Full Length Research Paper

Ab initio study of intramolecular hetero-Diels-Alder reaction of ABT-773

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Diels-Alder reaction is a known reaction in chemistry. Theoretical study of intramolecular hetero-Diels-Alder reaction of ABT-773 is the subject of the present research. Calculations have been performed in two method of Hartree-fock and B3LYP and by using 6-31G* basis set. The proposed transition state for the reaction was confirmed by DFT method, while the HF method has not been able to predict the transition state. Effect of the temperature and solvent has also been studied which is in good consistency with the experimental results.

Key words: DFT, transition state, Diels-Alder reaction, ABT-773.

INTRODUCTION

The Diels-Alder reaction is one of the useful synthetic reactions in chemistry which falls within the group of cycloaddition reactions. In this reaction one diene reacts with one olefin or acetylared dieneophile to produce a six member adduct.

The usefulness of the Diels-Alder reaction is related to its high degree of variation and its considerable stereochemistry. By changing the nature of diene and dieneophile different carboccylated structure could be produced (Domingo et al., 2003). These peculiarities were the reasons for the Diels-Alder reaction to become the subject matter of many articles in recent years (Noorizadeh and Maihami, 2006; Kotha et al., 2007; Zdravkovski, 2004; Alen et al., 2007; Mellese et al., 2006; Mekelleche and Benhabib, 2004).

Recently, Stoner et al. (2005) have reported a Diels-Alder reaction in which Abbott's ketolides **1** (ABT-773, a subclass of macrolide antibiotics based on the erythromycin skeleton) and its cis isomer **3** are converted into adducts **2** and **4** respectively. Structures of compounds used in this project have been shown in Figure 1. The experiments performed by Stoner et al. (2005) along with proposed mechanism are the subject of theoretical study

in this project.

CALCULATION METHOD

All calculations were done by using the *Gaussian98* package (Frisch et al., 1998). Optimized geometrical shape of structures under study have been obtained by using the HF and B3LYP (Lee et al., 1988) method and 6-31G* basis set. Frequency calculations for the structures under study have been performed by using the same methods and basis set. In order to study the solvent effect (here a mixture of water + methanol), PCM model (Tamasi and Persico, 2007) and B3LYP method were used.

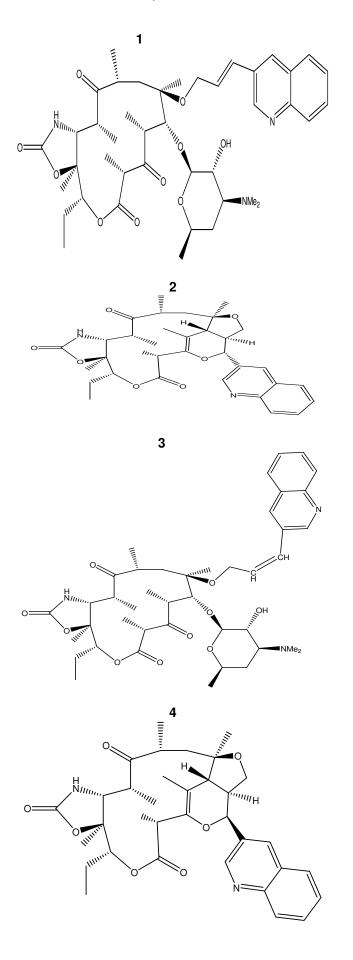The dielectric constant of mixed solvent is obtained by:

$$\langle \varepsilon \rangle = \frac{n_1 \varepsilon_1 + n_2 \varepsilon_2}{n_1 + n_2} \quad \text{formula,}$$

in which the n's are representatives of quantity of constituents of the solvent and ε are their corresponding dielectric constants (Munishkina et al., 2003).

RESULTS AND DISCUSSION

All optimized structures studied in this study have been shown in Figure 1. To study the issue that whether the process is stereoselective in relation to double bond geometry or not, the probability of conversion of different

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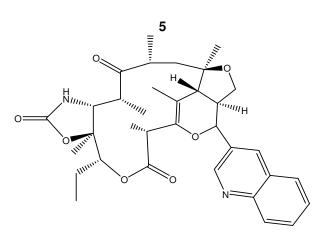
1

2

3

4

5

Figure 1. Structures of compounds used in this study.

structures ($1 \rightarrow 2$, $1 \rightarrow 3$, $2 \rightarrow 4$ and $3 \rightarrow 4$) with regard to the values of its gibbs free energy has been investigated. The different stages of conversions could be summarized as in Figure 2.

The Gibbs free energy values of each structure and its variations for different conversions shown in Figure 1 have been obtained with regard to frequency calculations as well as by considering the Zero Point Energy corrections, and reported in Table 1.

Regarding the values presented in the Table, it is observed that values of Gibbs free energy variations for conversions of **1** to **2** and **3** to **4** is negative and for conversion of **1** to **3** and **2** to **4** is positive, therefore there is no possibility of conversion of **1** into cis isomer and no possibility for internal conversion of their corresponding products. In other words, the process of cycloaddition relative to geometry of double bond is stereoselective, for this reason, in Figure 2 the conversions of **1** into **3** and **2** into **4** have been shown with dotted arrow. These results are consistence with the experimental results reported by Stoner et al. (2005).

