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Understanding the regio- and chemoselective polar [3+2] cycloaddition of the Padwa carbonyl ylides with α-methylene ketones. A DFT study

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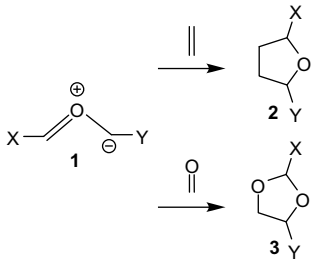
ABSTRACT

The regio- and chemoselective polar [3+2] cycloaddition (32CA) of the Padwa carbonyl ylide (CY) with α-methylene ketone (αMK) to yield the oxa-bridged spirocycloadduct has been studied using the DFT method at the B3LYP/6-31G(d) computational level. Six reactive channels associated to the stereo-, regio-, and chemoselective approach modes of the CY to the C=C and C=O reactive sites of the αMK have been analyzed. DFT calculations for this cycloaddition are in complete agreement with the experimental outcome, explaining the reactivity and selectivity of the formation of the [3+2] cycloadduct. Analysis of the global and local electrophilicity and nucleophilicity indices allows an explanation about the regio- and chemoselectivity of this 32CA reaction. Intrinsic reaction coordinate (IRC) calculations and the topological analysis of the electron localization function (ELF) of the relevant points of the favored reactive channel explain the one-step *two-stage* nature of the mechanism of this cycloaddition.

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 [3+2] cycloadditions (32CA) has grown from a fruitful interplay between theory and experiment.[1] The general concept of 1,3-dipolar cycloadditions was introduced by Huisgen and co-workers in the early 1960s.[2] Huisgen's work stated the basis for the understanding of the mechanism of concerted cycloaddition reactions. In the last decades, in addition of the reaction mechanism, the understanding of the selectivity behaviors of the 32CA reactions continues to present a real challenge. We note that the chemo-, regio-, and stereoselectivity of these reactions may be controlled either by choosing the appropriate substrates or by controlling the reaction using a Lewis acid or a metal complex acting as catalyst.

32CA reactions of carbonyl ylide (CY) **1** with π-bonds of olefins or carbonyl groups present an attractive strategy for the construction of tetrahydrofuran **2** or dioxolane **3** systems (see Scheme 1).[3] CYs are very reactive species that quickly react when they are formed with unsaturated systems. As a consequence, the cycloaddition reaction of CY systems constitutes the last step of a domino reaction, which is initialized by the formation of these reactive intermediates. There are mainly two methods to generate CYs (see Scheme 2): (i) reaction of a carbene generated in situ by the rhodium catalyzed decomposition of a diazo compound with a carbonyl compound[4] and (ii) the thermal[5] or photoinduced[6] ring-aperture of epoxides.



Scheme 1.

The 32CA reactions of the CYs have been theoretically studied using both semiempirical[6,7] and density functional theory (DFT)[8,9] methods. These studies reveal that the analysis of the different reaction channels of these cycloadditions explains correctly the stereo-, regio-, and chemoselectivities experimentally observed. Recently, Molchanov et al.[9] studied the 32CA reaction of a series of 3-substituted cyclopropenes **8** with the CY **9** to yield the formally [3+2] cycloadducts **10** (see Scheme 3). A frontier molecular orbital

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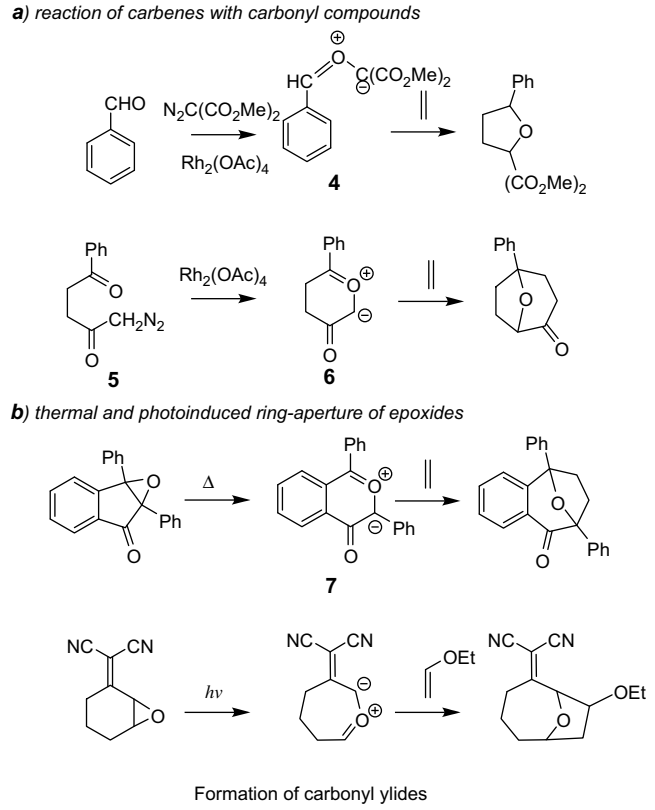
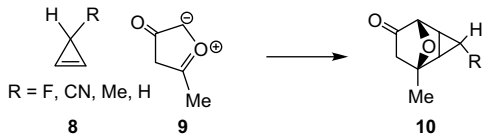


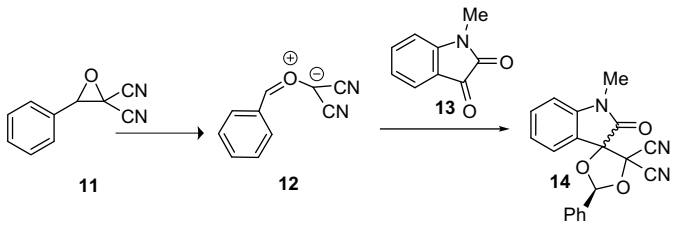
Scheme 2.

