A THEORETICAL STUDY OF THE CYCLOADDITION REACTION BETWEEN *N*-MESYLNITROINDOLES AND ISOPRENE ASSISTED BY MICROWAVE IRRADIATION. PROTIC IONIC LIQUIDS *VS* FREE SOLVENT.

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Abstract

In this study we analyzed the behavior of *N*-mesyl-nitroindoles acting as electrophilic dienophiles in polar Diels-Alder reactions joint to isoprene as nucleophilicdiene. The analysis was developed considering the experimental results when microwave irradiation with toluene or protic ionic liquids as solvents were used. In a similar way, the free solvent conditions were analyzed. These results were compared with the ones of conventional heating and it was found that the reactions under microwave irradiation are better than those developed in thermal conditions. Considering the mechanism study, a unique and notably asynchronous transition state was found. We can note that, in the presence of an ionic liquid, the charge transfer is higher in relation with free solvent conditions. Based on the vibration frequencies, the microwave effect looks to be independent of the solvent used. As a consequence of the theoretical study we can conclude that for these reactions the free solvent condition and protic ionic liquids as solvent offer similar results under microwave irradiation. However the solvent-free condition is far more favorable to environmental sustainability.

Keywords: Nitroindoles, Microwave Irradiation, Solvent Effects, DFT, Theoretical Study, Cycloaddition Reactions, Ionic Liquids.

INTRODUCTION

In organic synthesis, one of the more important reactions is the Diels-Alder (DA) cycloaddition. With its property to form carbon-carbon, carbon-heteroatom, and heteroatomheteroatom bonds, the reaction underlines the preparation of diverse carbocyclic and heterocyclic compounds. For this reason, the reaction has been used as a key step in the synthesis of many natural products with biological properties.[1] Its application not only leads to a strong increase in molecular complexity, but also can result in structures that lend themselves to additional amplification of complexity by the use of other powerful synthetic transformations.[2]

Due to our interest in the cycloaddition reactions of substituted aromatic heterocycles with electron-withdrawing groups, we have reported studies related to the electrophilic character of aromatic compounds with adequate substitution in their reactions with different dienes. In this process, the electrophiles react with dienes trough polar Diels-Alder (PDA) reactions to obtain in one step the respective cycloadducts aromatized. In general, these cited polar cycloaddition is a domino process initialized by a DA reaction to give the formally [$4\pi+2\pi$] cycloadduct, followed by the subsequent concert irreversible elimination of nitrous acid which is the responsible factor for the feasibility of the overall process.[3] Considering the potential influence of the solvents and its specific effect, the reactions were opportunely developed under conventional thermal conditions and using toluene or protic ionic liquids (PILs) as reaction media. The experimental results showed that using neoteric solvents the reactions were faster that those developed in traditional organic solvent. [4]

The microwave-assisted controlled heating has become a powerful tool in organic synthesis. This condition is being used to accelerate organic reactions and generally increase the yield. The region of the microwave (MW) irradiation is located between the infrared and radio waves. In the MW region, the electromagnetic energy affects the molecular rotation without changing in the molecular structure.[5] The application of MW in organic synthesis has been improved over the last years. This methodology results in better reaction rates and yields. Using MW irradiation, the reaction mixture undergoes heating by a combination of thermal effect, dipolar polarization and ionic conduction. Then the polar compound can absorb energy very efficiently.[6] This proceeding has been

employed successfully observing even modifications of the selectivity, although the MW effect is a topic of discussion yet.[7]

OBJECTIVES

Considering the influence of MW irradiation to improve organic reaction, the principal aim of this work is to study theoretically, using the Density Functional Theory (DFT), the cycloaddition reactions of *N*-mesyl nitroindoles with isoprene using MW irradiation in presence of PILs as solvent and complementary in free solvent conditions. Specially the last one could be important due to the favorable impact on the environment.

METHODOLOGY

All calculations were carried out within the DFT framework using the Gaussian 09 suite of programs.[8] For this purpose, the hybrid functional B3LYP was used together with the 6–31G(d) basis set.[9] Scan function of the Gaussian 09 program was used to obtain the potential energy surface (PES) and the transition state structures (TSs) were optimized. Optimization of reactants, products and TSs were carried out using the Berny analytical gradient optimization method.[10] The vibration frequencies were calculated in order to validate the optimized structures. In this sense, reactants and cycloadduct (CA) structures were verified by the absence of negative frequencies. On the other hand, the transition states (TSs) structures were verified by the presence of only one imaginary frequency and the intrinsic reaction coordinate (IRC) calculation. The electronic structures of critical points were analyzed by the natural bond orbital (NBO) method.[11] Solvent effects were considered at the same level of theory by geometry optimization of the system structures based on the supermolecular approach.

