THEORETICAL STUDY OF POTENTIALLY COMPLEX REACTIONS TO THE CYCLOADDITION PROCESS OF QUINOLINES IN HETERO DIELS-ALDER SYSTEMS.

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Abstract.

In previous works, reactivity of 3-nitropyridine acting as an electrophilic dienophile in polar Diels-Alder (P-DA) reactions with different dienes has been theoretically studied using DFT methods. It was observed that this aromatic heterocyclic system would suffer cycloadditions reaching isoquinoleine derivatives. The present DFT study establishes to continue with the computational calculation in this kind of systems, now using quinolines as dienes (azadienes) facing nitrofuran derivatives to get aza-compounds that can be used as precursors in organic chemical synthesis of biologically active molecules. Analysis of the DFT reactivity indices at the ground state of the reagents correctly explains the reactivity and regioseletivity of these P-DA reactions. Reaction mechanisms were also evaluated.

Keywords. Quinoline, DFT, Diels-Alder, Azadiene

INTRODUCTION

Diels-Alder (DA) cycloaddition is one of the most important and useful organic chemistry reaction since it is a widely used method to form carbon-carbon, carbon-heteroatom and heteroatom-heteroatom bonds. It is a [4π + 2π] pericyclic process, in which a conjugated diene undergoes addition reaction with another component (dienophile) in a stereospecific way, to produce a cyclic adduct of six members. Forming binding interactions occur only between occupied and unoccupied orbitals (one from each reaction component) according to the frontier molecular orbital theory (FMO). In normal demand, such interaction results from a charge transfer from the HOMO of the diene -which acts as nucleophile- to the LUMO of the dienophile -which acts as the electrophile- to form the first sigma bond. Consequently, the dienophile becomes more nucleophilic and the diene, which has lost electrons, more electrophilic. Then a new charge transfer occurs, this time from the dienophile to the diene, to form the second sigma bond.

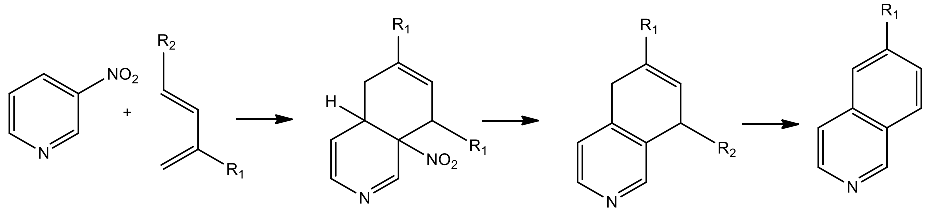
According to our studies of the mechanism involved, these cycloadditions are part of concerted asynchronous processes. Depending on the degree of asynchrony, the reaction can be carried out in the presence of one or two transition states.

In the last years it has been consider and proved that heterocycles could act as dienophiles in this kind of cycloaddition reactions when these compounds are properly activated with electron-withdrawing groups (EWGs). According to the mechanism of these reactions involving electrophilic heterocyclic aromatic compounds can be consider as *two-stage one-step* reactions via highly asynchronous transition states (TSs) with a high polar character, characteristic of polar Diels-Alder (P-DA) reactions.

In this way we have been working with P-DA reactions using aromatic carbo- and heterocyclic nitro-substituted dienophiles and different dienes. Now, and in a theoretical form, we add to the analysis some azaheterocycles acting as dienes or dienophiles.

Particularly, pyridines and quinolines are very important precursors in organic chemical synthesis, for example for the production of anticancer, anti-inflammatory and antimicrobial drugs.

The reactions of 3-nitropyridine with isoprene, 1-methoxy-1,3-butadiene, and the Danishefsky's diene yielding dihydroisoquinoleine or isoquinoleines are domino processes that comprises several steps (Figure 1). These domino reactions begin by a P-DA reaction between 3-nitropyridine and some dienes yielding the formal [4+2] cycloaducts (CA). The subsequent nitroso acid elimination in these CAs affords dihydroisoquinoleines, which may be aromatized forming quinoline derivatives.



