C6
	C6	0.375934		C6	0.415139	HOMO-1		
B	C2	0.196610	-164.813040	**C2**	**0.563898**	**HOMO-1**	-176.659440	C6
	C6	0.406361		C6	0.389300	HOMO-1		

As it can be seen in Table II, the site for *ortho*-cyanation reaction indicated by MOLPROJ corresponds to C2, which is does not correspond to the experimental results, pointing to C6 as the experimental site. The MOs analysis identified the HOMO-1 as the FERMO for the *ortho*-cyanation reaction instead of HOMO. The Γ_{HOMO-1} coefficients calculated by MOLPROJ showed higher values for C2 than for C6 for both **A** and **B**. In Figure 7, the shapes of their corresponding MOs are shown.

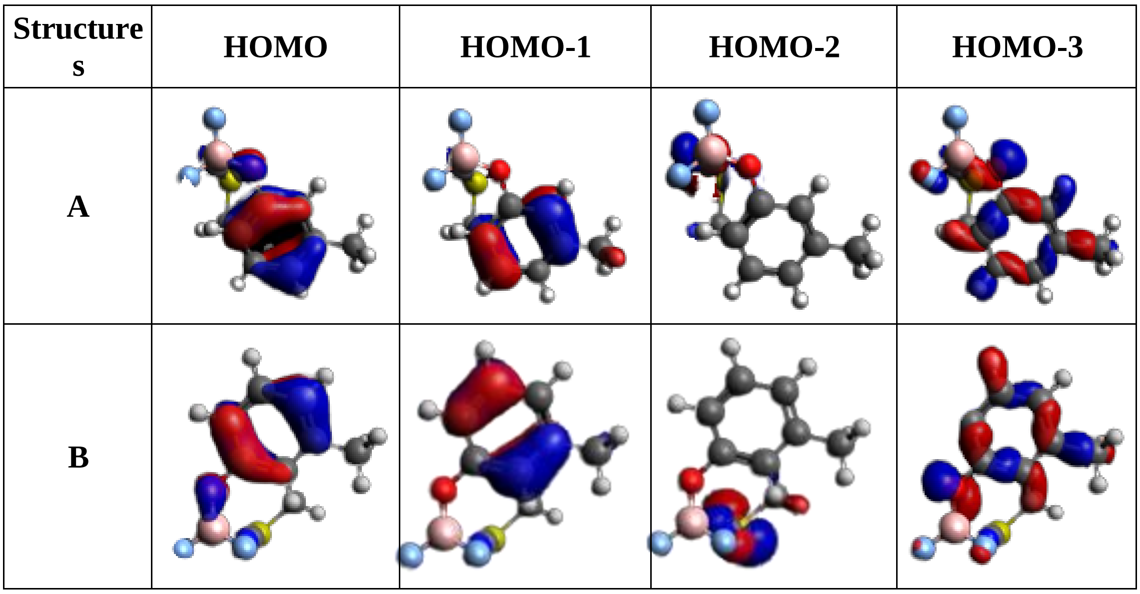


Figure 7. Shapes from HOMO to HOMO-3 for the structures **A** and **B**.

From these results, another question arose: would this reaction be coordinated bysteric or electronic effects (or even by both)? To answer this question, we decided to replace the 3-methyl group by an isoelectronic and smaller fluorine atom in the new structures **A’** and **B’** and running only single point calculations with the same base. We did this because 3-fluorophenol was one of the 3-substituted phenols examined in the scope of the selective *ortho*-cyanation reaction substrate in the article [38]. According tothe results returned by MOLPROJ, the main reaction site, when a *meta*-fluorine atom is present, remains at the C2 atom in the aromatic ring, as can be seen below in Table III.

Table III: results for the degree of localization of MOs from fluorinated structures **A’** and **B’** (derived from 3-fluorophenol) as returned by MOLPROJ.

