

Toward an understanding of the 1,3-dipolar cycloaddition between diphenylnitrone and a maleimide:bisamide complex. A DFT analysis of the reactivity of symmetrically substituted dipolarophiles

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Received 1 October 2006; accepted 5 December 2006

Available online 28 January 2007

Abstract

The 1,3-dipolar cycloaddition between diphenylnitrone and a maleimide:bisamide complex has been studied using density functional theory (DFT) methods at the B3LYP/6-31G* level. The molecular recognition of the bisamide receptor to maleimide favors the formation of the complex through three hydrogen bonds. However, they are not able to produce an efficient acceleration of the cycloaddition because the symmetric substitution of the dipolarophile sites. This poor capability is discussed in base of the transition state structures and the analysis of the reactivity indexes of the reagents.

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Keywords: 1,3-Dipolar cycloadditions; Molecular recognition; Hydrogen-bonds; DFT calculations

1. Introduction

Cycloaddition reactions are one of the most important processes with both synthetic and mechanistic interest in organic chemistry. Current understanding of the underlying principles in the Diels–Alder [1] (DA) reactions and the 1,3-dipolar cycloadditions [2] (13DC) has grown from a fruitful interplay between theory and experiment. Seminal works by Huisgen and co-workers in the early 1960's led to the elucidation of the mechanism, patterns of reactivity and selectivity in 13DC reactions.

The relative reactivity of cycloadditions was rationalized by Sustmann, who demonstrated that the interaction between the HOMO and LUMO with the smallest energy difference predominates. Within the Frontier Molecular Orbital [3,4] (FMO) theory, Sustmann categorized the 13DC reactions in three different types [5–7]. Type I involves a dominant interaction between the highest occu-

ried molecular orbital (HOMO) of the dipole and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile. An important number of 1,3-DC reactions, including the reaction of nitrones with electron-deficient dipolarophiles, have been accommodated within this classification. Type II is given by the interaction between the LUMO of the dipole and the HOMO of the dipolarophile. They are named also as inverse-electron demand 1,3-DC reactions. Type III may be characterized by the similarity of the HOMO and LUMO energies of the dipole/dipolarophile pair.

The extent to which each type of frontier molecular orbital predominates can be manipulated electronically via enhancement of the HOMO energy or lowering of the LUMO energy. Thus, α,β -unsaturated carbonyl compounds, which participate as activated dipolarophiles in 13DC reactions, can enhance its reactivity by lowering of its LUMO energy. Thus, co-ordination of the oxygen atom to a Lewis acid (LA) increases considerably the dipolarophile reactivity by an increase of the electrophilicity of the α,β -unsaturated carbonyl compound. Hydrogen-bond (HB) formation of polar protic solvents, such as H₂O or

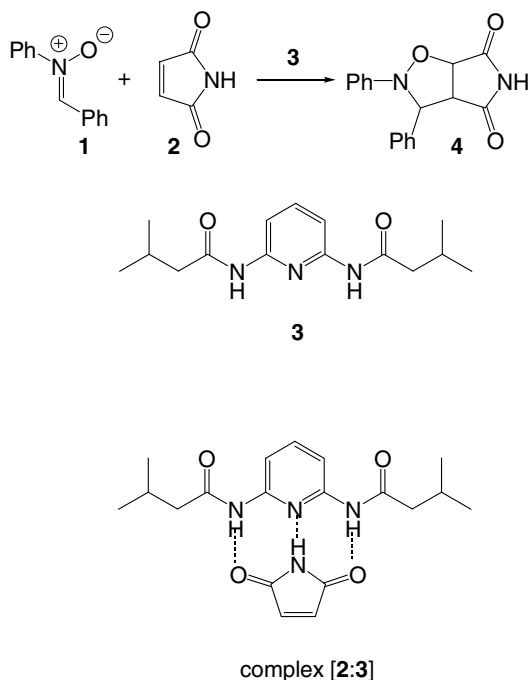
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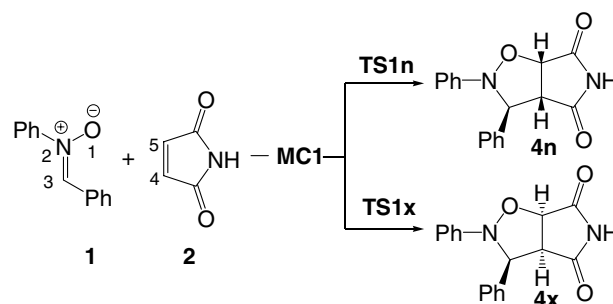
alcohols, to the carbonyl oxygen atom produce a similar activation to those caused by LA. Recently, we have shown that even CHCl_3 solvent is able to catalyze efficiently the DA reactions of carbonyl compounds by HB formation [8,9].