1

2 (R_1=CH_3, R_2=H)
3 (R_1=H, R_2= OCH_3)
4 (R_1=$OSi(CH_3)_3$, R_2=OCH_3)

5 (R_1=CH_3, R_2=H)
6 (R_1=H, R_2= OCH_3)
7(R_1=$OSi(CH_3)_3$, R_2=OCH_3)

8 (R_1=CH_3, R_2=H)
9 (R_1=H, R_2= OCH_3)
10(R_1=$OSi(CH_3)_3$, R_2=OCH_3)

11 (R_1=CH_3)
12 (R_1=H)
13 (R_1=OH)

Figure 1. *Reaction of 3-nitropyridine with different dienes*

Now, employing azadienes in hetero Diels-Alder reaction has become an important point in the formation of nitrogen heterocycles that are part of many natural and unnatural bioactive compounds.

On the other hand, computational methods are useful for a proper interpretation or rationalization of experimental facts and for planning chemical experiments or predicting behaviors, providing information about molecular geometry, chemical reactivity, energy of molecules, transition and intermediates states of the reaction, among other things.

In this work, theoretical calculations based on Density Functional Theory (DFT) were made in order to analyze the energy of the hetero Diels- Alder reaction when the quinoline is used as azadiene, so we can assess the feasibility of which it is carried out and the possibility of experimental realization.

OBJECTIVES

Considering the importance to synthesize nitrogen heterocyclic compounds, the possibility of using the quinolines substituted (with the groups: -Ph, -NH_2, -CH_3) in positions 2- and 4- as azadienes in aromatic hetero Diels-Alder reactions with 2- and 3-nitrofuran acting as dienophiles was studied. For this, a theoretical mechanistic study was enhanced based on the DFT. The analysis was made analyzing activation energy values of each of the reactions.

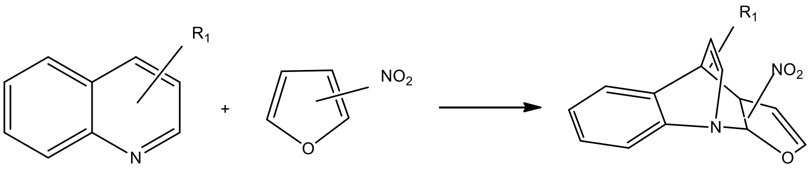
METHODOLOGY

DFT calculations were performed using B3LYP functional with 6-31G(d) basis set. Geometries of each of the molecules involved (reactants and products) were optimized and the calculations of their vibration frequencies were performed to ensure that we are in presence of a total minimum energy value.

Scan function of the Gaussian 09 program was used to obtain the potential energy surface and the transition state structure was optimized, verifying their validity with the calculation of the vibration frequencies and the intrinsic reaction coordinate (IRC). Thereafter the values of the activation energies of each of the reactions were calculated.

RESULTS

It was found that although the degree of asynchrony of the reaction varies depending on the substituents employed, the mechanism has a single transition state in all cases. (Figure 2)



$R_1 = NH_2$; Ph; Me

***Figure 2**. Reaction scheme of substituted quinolines with nitrofurans .*

Asynchrony react may be analyzing the values of the distances bond forming atoms involved in the transition state (Figure 3). C-N distance (1.69 Å) is shorter than the C-C (2.34 Å) one, which indicates that the degree of formation of C-N bond is higher than the C-C. This is expected since the greatest electron donor character of the nitrogen atom favors the initial load transfer from the diene to dienophile .

***Figure 3**. Structure of the transition state between the quinoline and 3- nitrofuran .*

The energy values of each of the molecules, as well as differences in energy to the sum of the energies of the starting reagents, are presented in Table 1 .