(FMO) study, based on the prediction of $HOMO_{cyclopropene}$–$LUMO_{CY}$ interactions, has been also performed by these authors.[9] However, it turns out that the FMO analysis fails to predict the order of reactivity of cyclopropenes **8**, which might be taken as the difference between the corresponding dominant $\Delta E_{(L-H)}$ values for different cyclopropenes. In return, the analysis of the electrophilicity, ω,[10] of CY **9** and the cyclopropenes **8** pointed out the electrophilic character of the CY **9** and the nucleophilic character of **8**. The difference in global electrophilicity, $\Delta\omega$,[11] of both reagents was in quantitative agreement with the experimental order of reactivity of the cyclopropenes. B3LYP/6-311++G(d,p) calculations performed for the preferential *exo* approach of the cyclopropene **8** (R=H) to the CY **9** showed that the cycloaddition has a very low activation barrier of about 2 kcal mol^{-1}.[9] The distances of the two forming bonds at the transition state structure (TS), 2.74 and 2.86 Å, indicated a slightly asynchronous concerted mechanism of this polar cycloaddition. The activation free energies associated to the cycloaddition increased with the electron-withdrawing substitution on cyclopropenes in clear agreement with the experimental outcomes.[9]

Very recently, Mongin and Domingo have experimentally and theoretically reported the 32CA reaction of isatin **13** with the electrophilically activated CY **12** generated by the thermal ring-aperture of the epoxide **11** (see Scheme 4).[12] This reaction presented a low stereoselectivity but a complete regio- and chemoselectivity to yield the spirocycloadducts **14**. The more favorable reactive channels were associated to the nucleophilic attack of the carbonyl oxygen



Scheme 3.



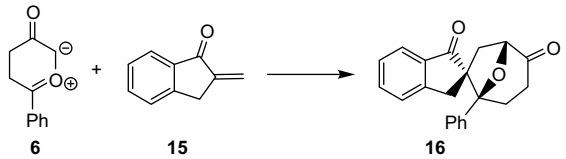
Scheme 4.

atom of isatin **13** to the more electrophilic center of the CY **12**, the phenyl substituted carbon atom. Analysis of the electrophilicity[10] of the reagents showed that the larger electrophilic character of the CY **12**, ω=4.29 eV, than the isatin **13**, ω=2.71 eV, is responsible for the nucleophilic behavior of the later.[12] This behavior, which is in complete agreement with the energy and geometry analysis of the TSs, allows to explain the regio- and chemoselectivity experimentally observed in these 32CA reactions. A further experimental and theoretical study of the 32CA reactions of the CY **12** with aldehydes and imines established the high electrophilic character of the CY **12** and its participation in polar 32CA reactions.[13]

Our aim in the present study is to perform a theoretical study of the 32CA reaction of the Padwa CY **6**, which is usually obtained by decomposition of diazo compound **5** in presence of rhodium acetate catalyst[14] (see Scheme 2). In this context, Muthusamy et al.[15] have recently reported the stereo-, regio-, and chemoselective synthesis of oxa-bridged spirocycles by the 32CA reaction of the Padwa CY **6** with the α-methylene ketone (αMK) **15** (see Scheme 5). Consequently, we have selected this reaction as a computational model for the cycloaddition reactions of the Padwa CYs. A comparative analysis of this 32CA reaction with those recently reported by us[12,13] will allow to give a deeper insight on the mechanism of the 32CA reaction involving CYs and an advanced understanding of the regio- and the chemoselectivity experimentally observed.

2. Computational methods

All calculations were carried out with the Gaussian03 suite of programs.[16] DFT calculations were carried out using the B3LYP[17] exchange-correlation functionals, together with the standard 6-31G(d) basis set.[18] The optimizations were carried out using the Berny analytical gradient optimization method.[19] The stationary points were characterized by frequency calculations in order to verify that TSs had one and only one imaginary frequency. The intrinsic reaction coordinate (IRC)[20] path was traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism using the second order González–Schlegel integration method.[21] The values of enthalpies, entropies, and free energies were calculated with the standard statistical thermodynamics at 298.15 K.[18] The frequency data used for thermochemical analysis were scaled by a factor of 0.96. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method[22] and the topological analysis of the electron localization function (ELF), $\eta(r)$.[23] The ELF study was performed with the TopMod program.[24]



Scheme 5.