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The strain-promoted alkyne-nitrone and alkyne-nitrile oxide cycloaddition reactions: A theoretical study

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ABSTRACT

Density functional theory (DFT) calculations were performed to study the mechanism of bioorthogonal strain-promoted dibenzocyclooctyne (DIBO)-nitrone and DIBO-nitrile oxide cycloaddition (CA) reactions at B3LYP/6-31G(d,p), M06-2X/6-31G(d,p) and B3LYP-D3/6-31G(d,p) levels of theory. The potential energy surface analysis, synchronicity indices and global electron density transfer (GEDT) calculations at the transition states (TSs) show that these cycloadditions take place through a nearly synchronous mechanism with non-polar character. The strain and electronic effects on the reactivity of DIBO with nitrone and nitrile oxide were studied using a distortion/interaction transition state model and compared with CA reactions of these dipoles with acetylene as a strain-free reaction. The electron-reorganizations along these CA reactions have been studied using the topological analysis of the electron localization function (ELF) at the B3LYP/6-31G(d,p) level. The ELF topological patterns indicate a one-step *two-stage* mechanism for both reactions in which the formation of C–O single bonds takes place after the formation of C–C bonds.

1. Introduction

The cycloaddition (CA) reaction of azides with alkynes, is a useful tool for the selective bioorthogonal chemical modification of living cells.[1] To avoid copper toxicity, strain-promoted azide–cyclooctyne couplings with appropriate reactivity was reported by Bertozzi and co-workers in 2004.[2] Intracellular azide-cyclooctyne reaction takes place within several hours at room temperature,[3] which permits in vivo biological imaging.[4,5] Dibenzocyclooctyne (DIBO) reagents, with more sp^2-centers, have further reactivity enhancements over cyclooctyne as a result of an increase in ring strain. Accordingly, the DIBO cycloaddition reaction with benzyl azide is almost three times faster than simple cyclooctynes.[1]

Nitrone and DIBO were used for the preparation of N-alkylated isoxazoline under copper-free conditions by Boons, Van Delft and co-workers in 2010.[6] An interesting observation of this study was that the reaction of DIBO with nitrone was 32 times faster than the CA reaction with benzyl azide. This method was used for peptide and protein modifications. Pezacki and co-workers, in 2011, reported the strain-promoted cycloadditions of cyclooctynes with cyclic nitrones, which were 59 times faster than the similar reaction of azides.[7] This strategy provides a convenient tool for the direct labeling of proteins and live cell imaging of cancer cells.[8–10]

In 2011, Singh and Heaney reported a solid phase modification of DNA through the strain-promoted cyclooctyne–nitrile oxide reaction.[11] This reaction occurred in an aqueous environment under atmospheric conditions at room temperature, and was completed in 10 min. Carell and co-workers also described a rapid copper-free [3 + 2] CA reaction between a nitrile oxide and norbornene-modified DNA to selectively label the oligonucleotides.[12] Boons et al. have reported bioorthogonal strain-promoted [3 + 2] CA reactions between nitrile oxide and nitrone derivatives with DIBO (Scheme 1).[6,13] The rates of these reactions were much faster than similar cycloadditions with azides. The anomeric center of the carbohydrates was functionalized with various tags by this method.

In 2007, Houk introduced a general theoretical model for [3 + 2] CA reactivity based on distortion/interaction energy.[14,15] In this model, the activation energy is the sum of destabilizing distortions and stabilizing interactions. However, the reactivity of 1,3-dipoles and dipolarophiles in CA reactions is controlled by the distortion energies of the reactants to their transition state geometries. They confirmed the applicability of this model in [3 + 2] CA reactions of nine dipoles with ethylene and acetylene.[14,15] Houk et al. also reported DFT calculations on the transition states of the [3 + 2] CA

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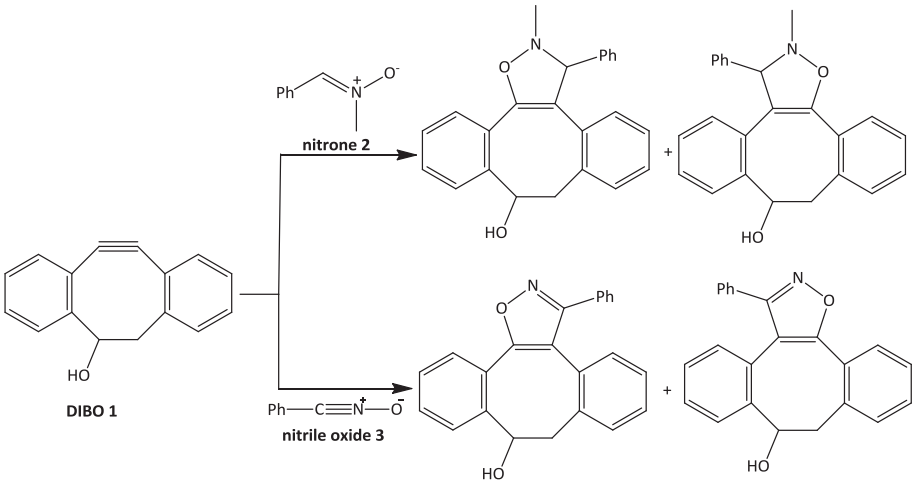