Structure	**HOMO**			**Shape-based FERMO**			
	Átomo	**Γ_{HOMO}**	**Energy (eV)**	**Átomo**	**Γ_{FERMO}**	**Relative Position**	**Energy (eV)**
A’	C2	0.128708	-178.436400	**C2**	**0.593728**	**HOMO-1**	-189.616440
	C6	0.459591		C6	0.325620	HOMO-1	
B’	C2	0.129347	-177.251760	**C2**	**0.591391**	**HOMO-1**	-189.246240
	C6	0.461176		C6	0.331944	HOMO-1	

Looking at the results, we can see that the reaction path depends on two factors: the size of the substituent and its position. This can be explained by the fact that, in the presence of substituents with heavy atoms, the steric effect will drive the reaction path. Knowing that the volume of an atom or any substituting group is practically expressed by its electronic density, thus, the steric effect can be interpreted as an electronic repulsion. This electronic repulsion then makes it difficult to approach the substituent, making the electrophilic substitution reaction unfeasible, as occurs in the studied reaction. Now thinking about lower size groups, as in the case of fluorine, we can think about non- classical models. In other words, we are analyzing the electronic density of FERMO to correctly predict which carbon atoms would be the reaction site of this reaction. Therefore, the attractive interactions between the frontier orbitals will be responsible forthe reaction site in the cyanation reaction in cases where the substituent is not bulky.

Conclusion

The MOLPROJ software, based on the use of projection operators for quantifying the FERMO localization, was employed again successfully now for phenol protonation. It is possible to obtain different values for the localization degrees of MOs according to any combination of AOs. It returns as results not only the localization degree of the MOs in the subspace of one or more AOs as well as the energy of each of them. The code allows identifying the FERMOs based on the joint analysis of the localization coefficients and orbital energies.

The FERMO concept can be applied to find the protonation site for phenols. It was possible, even with different environments in which the experimental compounds were inserted, to have an idea of the preferred protonation site of these molecules. We obtained approximately 86% of correctness of the protonation sites using our theoretical methodology. It was also possible to rationalize a reaction with only experimental results that the reaction path depended on two factors: the size of the substituent and its position. In the presence of bulky substituents, the steric effect will direct the path of the reaction. In lower size groups, the attractive interactions between the frontier orbitals will be responsible for the reaction site in the cyanation reaction.

Acknowledgements

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ARTIGO 3 - Toward Metal- and Catalyst-free Reactions: Deciphering the substituent and external electric field effects on the Diels-Alder reaction between Ethylene and Nitrosoethylene

Submited in Computational and Theoretical Chemistry

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 (BH_3) 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: $SnCl_4$, $ZnCl_2$, BH_3 or $AlCl_3$,, which can accelerate cycloaddition reactions [3,4], as occurs in the reaction catalyzed by $AlCl_3$ 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].

Computational studies seek diverse approaches to rationalize reactivity properties. The reactivity, regioselectivity, and stereoselectivity of Diels-Alder (DA) reactions can be comprehended by analyzing the molecular orbitals participating in the reaction [8]. 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 [9–12]. 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].

An alternative approach to consider involves utilizing electron density localizations at corresponding atomic positions as a reactivity metric [13,14]. Electron density refers to the distribution of electrons within a molecule [15]. The Hirshfeld method, pioneered by R. F. W. Bader and G. H. F. Diercksen, partitions the molecular electron density into contributions from individual atoms [16]. This method defines a set of atomic volumes that encompass the entire molecular space and assigns electron density to each atom based on its volume overlap with these atomic volumes. The Hirshfeld charges represent the proportion of electron density associated with each atom within the molecular framework [17].

Molecular orbitals and electron density are interconnected in comprehending the electronic structure of molecules. Molecular orbitals describe the permissible energy states of electrons, whereas electron density reveals the likelihood of locating electrons in different regions of the molecule based on the distribution of these molecular orbitals. Together, they offer a comprehensive depiction of the electronic behavior and properties of the molecule.

Molecular Electron Density Theory (MEDT) also examines the distribution of electron density in organic reactions [15,18]. This theory is founded on the notion that while the distribution of electron density in the ground state governs physical and chemical molecular properties, the capacity for changes in electron density is accountable for molecular reactivity. In recent theoretical investigations, this approach has discovered applications in establishing a contemporary rationale and comprehension of molecular mechanisms and reactivity in Organic Chemistry, notably in reactions such as the Diels-Alder reaction [18–20].

