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HDA cycloadditions of 1-diethoxyphosphonyl-1,3-butadiene with nitroso heterodienophiles: A computational investigation

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ABSTRACT

The hetero Diels–Alder (HDA) reactions of 1-diethoxyphosphonyl-1,3-butadiene with various nitroso dienophiles have been studied at the B3LYP/6-31G** level. Structural, energetic and electronic properties are discussed. These cycloadditions with nitroso dienophiles are characterized by a total proximal regioselectivity and an endo selectivity. The influence of the nitroso substitution on the activation barrier and the regiochemistry of the reaction is presented. The analysis of the chemical rearrangement along the intrinsic reaction pathway (IRC), based on bond order and on natural bond orbital (NBO) calculations, emphasizes the polar nature of these cycloadditions. Despite the early and the cyclic nature of the corresponding transition states, a two-center interaction governs this mechanism: these cycloadditions are Polar Diels–Alder reactions (P-DA).

1. Introduction

The hetero Diels–Alder (HDA) reaction is a powerful tool used to build up six-membered heterocycles in one convergent step [1]. By contrast to the typical Diels–Alder reaction, at least one of the six reacting carbons is replaced by a heteroatom (mainly oxygen, nitrogen or sulfur) [2]. Among these reactions, HDA reactions of nitroso compounds have been studied as an entry towards aza-heterocycles [2,3]. Depending on their substitution, the nitroso derivatives can be considered as heterodienes or heterodienophiles. Less attention is dedicated to the former as a consequence of their instability and high reactivity [4]. Contrastingly, the nitroso dienophiles are recognized as useful partners for HDA reactions even cycloadding with low activated dienes. Several computational studies have been dedicated to nitroso HDA reactions in order to predict their regioselectivity [5]. Among these, a study by Leach and Houk provides some rules [5a]. This study focuses on some model nitroso dienophiles and a set of representative dienes. Its conclusion is that the regiochemistry mainly results from the diene substitution (both the position and the nature of the substituent). The experimental data from the literature reinforce the driving effect of the diene substitution (Fig. 1): the lower the diene activation, the lower the regioselectivity. In this case, the reaction leads often to a mixture of the proximal and distal regiosomers [6].

Among the low activated butadienyl compounds, dienes possessing a dialkoxyphosphonyl moiety in 1-position (e.g. diene **1a**) are known to display poor reactivity in Diels–Alder (DA) reactions [7]. The slight phosphonate activation of the butadienyl system proceeds by partial polarization [8], in a very different way of the widely illustrated α-negative charge stabilization [9]. Their cycloadditions with classical dienophiles have been studied in the past [8a], but there is no data concerning their nitroso HDA cycloadditions.

Accordingly, the expected regioselectivity for the reaction of **1a** with a nitroso dienophile should be low. This is in contradiction with a recently reported example of a regioselective and efficient HDA cycloaddition of diene **1a** with 2-nitrosotoluene (**2b**) (Fig. 2) [10a]. This opens the way towards the synthesis of aliphatic and alicyclic aminophosphonic compounds [10,11]. In such a strategy, the regiochemical outcome of the key HDA reaction has a drastic incidence on the whole efficiency.

The present study aims to provide quantitative information and mechanism insights regarding the HDA reactions of 1-diethoxyphosphonyl-1,3-butadiene (**1a**) and a model (**2a**) or nitroso dienophiles of potential synthetic interest (**2b–g**). In particular, the reaction mechanism and the implication of the phosphonate in the proximal regioselectivity will be investigated. For that purpose, the results obtained for diene **1a** will be compared with classical dienes both activated (**1b, c**) or not (butadiene, etc.). The governing

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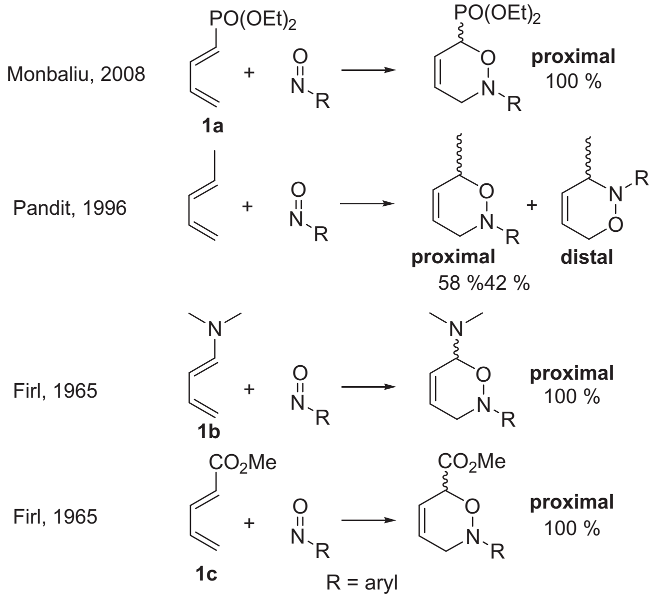

Fig. 1. Experimental regioselectivities.