Scheme 1. The strain-promoted cycloaddition reactions of **nitrone 2-DIBO 1** and **nitrile oxide 3-DIBO 1**.[6,13]

reaction of phenyl azide with acetylene, cyclooctyne, and difluorocyclooctyne.[16] A good correlation between distortion energy of reactants and the activation energy of the cycloadditions was established. In addition, they found that the rate of cycloaddition of fluorocyclooctynes increased through increasing interaction energies.

A powerful tool for the study of the bonding changes along an organic reaction is the electron localization function (ELF).[17] Recent ELF studies along [3 + 2] CA reactions revealed that both non-polar[18] and polar[19] processes take place through pseudoradical centers. On the other hand, formation of two new single bonds proceeded at two different phases of the intrinsic reaction coordinate (IRC), thus these reactions were characterized by a one-step *two-stage* mechanism.[20]

In this work, as a part of our research program on [3 + 2] CA reactions,[21–28] a density functional theory (DFT) study on the strain-promoted alkyne-nitrone and alkyne-nitrile oxide cycloaddition reaction (Scheme 1), reported by Boons and co-workers,[6,13] was carried out. Nitrones and nitrile oxides are allyl anion and propargyl/allenyl anion dipoles with C–N–O motifs, whereas nitrones are bent dipoles and nitrile oxides are linear. Here, the strain and electronic effects on the reactivity of DIBO with nitrile oxide and nitrone were investigated using the distortion/interaction transition state model. For the first time, the mechanisms of these [3 + 2] CA reactions have been described on the basis of the electron localization function (ELF) topological analysis.

2. Computational methods

DFT calculations were carried out with the Gaussian 09 suite of programs,[29] using the B3LYP, M06-2X and B3LP-D3, together with the standard 6-31G(d,p) basis set. The optimizations of transition states were carried out using the Berny analytical gradient optimization method and no symmetrical restriction was applied through geometrical optimizations. The stationary points were characterized by frequency computations in order to confirm that the TSs have one and only one imaginary frequency. The intrinsic reaction coordinate (IRC) path[30] was traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO)[31,32] method and by the topological analysis of the ELF. The ELF study was performed with the TopMod program.[33]

3. Results and discussions

The global electrophilicity index, which measures the total ability to attract electrons, is the ratio $\omega = \mu^2/(2\eta)$, where μ is the electronic chemical potential and η is the chemical hardness.[34] The electronic chemical potential (μ) is defined as the mean value of the one electron energies of the frontier molecular orbitals and η is the difference between these energies ($\mu = (E_{HOMO} + E_{LUMO})/2$ and $\eta = (E_{LUMO}-E_{HOMO})$).[34] In Table 1, global indices named the electronic chemical potential, chemical hardness and global electrophilicity index are displayed for the reactants.

Four possible CA reaction pathways of **nitrone 2** and **DIBO 1** are shown in Scheme 2. The similarity of the electronic chemical potentials of the nitrone and DIBO, as well as their electrophilicity indices, chemical hardness and HOMO–LUMO energy gaps imply that both charge transfer directions are important. The polar nature of the [3 + 2] CA reaction between the nitrone and DIBO was investigated from the global electron density transfer (GEDT)[35] for the possible TSs. The GEDT along possible pathways of this reaction was computed from the natural population analysis (NPA) between the dipole and dipolarophile frameworks in the transition states. The calculated charge transfer values that flux from **nitrone 2** to **DIBO 1** at *cis*-TSs and *trans*-TSs are 0.07e and 0.06e, respectively. The low values suggest that this reaction has a non-polar character, in accordance with the similarity in chemical potential and electrophilicity of the reactants.

The mechanisms of four possible reaction pathways were investigated, as shown in Scheme 2. The calculated activation energies, enthalpies and Gibbs free energies as well as the reaction energies, enthalpies, Gibbs free energies, synchronicity (Sy) indices[36] and nucleus independent chemical shifts (NICS)[37] for possible reaction pathways are reported in Table 2. As shown in Table 2, the activation energy barriers associated with these CAs at B3LYP are: 10.2 kcal/mol (TS1-TRA), 12.3 kcal/mol (TS1-CIS),

Table 1
The calculated global properties of **nitrone 2**, **DIBO 1** and **nitrile oxide 3** at HF-311++G(2d,p)//B3LYP/6-31G(d,p).

Structure	μ(a.u.)	η(a.u.)	S(a.u.)	ω (eV)
Nitrone 2	−0.134	0.332	1.506	0.738
DIBO 1	−0.128	0.326	1.536	0.681
Nitrile oxide 3	−0.155	0.367	1.362	0.891