Within MEDT, properties such as reactivity, regioselectivity, and stereoselectivity are regulated by the electrophilic and nucleophilic behavior of the reactants, as well as by the polar nature of the reactions [21,22]There are artifices to catalyze chemical reactions, in particular the Diels-Alder reactions, such as, for example, the application of an electric field along the reaction axis [23–25]. Chemical reactions can be elucidated through alterations or shifts in electron density. Thinking about it, we can understand that they can then be influenced by external electric fields. Whether 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 [24].

This fact was announced some time ago by Shaik and collaborators for the Diels-Alder reaction [26] and in another work for simple reactions of halogen and hydrogen transfer by Bertrán and collaborators [27,28]. Thus, there is a great interest in metal-free catalysis and specifically in catalysis by hydrogen bonding models [29].

In this scenario, the existence of an external electric field (EEF), properly oriented, has the potential to further stabilize or destabilize these electron density contributors and thus influence the energy [18,23,30–32]. 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 [24,33].

Theoretical predictions were confirmed experimentally in 2016 by means of intermittent tunneling scanning microscopy (STM) experiments [23]. 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 [33]. 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 [33]. 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 [24].

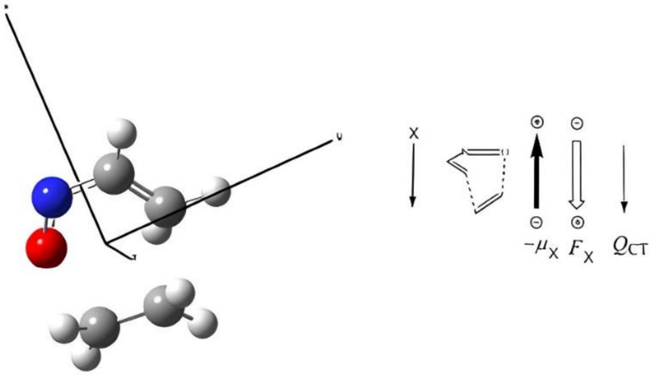
Since electrostatic catalysis remains one of the least developed forms of catalysis in synthetic chemistry [23], the objective of this study was to contrast the activation barriers of electric field catalysis with those of Lewis acid catalysis, and to examine the impact of substituents on the diene and dienophile of the Diels-Alder reaction between ethylene and nitrosoethylene. This comparison aims to establish that electric field catalysis holds promise as a significant branch of catalytic processes.

2 Methodology

Gaussian09 software was used for all calculations [34]. 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 Hirshfeld charges are derived through population analysis using the 'pop=Hirshfeld' keyword. In Gaussian software, conducting a Parr analysis on a Diels-Alder reaction entails the computation of atomic charges for the reactants. For each optimized geometry, a Mulliken population analysis was executed within the Gaussian input file, utilizing the keyword 'pop=(Mulliken)'. The dipole moment was determined for the reaction both without an electric field and with an electric field aligned along the reaction axis, where the field strength was set to -0.125 atomic units. This computation employed the 'Polar' keyword within the Gaussian input file.

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 $F_{x,y,z}$ 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 [25]. Thus, whenever the dipole moment (μ) 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. The arrows establish the positive direction of the field and align with the z-component of the molecular dipole moment, denoted as m_x, following Gaussian 03's convention. Referring to Scheme 1, it becomes evident that a positive Fx causes a negative mx to manifest within the molecule [24,25,35].



Scheme 1: Definitions of the x, y and z directions and The stabilizing interaction mode of F_x with mx, and the direction of electron flow. The empty arrow shows the positive F_x direction. Q_{CT} is the amount of charge transfer in the noted direction.

