

Understanding the influence of Lewis acids in the regioselectivity of the Diels–Alder reactions of 2-methoxy-5-methyl-1,4-benzoquinone: A DFT study

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ABSTRACT

The mechanisms of the Diels–Alder (DA) reactions of 2-methoxy-5-methyl-1,4-benzoquinone **1** with 2-methyl-1,3-butadiene **2**, in the absence and in the presence of LA catalysts, have been studied using the DFT method at the B3LYP/6-31G(d) level of theory. The uncatalyzed DA reactions between **1** and **2** take place via synchronous concerted TSs. The large activation barrier as well as the low stereo and regioselectivity associated with the uncatalyzed process are in clear agreement with the non-polar character of the cycloaddition. Coordination of the LA catalysts, BF₃ or SnCl₄, to the oxygen atoms of the benzoquinone **1** produces a large acceleration of the reaction, which can be associated with the large polar character of the cycloaddition. The different coordination modes of BF₃ and SnCl₄ LA catalysts to the oxygen atoms of benzoquinone **1** allow explaining the reverse *para/meta* regioselectivity observed in these LA-catalyzed DA reactions. The analysis based on the global and local electrophilicity indices of the reagents correctly explains the polar nature of the title reactions, as well as the change of regioselectivity experimentally observed.

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1. Introduction

The Diels–Alder (DA) reaction is a powerful tool employed frequently in the synthesis of six-membered ring systems with excellent regio and stereoselective control [1]. In this process a 1,3-diene reacts with an olefinic or acetylenic dienophile to form a six-member ring adduct. The usefulness of DA reactions arises from its versatility and from its remarkable stereochemistry. By varying the nature of the diene and dienophile many types of carbocyclic structure can be built up.

The use of quinones as dienophile component in DA reactions provides access to a range of structures that are part of the fundamental skeleton of natural products and biologically active molecules [2]. The effects of the substituents on the quinone system are important because they determine the regiochemistry of the DA reactions. Electron-releasing substituents effects, CH₃O > CH₃, on the quinone decrease the reactivity of the double bond to which they are attached. In addition, the methoxy group produces an influence on the orientation at the unsubstituted double bond [3]. The interactions between unsymmetrical dienes can give two isomeric cycloadduct, depending upon relative positions of the substituent in the cycloadduct. For 1-substituted dienes head-to-head interactions corresponds to *orto* channel and head-to-tail

interactions corresponds to *meta* channel. For 2-substituted dienes, head-to-head corresponds to *meta* channel and head-to-tail corresponds to *para* channel. This substitution usually directs the DA reaction with 2-substituted dienes to give the *para* cycloadducts.

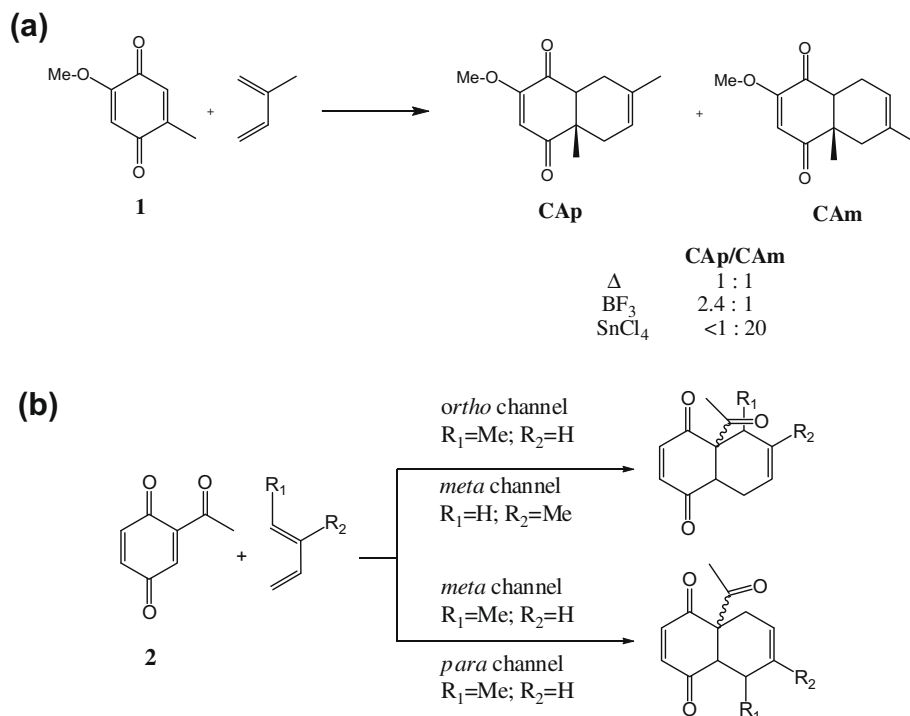
Tou and Reusch [4] reported that the regiochemistry of 2-methoxy-5-methyl-benzoquinone **1** with alkyl-substituted dienes like 2-methyl-1,3-butadiene **2** can be directed to favor either of the regioisomeric adducts by using appropriate Lewis acid (LA) catalysts (Scheme 1a). Thus, while the use of BF₃·OEt₂ produce a 2.4:1 ratio of the *para/meta* regioisomeric cycloadducts, thereby indicating that this cycloaddition proceeds with very low regioselectivity; the use of SnCl₄ produces an inverse relationship with a higher regiochemistry in favor of the *meta* regioisomeric cycloadduct 1:20 *para/meta*. In absence of a LA, the *para* and *meta* cycloadducts are formed in a 1:1 ratio [4].

