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Quantum chemistry study on the regioselective behavior of 1,3-dipolar cycloaddition reaction of azides with various substituted cyclooctynes

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ABSTRACT

The 1,3-Dipolar cycloaddition reactions are the classic reaction in modern synthetic organic chemistry.The Huisgen cycloaddition is the reaction of a dipolarophile with a 1,3-dipolar compound that leads to 5-membered heterocycles. With the goal of identifying alkyne-like reagents for use in azide-alkyne Huisgen cycloaddition reactions, we used density functional theory (DFT) and polarized continuum model (PCM) computations. In this respect, we investigated the structure and energy of transition states in the reaction path and assessed the trends in the calculated activation barriers for the1,3-dipolar cycloaddition of azides with various substituted cyclooctynes in the gas and solution phases to interpret theoretically the origin of regioselectivity in the synthesis of disubstituted 1,2,3-triazole derivatives.

Keywords: 1,3-Dipolar cycloaddition; density functional theory; 1,2,3-triazole; polarized continuum model**.**

1. Introduction

The azide-alkyne Huisgen cycloaddition is a 1,3- dipolar cycloaddition reaction between an azide and a terminal or internal alkyne to give a 1,2,3-triazole compound. Rolf Huisgen

[1] was the first to understand the scope of this organic reaction (Fig. 1).

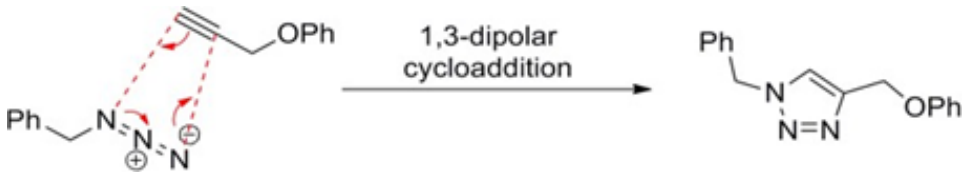

Fig. 1: 1,3-dipolar cycloaddition reactions.

In 2001, Sharpless and Meldal independently proposed processes in which azide and alkyne produce 1,2,3 triazoles in the presence of copper catalyst at room temperature, entitled as click reaction [2]. 1,2,3-Triazole derivatives are pharmacologically important class of compounds. They are chemically stable, inert to severe hydrolytic, oxidizing and reducing conditions even at high temperatures. Their derivatives show anti-HIV [3], anti-bacterial [4], anti- histamine [5] and anti-tumor [6] activity. Besides their pharmacological features, they are used in agro chemistry, dye industry and anti-corrosion agent [7].

Recently, the Bertozzi group [8] demonstrated a new strain-release cyclooctyne labelling reagent (Fig. 2) that proceeds azide-alkyne cycloaddition reaction in the absence of a Cu catalyst at physiological temperatures. Thus, these labeling reagents that avoid using copper are highly desirable.

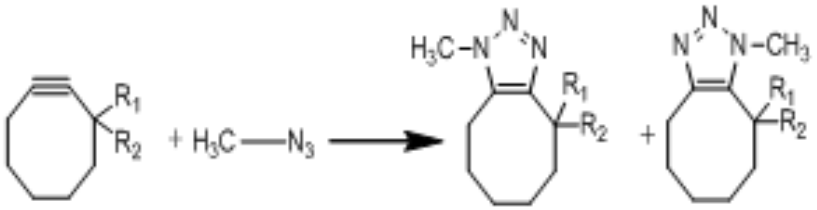

Fig. 2: azide–alkyne cycloaddition reactions.

In this research, we have focused on the regioselective behaviour of the aforementioned azide-alkyne cycloaddition reaction in the presence of various substituted cyclooctynes (with hydrogen and fluorine) using density functional theory (DFT) [9] and polarized continuum model (PCM) [10] approaches. Quantum calculation of molecular energies and energy gradients in solution by a conductor solvent model.

2. Experimental

Computational details

All calculations were performed using the M08-HX/6- 311+G** level of theory with no symmetry constrains in geometry optimization procedure. It is important to mention that M08-HX functional has been introduced as a modern hybrid meta-GGA (generalized gradient approximation) exchange-correlation functional combined with Hartree-Fock exchange contribution [11].

We also utilized harmonic frequency analysis to confirm that the found optimized geometries correspond to the true minima or saddle points. In order to assess the solvent effects, PCM calculations have been performed based on a continuum representation of the solvent surrounding the substances. The GAMESS suite of programs [12] has been employed in DFT calculations.

3. Results and discussion

We first concentrated on non-substituted cyclooctyne and two fluorinated cyclooctyne models. To determine how various substituents affect the reactivity of cyclooctyne with methyl azide.

Table1: Activation energy for transition states TS1 and TS2 and reaction energy for the production of Isomer1 and Isomer 2 (in kcal/mol), calculated at M08-HX/6-311+G** level of theory.