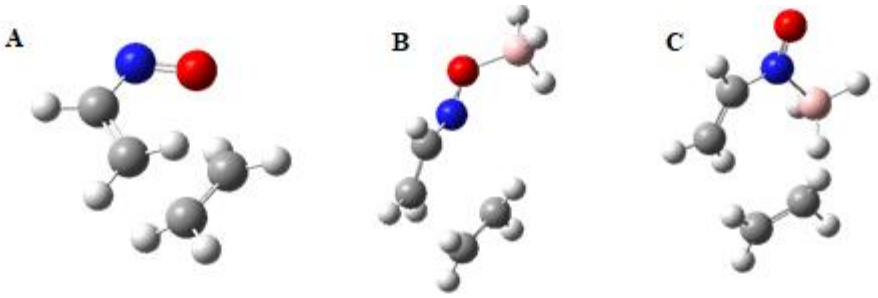


Figure 1: Reactants (A) nitrosoethylene and ethylene, (B) nitrosoethylene with borane connected to oxygen and ethylene and (C) nitrosoethylene with borane connected to nitrogen and ethylene.

The optimized compounds, as shown in Figure 1, were analyzed using the MOLPROJ software [36,37]. 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. [38]. For comparison, degree of localization coefficients were calculated for the molecular orbitals Γ_{HOMO} and Γ_{FERMO}. We define that the degree of localization Γ_{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 C, is the matrix of molecular orbital coefficients and S is the overlap matrix:

$$\Gamma_{FERMO} = \sqrt{\sum_{l} \sum_{i \in G} \sum_{j \in G} \sum_{k} C_{l\mu} S_{li} S_{ij}^{-1} S_{jk} C_{k\mu}}$$

Equation 1: degree of localization Γ_{FERMO}

3 Results

3.1 The Reaction of Ethylene and Nitrosoethylene - Catalysis of a Diels-Alder reaction using a Lewis acid and effect of the substituents to check if the reaction rate becomes even lower when they are related to some type of catalyst

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. In recent years, there has been a renewed surge of interest in the chemistry of nitrosoarenes. This revived attention is attributed, in part, to their multifaceted applications in synthetic organic chemistry, their importance as reactive metabolites, and their value as spin traps [39]. C-nitroso compounds have found widespread use in synthetic organic chemistry, enabling the incorporation of a broad spectrum of moieties containing nitrogen and/or oxygen-based functional groups [40].

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 α-haloximes. Jursic and Zdravkovski, in 1995 [41], showed in a study the difference in the activation barrier when BH_3 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 [41] 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})

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 [41]. 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 [42]. So, as BH_3 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.

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: CH_3, Cl and F. Viewing the reaction as an inverse electron-demand process, interactions take place from the dienophile's HOMO/FERMO to the diene's LUMO, as illustrated in Figure 2A. Table 1 presents the activation barrier values obtained when substituting a diene hydrogen with X = halogen (Y = Cl and F), as well as replacing a dienophile hydrogen with methyl.

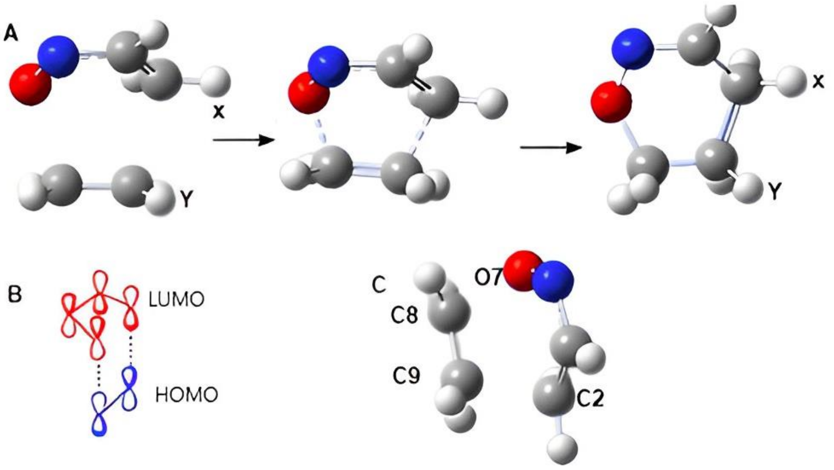


Figure 2: reaction scheme for the Diels-Alder reaction between ethylene and substituted nitrosoehtylene. (A) structures of reactants (left), transition state (middle) and products (right); (B) molecular orbitals involved in the reaction; (C) numbering of the atoms involved in Diels-Alder reaction.