		E (kcal/mol)	ΔE
1	Quinoline	-252130.07	-
	3-nitrofuran	-272618.27	-
	TS	-524697.20	**51.14**
	CA	-524717.78	**30.56**
2	2-fenilquinoline	-397071.89	-
	3-nitrofuran	-272618.27	-
	TS	-669642.20	**47.96**
	CA	-669661.78	**28.38**
3	4-aminoquinoline	-286856.15	-
	3-nitrofuran	-272618.27	-
	TS	-559429.99	**44.43**
	CA	-559435.91	**38.51**
4	2-aminoquinoline	-286861.38	-
	3-nitrofuran	-272618.27	-
	TS	-559431.21	**48.44**
	CA	-559446.99	**32.66**
5	2-methylquinoline	-276787.35	-
	3-nitrofuran	-272618.27	-
	TS	-549356.00	**49.62**
	CA	-549376.25	**29.37**
6	Quinoline	-252130.07	-
	2-nitrofuran	-272617.04	-
	TS	-524697.25	**49.86**
	CA	-524715.95	**31.16**

***Table 1**. Energy of activation and reaction enthalpies .*

ΔE values for TS correspond to the activation energy of this reaction and ΔE values for resulting cycloadducts (CA) correspond to the enthalpy of the reaction (Figure 4).

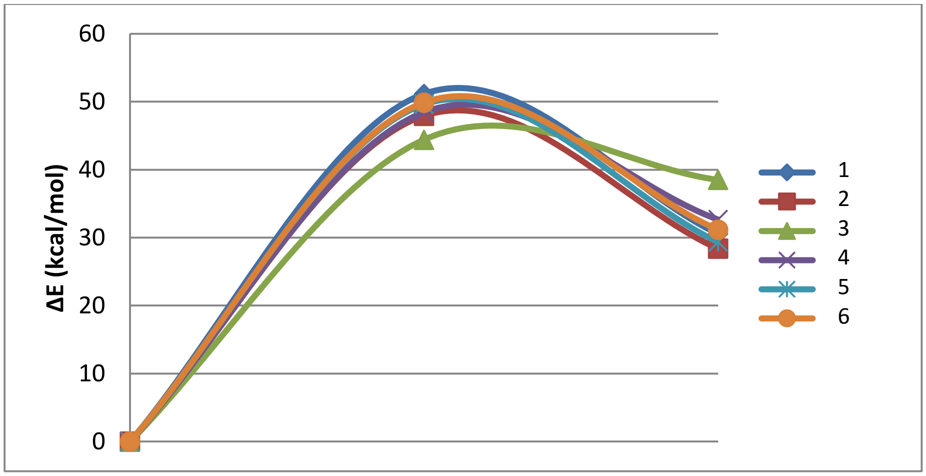


***Figure 4**. Reaction coordinate diagrams*

It is noted that the value of activation energy for the reaction of the quinoline with 3-nitrofuran is slightly larger (about 1.30 kcal / mol) to 2-nitrofuran.

Furthermore, the electron donor substituents in position 2- of the quinoline increases its nucleophilic character as the initial stage of the reaction is a charge transfer from the diene to the dienophile, reducing the activation energy reaction. It is observed that the methyl group produces a decrease of about 1.5 kcal/mol, the amino group of 2.7 kcal/mol and the phenyl group of 3.2 kcal/mol. The biggest donor character of the substituent is accompanied by a larger decrease in activation energy.

When the donor substituent is incorporated into the position 4 of quinoline, the effect of decreasing the energy is greater, resulting in a decrease of 6.7 kcal/mol when the amino group is employed.

Finally, it is noteworthy that the energy difference values of cycloadducts over the amount of energy of the reactants are positive, indicating that the reaction is endergonic and reversible.

CONCLUSIONS

The hetero Diels -Alder reaction using quinoline as azadiene has an asynchronous concerted mechanism in the presence of a single transition state.

The activation energy is within the expected values for cycloadditions, whereby the reaction is feasible in experimentally if the reversibility thereof is controlled.

The electron donores substituents on the quinoline favor the reaction decreasing the activation energy, and its most marked effect is on the position 4.

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