			Activation energy		**Reaction energy**	
Reactant	**R_1**	**R_2**	**TS1**	**TS2**	**Isomer1**	**Isomer2**
1a	H	H	10.805	-	-82.887	-
1b	H	F	9.532	6.327	-78.825	-78.930
1c	F	F	7.507	4.219	-80.905	-86.118

We calculated the activation energies and the reaction energies in gas phase at M08-HX/6-311+G** level of theory (that were reported in Table 1) for the formation of 1,2,3- triazole regioisomers (as illustrated in Fig. 3).

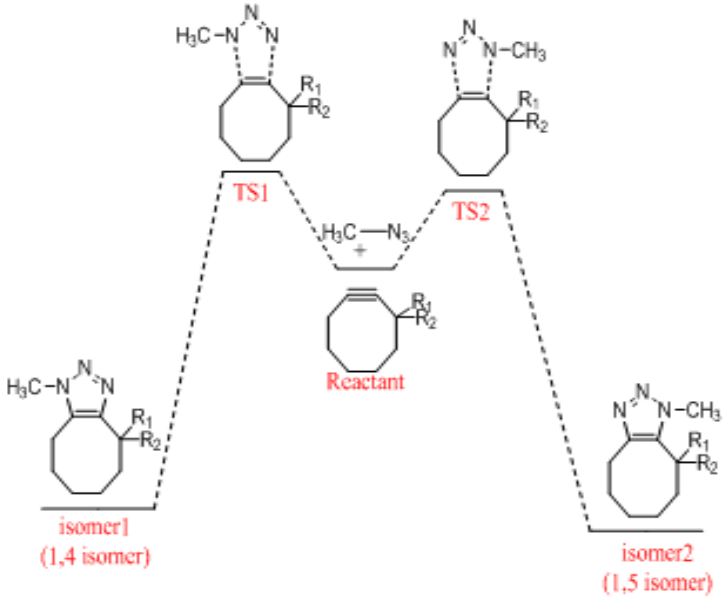

Fig. 3: azide–cyclooctyne cycloaddition reaction pathways.

In Fig. 4, we have presented the obtained structure of TS1 and TS2 calculated at M08-HX/6-311+G** level of theory.

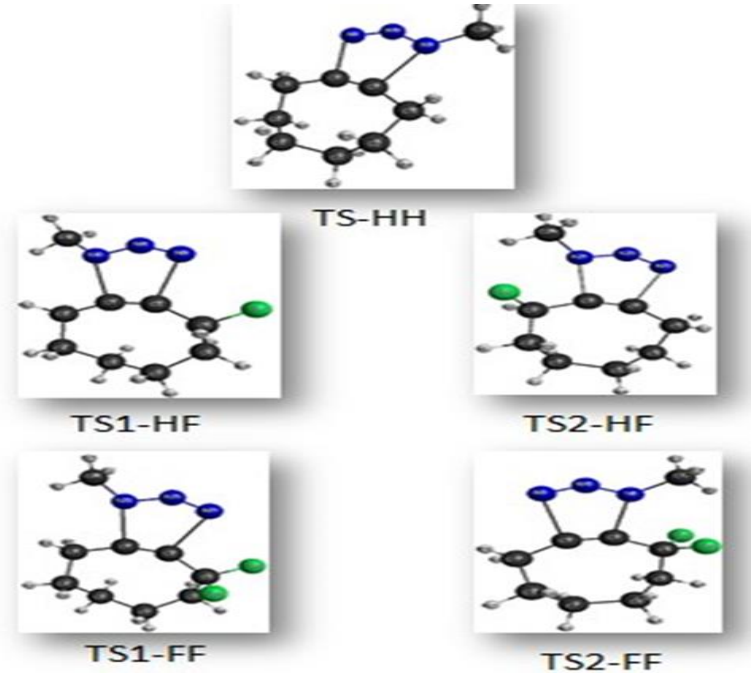

Fig. 4: The obtained structures of TS1 and TS2 calculated at M08-HX/6-311+G** level of theory

Then, we calculated reaction energies in solution phase at M08-HX/6-311+G** level of theory in two solvents, dimethyl formamide (DMF) and ethanol (Table 2).

Table 2: Reaction energy, ΔE_r, (in kcal/mol) for the production of Isomer1 and Isomer2 in two solution phases atcalculated M08-HX/6-311+G** level of theory

		Solution phases ΔE_r	
R_1	**R_2**	**DMF**	**ethanol**
H	**H**	Product=-85.774	Product=-85.714
H	**F**	Isomer1=-86.872 Isomer2=-85.689	Isomer1=-86.870 Isomer2=-85.667
F	**F**	Isomer1=-84.480 Isomer2=-85.893	Isomer1=-84.405 Isomer2=-85.890

4. Conclusions

The comparison of calculated reaction energies in the gas and solution phases reveals that there is no considerable preference between the productions of two region-isomers. While our calculated reaction activation energies indicate that the production of Isomer2 is more favorable from the kinetic viewpoint. Moreover, cycloaddition of methyl azide and FF substituted cyclooctyne corresponds with the lower activation energy and is more convenient kinetically. Comparative analysis of PCM computations show that applying DMF as solvent decrease the reaction energies and so can be considered as more appropriate solvent.

Acknowledgment

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