Recently, D. Philp et al. [10] have reported the acceleration of a 13DC reaction of diphenylnitronone **1** with maleimide **2** using a simple symmetric bisamide receptor (see Scheme 1). Kinetic investigations revealed that the formation of 1:1 complex increases the rate of the cycloaddition fivefold. The origin of this acceleration was the formation of a HB complex between the host bisamide and the dipolarophile maleimide **2**.

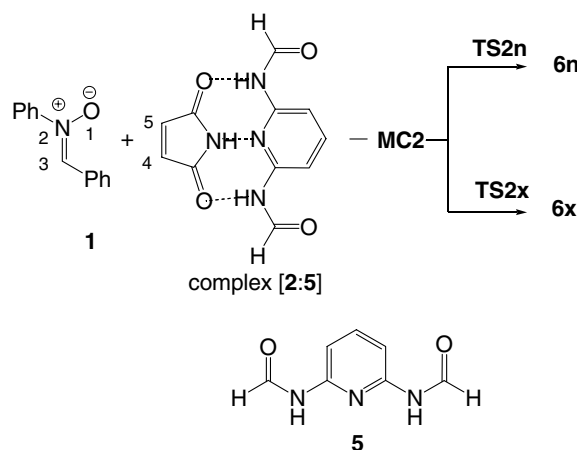
Our interest for the mechanism of cycloaddition reactions, and especially for the effects of the catalysts on the course of the reaction, instigated us to perform a theoretical study for the reactions experimentally studied by Philp. [10] In the present paper, the 13DC reactions of diphenylnitronone **1** with maleimide **2** in absence and in presence of the bisamide **5**, as a reduced model of the bisamide **3** used by Philp, will be studied using the density functional theory (DFT) (see Schemes 2 and 3). Both complete exploration of the potential energy surface (PES) and analysis of the reactivity indexes of the reagents defined within the DFT will be used to understand the poor effect found on the reduction of the activation energy caused by the molecular recognition. Finally, the 13DC reactions between *N*-methylphenylnitronone **10** and acrolein **11** in absence and in presence of pyrocatechol **12** will be analyzed as theoretical reaction models of HB catalyzed 13DC reactions involving asymmetric electron-deficient dipolarophiles (see Scheme 5).



Scheme 1.



Scheme 2.



Scheme 3.

2. Computational methods

DFT calculations were carried out using the B3LYP [11,12] exchange-correlation functionals, together with the standard 6-31G* basis set [13]. The optimizations were carried out using the Berny analytical gradient optimization method [14,15]. The stationary points were characterized by frequency calculations in order to verify that the transition structures (TSs) have one and only one imaginary frequency. The intrinsic reaction coordinate (IRC) [16] path was traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism by using the second order González–Schlegel integration method [17,18]. The electronic structures of stationary points were analyzed by the NBO method [19,20]. All calculations were carried out with the Gaussian 03 suite of programs [21].

Solvent effects have been considered by B3LYP/6-31G* single-point calculations on the gas phase structures using a self-consistent reaction field (SCRF) [22,23] based on the polarizable continuum model (PCM) of the Tomasi's group [24–26]. Since these cycloadditions are carried out in dichloromethane, we have selected its dielectric constant at 298.15 K, $\epsilon = 8.93$.

The global electrophilicity index [27], ω , which measures the energy stabilization when the system acquires an additional electronic charge ΔN from the environment, has

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