Table 1: activation barrier values when we replace a diene hydrogen with halogen (Cl and F) and a dienophile hydrogen with methyl.

Electron-donating(X)	**Electron-withdrawing (Y)**	**$\Delta E^{\#}$ (kcal.mol^{1}) MP3/631G(d)**
Cl	**CH_3**	18.7730
F		18.0871

As evident, the substituents accelerated the reaction by about 1.93 kcal/mol when contrasting the reaction without any catalyst. According to Jursic and Zdravkovski [28], the reaction between ethylene and nitrosoethylene follows an inverse demand mechanism. Thus, a withdrawing substituent from the diene is capable of reducing the energy of the LUMO. Upon attachment of a withdrawing substituent to the molecule, it draws electron density towards itself, affecting not only the overall electron distribution but also the electron distribution within molecular orbitals, including the LUMO [43]. Conversely, methyl, an electron-donating substituent that contributes electron density through hyperconjugation, can elevate the energy level of the dienophile's HOMO orbital. This reduction in energy gap between the HOMO and LUMO orbitals leads to a reaction acceleration of approximately 1.93 kcal/mol.

Comparing the activation barrier values of Cl and F substituents, it becomes evident that the lowest activation barrier is observed when hydrogen is replaced by a fluorine atom, as anticipated. This disparity can be attributed to electronegativity: atoms or groups with higher electronegativity tend to withdraw electron density more effectively from the molecule, resulting in greater LUMO stabilization.

3.2 Effect of the electric field in the reaction between ethylene and nitrosoethylene

Table 2 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 F_y and F_z 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 $F_x > 0$, the barrier remains constant. However, when F_x is negative ($F_x < 0$) 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 2: values of activation barrier ($\Delta E^{\#}$) with electric field applied in x-, y- and z-axes for two magnitude values of electric field.

F (au)	**$\Delta E^{\#}$ (kcal.mol^{-1}) MP3/6-31G(d)**		
	x	**y**	**z**
0.080	21.0811	18.0074	18.3262
-0.080	17.9453	18.2201	18.3186
0.0	18.3262	18.3262	18.3262
0.125	20.9811	18.2000	18.6625
-0.125	6.3938	18.0000	18.4103

As the field becomes more negative, the dipole moment becomes more positive. The total dipole moment for the reaction without an electric field was 2.8733 Debye, whereas for the catalyzed reaction with EEF=-0.125 au, the dipole moment was 3.5939 Debye. When an external electric field is introduced to a molecule or system, it imparts force upon the charges within the molecule, inducing a torque on them. The charges strive to align themselves with the direction of the electric field, leading to an augmentation in the molecule's dipole moment magnitude. This alignment effect can cause an increment in the molecule's dipole moment, and the response is characterized by its molecular polarizability. A higher polarizability signifies that the molecule is more susceptible to the influence of the electric field, resulting in a greater alteration in the dipole moment [44].

This change in dipole moment is accompanied by transferring eléctron density between the reactants in the TS. As the value of F_x increases, the direction of electron density 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 electron density in its own direction, from nitrosoethylene to ethylene. At 0 atomic units (a.u.) of electric field, no external electric field is exerted. As a result, the molecule's dipole moment is solely determined by its inherent structure and polarity. 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 [24]. EEF changes distribution of the electron density. Figure 3 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 [45]. 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 [46].

We used the FERMO concept [36] 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 [47].

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 [36,38].