RESULTS AND DISCUSSION

In order to understand the effects of PILs and free solvent conditions under MW irradiation in P-DA processes, the reactions between 2-nitro-*N*-mesylindole **(1)**, 3-nitro-*N*-mesylindole **(2)**, and 5-nitro-*N*-mesylindole **(3)** with isoprene **(4)**, as models in the absence and in the presence of [HMIM][BF$_4$] as a PIL were theoretically studied. For this purpose, in all cases the reactions were analyzed until the formation of the DA product (cycloadduct) result of the endo/para approach mode of **4** respect to the electron-withdrawing (EW) nitro group was analyzed **(Scheme 1)**.
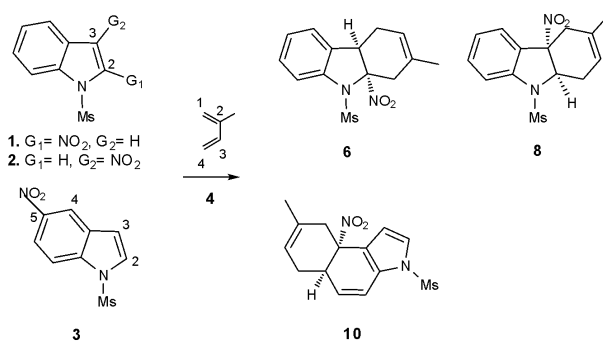
Scheme 1. Diels-Alder reactions of *N*-mesyl-nitroindoles with isoprene.

Analysis of the potential energy surfaces (PES) associated with this process indicates that the cycloaddition takes place through a one-step mechanism via a high asynchronous TS. Therefore, reagents, one TS and the formal [4+2] CA were located and characterized.

The effects of the [HMIM][BF$_4$] in this P-DA reactions were evaluated employing the supermolecular approach, particularly considering the implicit effects of the PIL by forming a hydrogen bond (HB) between the acidic hydrogen of HMIM cation and the oxygen of the nitro group. The counter BF$_4$ anion was also included to minimize the positive charge present in the HMIM cation. The results of relative energy are summarized in **Table 1**.

In the gas-phase, the activation energy associated with the nucleophilic attack of the C$_1$ carbon of **4** on the C$_3$ carbon of **1** via TS **(5a)** presents a value of 18.09 kcal/mol and the formation of the CA **(6)** is exothermic by −29.67 kcal/mol. When the effect of the PIL is considered **(5b)**, the activation energy value decreases to 13.53 kcal/mol and the

formation of the CA value changes to -28.46 kcal/mol. In the case of the reaction between **2** and **4**, the nucleophilic attack of the C_1 of the diene on the C_2 carbon of dienophile via TS **(7a)** presents an activation energy value of 17.37 kcal/mol and the formation of the CA **(8)** is exothermic by –25.94 kcal/mol. When the effect of the PIL is considered **(7b)**, the activation energy value decreases to 12.49 kcal/mol and the formation of the CA value changes to -22.34 kcal/mol. On the other hand, in the reaction between **3** and **4** the activation energy associated with the nucleophilic attack of the C_1 of the diene on the C_4 carbon of dienophile via TS **(9a)** presents a value of 29.80 kcal/mol and the formation of the CA **(10)** is exothermic by –5.34 kcal/mol. Once again, under the effect of the PIL **(9b)**, the activation energy value, decreases to 26.11 kcal/mol and the formation of the CA value changes to -4.36 kcal/mol. In this sense, the P-DA reactions involving 2- and 3- *N*-mesyl-nitroindoles are thermodynamically more favorable and the activation energies lower in relation to the reaction that involves *N*-mesyl-5-nitroindole. This is expected because in the last case the reaction involves the loss of the aromaticity of the benzene ring. Besides, the activation energies decrease when PILs are used making the process more favorable. As expected, the presence of the nitro group in the heterocyclic moiety is more favorable that when it is in benzene moiety.

Table 1. Activation energies and enthalpies of reaction of Diels-Alder reactions of *N*-mesyl-nitrolindoles with isoprene in presence and in absence of [HMIM][BF$_4$] as PIL.

Molecule	ΔE(kcal/mol)	
	Gas-Phase	[HMIM][BF$_4$]
2-nitro-*N*-mesylindole	-	-
Isoprene	-	-
TS	18.09	13.53
CA	-29.67	-28.46
3-nitro-*N*-mesylindole	-	-
Isoprene	-	-
TS	17.37	12.49
CA	-25.94	-22.34
5-nitro-*N*-mesylindole	-	-
Isoprene	-	-
TS	29.8	26.11
CA	-5.34	-4.36

The gas-phase geometry of the TS and TS-PIL of every reaction is given in **Figure 1**. The lengths of C_3–C_1 and C_2–C_4 forming bonds at TS are 1.99 and 2.71 Å (Δr = 0.72 Å), respectively in the reaction between **1** and **4**. When the effect of the PIL is considered, this values changes to 1.95 and 3.07 Å (Δr = 1.12 Å), respectively. The lengths of C_2–C_1 and C_3–C_4 forming bonds at TS are 1.89 and 3.02 Å (Δr = 1.13 Å), respectively in the reaction between **2** and **4**. When the effect of the PIL is considered, this values changes to 1.92 and 3.22 Å (Δr = 1.30 Å), respectively. The lengths of C_4–C_1 and C_5–C_4 forming bonds at TS are 1.74 and 2.67 Å (Δr = 0.93 Å), respectively in the reaction between **3** and **4**. When the effect of the PIL is considered, this values changes to 1.68 and 2.63 Å (Δr = 0.95 Å), respectively. These values suggest a mechanism with highly asynchronous TS. The bond formation between the most nucleophilic center of the diene and the most electrophilic center of dienophile takes place in the first stage of the reaction, and the second bond formation takes place at the second stage of the reaction. The effect of the PIL increases the asyncronism of the reactions considering the changes in the values of Δr.