Study of transition state

Regarding the experimental observations rendered by stoner et al. (2005) a probable mechanism for conversion of structure **1** into structure **2** has been suggested in which the initial enolization of the diene system causes β-elimination of the desosamine suger, culminating in the production of the presumed transitional enone **5**, in subsequent stage after the **5** react with 6-o-quinolin during Diel-Alder reaction, **2** is formed. To investigate this transition state, structure **1** was used as an archetype and by elimination of two hydrogen and desosamine sugar the intermediate **5** was formed. To obtain probable reaction vector, torsion angle of 6-o-quinoline was arranged in such a way that olefin and 6-o-quinolin were located fairly parallel with each other. The structure form

Table 1. The Gibbs free energy values of different structures under study along with Gibbs free energy variations for different conversions.

Compound	1	2	3	4
G (KJ/mol)	-393901.0	-420730.5	-371848.0	-416284.0
	$\Delta G_{1\rightarrow 2}$	$\Delta G_{1\rightarrow 3}$	$\Delta G_{2\rightarrow 4}$	$\Delta G_{3\rightarrow 4}$
	-26829.5	+22053.0	+4446.5	-44436.0

Table 2. Gibbs free energy values of structures **1** and **5** along with $\Delta G^*_{1\rightarrow 5}$ and rate constants of conversion of **1** to **2** in two temperature 298 (K) and 348 (K).

G (KJ/mol)	298(K)	348(K)
1	-393901.0	-646844.0
5	-426085.0	-683971.0
$\Delta G^*_{1\rightarrow 5}$	-3284.0	-37127.0
k	2.69×10^{18}	2.73×10^{18}

Table 3. Gibbs free energy values of structures 1 and 2 along with equilibrium constant of its conversion.

G (KJ/mol)	Gas phase	Solvent phase
1	-393901.0	-288590.3
2	-420730.5	-320425.1
$\Delta G_{1\rightarrow 2}$	-26829.5	-31834.8
K	50186.5	378029.8

in this circumstance was optimized by the two methods of HF/6-31G* and B3LYP/6-31G*.

In order to specify whether this structure is corresponding to a minimum or to a transition state, frequency calculations were performed for the optimized structure of pervious stage with same methods. The transition state is a saddle point on potential energy surface which correspond to one and only one imaginary frequency in frequency calculations. The number of imaginary frequencies for structure **5** by using two methods of HF and B3LYP were *zero* and *one* respectively, meaning that structure **5** corresponds to a transition state in B3LYP method. Lack of ability of HF method in predicting the transition state could be attributed to ignoring the electron correlation effect in this method.

Study of temperature effect

To study the effect of temperature, frequency calculations were performed on structures **1** and transition state **5** by using B3LYP/6-31G* method in two temperatures 25 C and 50 C. with regard to the following equations, rate constant of conversion of **1** to **2** in the two temperatures were obtained.

$$\Delta G^* = G^*_{TS} - G_1 \tag{1}$$

$$k = \frac{\kappa T}{h} \exp\left(-\frac{\Delta G^*}{RT}\right) \tag{2}$$

Gibbs free energy values along with rate constants have been presented in Table 2.

Regarding the values obtained for rate constant, it is recognized that the rate of reaction increases with increase in temperatures, although increase in the rate constant is not high. This is consistent with experiments performed by stoner et al. (2005).

Solvent effect

To study solvent effects, frequency calculations have been done for compounds **1** and **2** in water + methanol solvent with ratio of 1:1. regarding the calculations performed, Gibbs free energy values have been obtained for two structures in solvent. Equilibrium constant for conversion of **1** into **2** has been obtained by the following equations and reported in Table 3 along with Gibbs free energy values.

$$\Delta G_{1\rightarrow 2} = G_2 - G_1 \tag{3}$$

$$\Delta G = -RT \ln K \tag{4}$$

Regarding the values obtained for equilibrium constant it is recognized that the ratios of **1** to **2** increase in solvent phase.

Conclusion

To study the new Diel-alder reaction introduced by Stoner et al. (2005) we used HF and B3LYP *ab initio* method along with 6-31G* basis set. Proposed transition state confirmed with B3LYP/6-31G*, while HF method unable to predict this transition state. Also, temperature and solvent effects studied, which is in good consistency with the experimental results.

REFERENCES

Alen J, Smets WJ, Dobrzańska L, De Borggraeve WM, Compernolle F,Hoornaert GJ (2007). Eur. J. Organ. Chem. (2007). p. 965.
Al-Laham MA, Peng CY, Nanayakkara A, Gonzalez C, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C,

Head-Gordon M, Replogle ES, Pople JA (1998). Gaussian 98, Revision A.7. Gaussian, Inc., Pittsburgh PA.

Domingo LR, Jose AM, Perez P, Conteas R (2003). J. Org. Chem. 68: 3884.

Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery Jr. JA, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Kotha S, Kalyaneswar M, Banerjee S, Mobin SM (2007). Eur. J. Organ. Chem. p. 1244.

Lee C, Yang W, Parr RG (1988). Phys. Rev. B 37: 785.

Mekelleche SM, Benhabib R (2004). J. Mol. Structure (Theochem). 709: 31.

Mellese EM, Bayer A, Lars KH, Odd Gautun R (2006). Eur. J. Organ. Chem. p. 5249.

Munishkina LA, Phelan C, Uversky VN, Fink AL (2003). Biochem. p. 422720.

Noorizadeh S, Maihami H (2006). J. Mol. Structure (Theochem) 763: 133–144.

Stoner EJ, Allen MS, Christesen AC, Henry RF, Hollis LS, Keyes R, Marsden I, Rehm TC, Shiroor SG, Soni NB, Stewart KD (2005). J. Org. Chem. 70(8): 3332.

Tamasi J, Persico M (2007). Chem. Rev. 94: 2027.

Zdravkovski Z (2004). J. Mol. Structure (Theochem) p. 68499.