The values in Table 3 to four atoms involved in the Diels-Alder reaction (carbons: C2, C8, C9 and O, as shown in the Figure 2C) 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 [36]. The degree of localization of molecular orbitals pertains to the extent to which the electrons within the orbital are confined within a molecule's spatial domain. This measurement characterizes the degree of localization or delocalization of the electron density within the molecular orbital [48]. When electron density experiences augmentation due to the presence of an electric field, it signifies that the field induces a redistribution of electron density within the molecule or system. The heightened localization of the Highest Occupied Molecular Orbital (HOMO) implies that the field is impacting the distribution of charge and electron density around the Frontier Molecular Orbital (FERMO), suggesting the molecule's response to the electric field and its adjustment of electronic structure accordingly. The increased polarizability of the molecule under the influence of an electric field can impact its interactions with other molecules or external stimuli.

Table 3: Results for the degree of localization of MOs from TS between ethylene and nitrosoethylene.

Without EEF						
Atom	**HOMO**	**Energy (eV)**	**HOMO-1**	**Energy (eV)**	**HOMO-2**	**Energy (eV)**
O	0.643098	-140.3058	0.3750	-181.1018	0.348421	-225.0075
C2	0.158948	-140.3058	0.2003	-181.1018	0.550036	-225.0075
C8	0.034416	-140.3058	0.4971	-181.1018	0.282893	-225.0075
C9	0.174964	-140.3058	0.2854	-181.1018	0.550790	-225.0075
With EEF						
Atom	**HOMO**	**Energy (eV)**	**HOMO-1**	**Energy (eV)**	**HOMO-2**	**Energy (eV)**
O	0.637059	-141.4904	0.342834	-185.2480	0.370436	-218.3439
C2	0.167188	-141.4904	0.164733	-185.2480	0.565620	-218.3439
C8	0.042363	-141.4904	0.505992	-185.2480	0.214219	-218.3439
C9	0.188071	-141.4904	0.326526	-185.2480	0.521364	-218.3439

Comparing the MOLPROJ results with the values derived from the Hirshfeld charges (Table 4), certain similarities can be discerned in the alterations in the degree of localization and the changes in Hirshfeld charges for individual atoms. To illustrate, in the case of oxygen

(O), both the degree of localization and the Hirshfeld charge exhibited reduction when subjected to the applied electric field, signifying a decrease in electron density or localization around the oxygen atom. Conversely, for Carbon 8 and Carbon 9, both the degree of localization and the Hirshfeld charges demonstrated augmentation upon exposure to the electric field, implying an upsurge in electron density or localization around these carbon atoms. Nevertheless, distinctions between the two datasets also manifest. For instance, in the case of Carbon 2, while the degree of localization increased, the Hirshfeld charge decreased in response to the electric field. These variations can be attributed to the intricate interplay of factors that impact molecular orbitals and electron densities, encompassing the influence of the applied electric field and the specific molecular environment.

Furthermore, the electron density can also be comprehended in terms of the Parr function(P_k^+, P_k^-). The Parr function is a method used to partition the electron density of a molecule or system into contributions corresponding to individual atomic nuclei. When an electric field is introduced, it can influence the distribution of electron density, resulting in alterations to the values of the Parr function. According to Domingos [21], Parr functions are obtained through straightforward unrestricted calculations conducted on the radical anion (dienophile) and the radical cation (diene) of a molecule. The dienophile component, representing the Highest Occupied Molecular Orbital (HOMO) in the reaction, experiences electrophilic attack, whereas the diene component undergoes nucleophilic attack [22,43].

Examining the values presented in Table 5 reveals that, in the case of the diene, the Parr function values for both oxygen and carbon atoms rise upon application of an electric field. This observation suggests that the electron density surrounding these atoms is influenced, leading to a redistribution of electron density due to the presence of the external electric field. For the dienophile, alterations in the Parr function values indicate that the electron density around carbon atoms C8 and C9 in the dienophile undergoes redistribution due to the applied electric field. The decrease in the Parr function value for C8 implies a reduction in electron density around that carbon atom, while the increase in the Parr function value for C9 suggests an augmentation in electron density around that carbon atom. Upon analyzing the trend in the distribution of electronic density when the electric field is applied to the diene and dienophile components, a similarity emerges among the MOLPROJ, Hirshfeld charges, and Parr function data, indicating a consistent pattern regarding electronic density distribution.