The polar nature of the DA reactions was evaluated analyzing the charge transfer (CT) at TSs. The natural charges were shared between the indole derivatives and the isoprene frameworks. At TS, the CT that flows from isoprene to the dienophile is 0.25 eV, 0.90 eV and 0.27 eV in the reaction of **1**, **2** and **3**, respectively. When PIL is considered, the CT values increase to 0.35 eV, 0.96 eV and 0.36 eV, respectively. This values point out the zwitterionic character of the TSs.

The large acceleration found, in terms of reaction times in the presence of the PIL ionic pair can be understood as an increase of the polar character of the reaction as a consequence of the HB formation, which favors the CT process.[12] This leads to a lower activation energies values and high asynchronous reactions.

Electron localization function (ELF)[13] studies devoted to the bonding changes along P-DA reactions have suggested that the main electronic changes from reagents to TSs are related to the reduction of the C–C double-bond character in the diene and dienophile.[14] An analysis of the displacement vectors of the IR frequency vibrations of

the reactive systems shows the presence of stretching vibrations with atomic movements similar to the electronic changes involved in the formation of the corresponding TSs.

The stretching vibration of **5a** and **5b** are 1393 cm-1 and 1390 cm-1 respectively. In the case of **7a**, the stretching vibration is 1404 cm-1 and 1401 cm-1 for **7b**. Similarly, the stretching vibration of **9a** is 1383cm-1 and 1380 cm-1 for **9b**. This means that any additional energy comprised between 1700 and 1400 cm-1 can favor the process by favoring the electronic changes needed to reach the TS geometry. Consequently, experimentally it's observed a decrease in the reaction time. Note that the stretching vibration values between TS and TS-PIL are similar within systems, which means that the MW effects should be similar in both cases. This is in agreement with the experimental results of similar yields and reaction times.
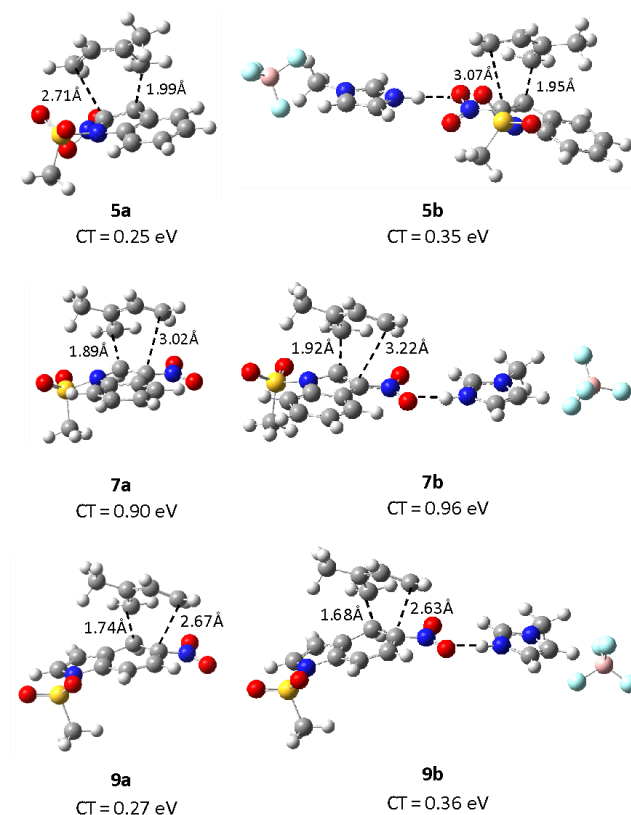

Figure 1. Transition states of Diels-Alder reactions of *N*-mesyl-nitrolindoles with isoprene in presence and in absence of [HMIM][BF$_4$] as PIL.

CONCLUSIONS

The *N*-mesyl-nitroindoles explored in this work react as dienophilic electrophiles with isoprene under microwave heat following a polar cycloaddition process with normal electron demand. The presence of the nitro substituent induces the electrophilic behavior in the ring in which it is present. This group is responsible of the reaction orientation and the selectivity observed.

The mechanistic analysis of this reactions shows that the TS is unique and asynchronous. Moreover, the theoretical calculations are coincident with the experimental results. We can note that, in the presence of a PIL, the charge transfer is higher in relation with free solvent conditions. This is traduced in a more polar reaction and a decrease of the activation energy. However, based on the ELF, we can consider that the effect of MW is practically the same when we use a PIL or free solvent conditions due to the similar stretching vibrations observed in both cases. Then, the MW effect looks to be independent of the solvent used. Moreover, the reactions under MW irradiation are better than those developed in thermal conditions.

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