The activation energy associated to the DA reactions has been related with the polar character of the TS involved in such processes [5,6]. The characterization of the electrophilic/nucleophilic character of the reagents allows predicting the polar character of the reaction and in consequence the feasibility of the process. In this context, it is worth noting that the LA-catalyzed DA reactions take place through TSs with a larger zwitterionic character [7,8].

The global electrophilicity index ω proposed by Parr et al. [9] has been used to classify the dienes and dienophiles currently used in DA reactions within a unique scale of electrophilicity [10,11].

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Scheme 1. (a) Regiochemistry of 2-methoxy-5-methyl-benzoquinone **1** with alkyl-substituted dienes as 2-methyl-1,3-butadiene **2** Ref. 4 (b) DA reactions of 2-acetyl-1,4-benzoquinone **3** with methyl substituted 1,3-butadienes. Regiochemical channels.

A good correlation between the difference in electrophilicity of the diene and dienophile pair, $\Delta\omega$, and the feasibility of the cycloaddition was found. A high electrophilicity at the dienophile and a high nucleophilicity at the diene will in general result in a highly polar transition state, associated with a favorable diene – dienophile interaction, thereby facilitating the cycloaddition [10]. In addition, the static charge transfer (CT) model proposed by Pearson [12] gave a good correlations with the actual CT found at the corresponding highly asynchronous TSs [10]. Therefore, $\Delta\omega$ for a diene/dienophile pair is a valuable tool to predict the polar character of a DA reaction. In addition, the local counterpart condensed to atom k , ω_k [13], has been found to be a useful tool that correctly explains the regioselectivity of the polar DA reactions. The local electrophilicity together with the Fukui functions for electrophilic attack, [14] f_k^- , allow the identification of the most electrophilic and nucleophilic centers in the reactants [13].

Recently, we have studied the DA reactions of 2-acetyl-1,4-benzoquinone **3**, an electrophilically activated benzoquinone, with methyl substituted 1,3-butadienes [15] (Scheme 1b). These reactions were characterized by the nucleophilic attack of the unsubstituted ends of 1,3-dienes to the β conjugated position of the 2-acetyl-1,4-benzoquinone followed by a ring-closure. These DA reactions have low activation energies, between 9.5 and 14.8 kcal/mol (B3LYP/6-31G(d)), [16] and a large *endo* selectivity.

In this work we present a theoretical study about the mechanisms of the DA reactions of 2-methoxy-5-methyl-benzoquinone **1** with 2-methyl-1,3-butadiene **2**, in the absence and in the presence of LA catalysts, BF_3 and SnCl_4 (see Scheme 2). We first make a reactivity analysis based on static reactivity indices to discuss the origin of the polar character and the regioselectivity of these cycloadditions. Then, the mechanism of DA reactions between the benzoquinone **1** and the 2-methylbutadiene **2** in absence and in the presence of LA catalysts coordinated to different positions of the benzoquinone **1** is discussed. The purpose of our work is to contribute to a better understanding of the changes in the reg-

iochemistry due to different modes of LA coordination in these DA reactions and to shed some light on the mechanistic details of these polar cycloadditions.

2. Methodology

DFT calculations were carried out using the B3LYP [17,18] exchange-correlation functional, together with the standard 6-31G(d) basis set [19] for hydrogen, carbon, oxygen, boron, fluorine and chlorine and the Hay–Wadt small-core effective core potential (ECP) including a double- ξ valence basis set for Tin [20] (LandL2DZ keyword). The optimizations were carried out using the Bery analytical gradient optimization method. [21] The intrinsic reaction coordinate (IRC) [22] path was traced to check the energy profiles connecting each transition structure to the two associated minima of the proposed mechanism by using the second-order González–Schlegel integration method [23,24]. All calculations were carried out with the Gaussian 03 suite of programs [25]. The stationary points were characterized by frequency calculations. The electronic structures of TSs and ground states were analyzed in term of the bond orders (BO) [26] and the natural charges obtained from the natural bond orbital (NBO) method [27,28] at the same calculation level. Solvent effects were evaluated by performing single-point B3LYP/6-31G(d) calculations at the gas-phase stationary points involved in the reaction using the polarizable continuum model (PCM) of Tomasi's group [29,30]. Since the solvent is usually dichloromethane, we used a dielectric constant value $\epsilon = 8.93$.

Global reactivity indexes such as the electronic chemical potential, μ , chemical hardness, η , and electrophilicity ω , were approximated in terms of the one electron energies of the frontier molecular orbital (FMO) HOMO and LUMO, ϵ_H and ϵ_L , using the expressions $\mu \approx (\epsilon_H + \epsilon_L)/2$ and $\eta \approx (\epsilon_L - \epsilon_H)$ and $\omega = \mu^2/2\eta$, respectively, at the ground state of the molecules [32]. The local electrophilicity [10], ω_k , condensed to atom k is easily obtained by

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