To ascertain which component is more susceptible to electrophilic attack based on Parr function values, it is necessary to identify the component with comparatively lower electron density, usually manifested by less negative or positive Parr function values [43]. Electrophilic attacks manifest in regions characterized by lower electron density, corresponding to less negative or positive values within the Parr function. By comparing the Parr function values for the carbon atom in the diene (-0.4846) and the carbon atom in the dienophile (-0.1700), it is evident that the carbon atom in the dienophile exhibits a less negative value, indicative of lower electron density. As a result, the carbon atom in the dienophile is more likely to experience electrophilic attack.

Electrophilic attacks are facilitated by electron-deficient species known as electrophiles. In this scenario, the carbon atom in the dienophile emerges as a prospective electrophile owing to its reduced electron density. It can undergo an attack from a nucleophile, such as the oxygen atom in the diene, leading to the establishment of a fresh chemical bond within a reaction, such as the Diels-Alder reaction.

Table 4: Results for the charge Hirshfeld of atoms involved in the Diels-Alder reaction between ethylene and nitrosoethylene.

	Atom	**Hirshfeld**
Reactants without EEF	O	-0.1769
	C2	-0.0244
	C8	-0.0699
	C9	-0.0692
Reactants with EEF (x-0.125 au)	O	-0.1650
	C2	-0.0215
	C8	-0.0787
	C9	-0.0856

Table 5: Results for the Parr function of atoms involved in diene and dienophile without and with EEF in the Diels-Alder reaction between ethylene and nitrosoethylene.

	Atom	(P_k^+/P_k^-)
Diene without EEF	O	-0.3225
	C2	-0.3438
Diene with EEF (x-0.125 au)	O	-0.6138
	C2	-0.4846
Dienophile without EEF	C8	-0.3529
	C9	-0.3529

Dienophile with EEF (x-0.125 au)	C8	-0.1700
	C9	-0.4846

The electric field exerts a force on charged particles, such as electrons, and can induce changes in the spatial distribution of electrons. 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 [49,50]. Molecular orbitals and electron density are intertwined in comprehending the electronic structure of molecules. Molecular orbitals delineate the permissible energy states of electrons, while electron density discloses the likelihood of encountering electrons within various regions of the molecule, contingent upon the distribution of these molecular orbitals. Together, they can promote a comprehensive depiction of the electronic behavior and properties of the molecule.

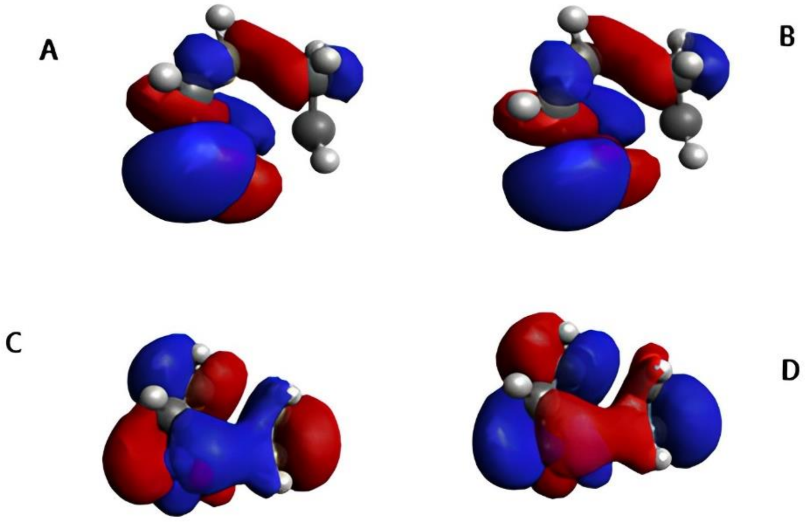


Figure 3: TS between ethylene and nitrosoethylene. A) HOMO of TS without EEF; B) HOMO of TS with EEF; C) LUMO of TS without EEF; and D) LUMO of TS with EEF.

Table 6: Values of activation barrier ($\Delta E^{\#}$) with an external electric field applied in x-, y- and z-axes for two electric field magnitudes for substituents Cl/CH_3 and F/CH_3.

Cl /CH_3			
F (au)	**$\Delta E^{\#}$ (kcal.mol^{-1}) MP3/6-31G(d)**		
	x-axis	**y-axis**	**z-axis**
0.080	18.1957	19.2015	18.7811
-0.080	19.1200	18.1938	19.0760
0.125	18.1097	19.4795	18.7799
-0.125	19.4149	17.2180	19.8849

F/ CH_3			
F (au)	**$\Delta E^{\#}$ (kcal.mol^{-1}) MP3/6-31G(d)**		
	x-axis	**y-axis**	**z-axis**
0.080	19.8002	17.4327	17.6611
-0.080	17.4740	16.3609	18.2930
0.125	16.3985	17.4013	17.3756
-0.125	19.8849	16.0804	18.6958

As it can be seen in Table 6, only the substituent effect shows a decrease in activation barriers, the value was 18.7730 and 18.0871 kcal.mol^{-1} to CH_3/Cl and CH_3/F, respectively. However, when the electric field is applied, its value decreases by around 1,6 kcal.mol^{-1} Cl/CH_3 and 2,0 kcal.mol^{-1} F/CH_3. 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 [41], the reaction between nitrosoethylene and ethylene, when catalyzed with borane, is a Diels-Alder reaction with inverse electron demand. Therefore, when we introduced electron withdrawing groups in the diene, we would find a lower value in the activation barrier, as it can be seen in the tables. It is noted that when substituting hydrogen atoms with withdrawing and donor substituents in the constituents of the Diels-Alder reaction, the reaction axis yielding the lowest activation barrier value remains consistent in both instances as the Y axis, even though the field value remains at -0.125. The addition of substituents to a molecule can lead to a change in the reaction axis in a chemical reaction due to a variety of electronic and steric factors. These effects modify the electron density distribution and the spatial configuration of atoms within the reacting molecules, subsequently influencing the favored approach or orientation during the reaction. 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 4 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.

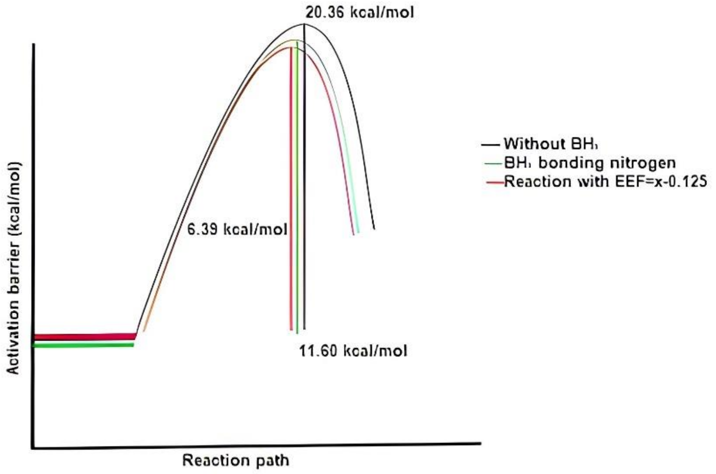


Figure 4: Difference in the energy of the activation barrier without BH_3, with the borane bonding in nitrogen and reaction with EEF.

Conclusion

In this study, the DA reaction between ethylene and nitrosoethylene with/without BH_3, 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.

Using 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. This principle can align with the analysis of electron density through Hirshfeld charges and the Parr function. The substituent effect does show a decrease in activation barriers: accelerated the reaction by around 1.93 kcal.mol^{-1} when comparing the reaction without any type of catalyst. When the electric field was applied, its value decreases on average 1.8 kcalmol^{-1}.

Our findings revealed that the most effective approach to accelerate the Diels-Alder reaction between nitroethylene and nitrosoethylene was by employing the electric field as a "catalyst" along the x-axis, with a value of EEF=-0.125 au, closely followed by BH_3, which can decrease the energy gap between the HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) orbitals.

Acknowledgements

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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6 ANEXO

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