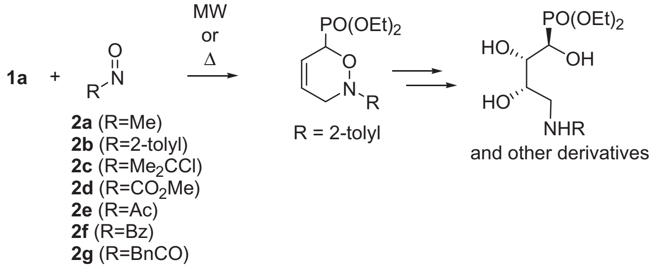

Fig. 2. HDA cycloadditions of diene **1a** and nitroso dienophiles **2a-g**.

parameters will be determined at the B3LYP/6-31G** level. A kinetic study (**1a** + **2b**) is presented. A global electrophilicity index is used to classify the dienophiles according to their intrinsic reactivity.

2. Methodology

All calculations are performed with the density functional theory (DFT) using the B3LYP[12] functional with the GAUSSIAN 98 series of programs [13]. The Pople 6-31G** double zeta polarized basis set is selected [14]. The analytical second derivatives are used to determine the nature of the stationary points. The Intrinsic Reaction Coordinate (IRC) [15] has been followed for a few representative cases. A Natural Bond Orbital (NBO) analysis brings some further insight on the electronic structure and charge distribution [16,17].

A question often raised by experimentalists concerns bond formation and synchronicity (S_y). For a Diels–Alder reaction, the synchronicity is defined as the relative extend of bond breaking and making process. This concept is in general only qualitatively descriptive. A way to have a more quantitative definition of the synchronicity requires Wiberg's indexes and bond order calculations using the procedure introduced by Moyano and co-workers [17a]. According to this procedure, reactions could be classified on the synchronicity scale: from stepwise mechanisms ($S_y = 0$) to concerted synchronous mechanisms ($S_y = 1$).

Several theoretical studies, particularly in the field of cycloaddition reactions, have shown that the analysis of reactivity indexes defined within DFT at the ground state of the reagents are able to furnish information about the reactivity [18]. These indices are based on the HSAB theory extended to global properties. The electrophilicity index (ω) measures the capability of a molecule to accept electrons. It has been defined in terms of static global properties, namely chemical potential (μ) and chemical hardness (η). This global electrophilicity index is calculated by the procedure introduced by Domingo [19,20].

3. Results and discussion

3.1. Model HDA reaction with nitrosomethane (**2a**)

Nitrosomethane (MeNO, **2a**) is selected as a model hetero dienophile for a preliminary investigation. Its cycloaddition onto phosphonodiene **1a** is computed (Fig. 3) to establish the general features of this HDA reaction. The most relevant results are discussed here, related to the most stable conformer of diene **1a**, i.e. with the P=O in *syn* conformation to the butadienyl moiety.

Considering the structures of **2a** (MeNO), the diene **1a** and the cycloaddition products (**4p**,**d** in Fig. 3), overall energy changes of 23 kcal mol^{-1} for the proximal adduct and 19 kcal mol^{-1} for the distal one are calculated. There are only two cycloadducts (**4p**,**d**) to be expected from this reaction, despite the fact that endo/exo transition states (**TS**s) are isolated for each regioisomeric pathway. These TSs are labelled **TS1pn**, **TS1px**, **TS1dn** and **TS1dx**. Where **p**, **d** stand for proximal and distal and **n**, **x** are relative to endo/exo approaches (Fig. 3).

The results from Fig. 3 indicate that the activation barrier for **TS1pn** is the lowest. The stereoselectivity, given by the relative energy between the *exo* TS and its *endo* counterpart, shows that the *exo* TS is disfavoured over the *endo* one by some 2.7–7.1 kcal mol^{-1}. This feature retrieves the conclusions of Leach and Houk for other systems and is attributed to the "*exo* lone pair" effect [5a]. Similar stereoselectivities are computed for butadiene or piperylene (6.7–6.8 kcal mol^{-1}, Fig. 4) leading to conclude that the phosphonate moiety does not induce a specific stereoselectivity.

Further on, the regioselectivity ($\Delta\Delta E^{\neq}$) can be expressed by the energy differences between the two lowest **TSs** on each regioisomeric channel, namely **TS1pn** and **TS1dn** (Fig. 3 and Table 1). In order to obtain more information concerning the phosphonate effect on the regioselectivity, these values have been compared with the activation barriers for the HDA reactions of other dienes with nitrosomethane (**2a**, Table 1). As expected, the effect of the phosphonate moiety on the activation barrier is low (entries 1–4). Contrastingly, activated dienes such as (*E*)-N,N-dimethylbuta-1,3-dien-1-amine (**1b**) or (*E*)-methyl penta-2,4-dienoate (**1c**) show significant activation effect on this HDA reaction (entries 5–6). Another interesting observation is the emergence of a proximal regioselectivity for diene **1a**, that is not observed for piperylene (Table 1, entry 3). The computed regiodiscrimination for diene **1a** (5.8 kcal mol^{-1} in favour of the proximal adduct) is 15 times higher than for piperylene.

From the structural point of view, the N_5–$C_{4,1}$ bond shows significant formation compared to the O_6–$C_{1,4}$ bond, whatever the proximal or distal channel. Geometrically, these TSs are similar to those obtained for butadiene and piperylene (**TS2n**, **TS2x**, **TS3pn** and **TS3px** in Fig. 4). The C_4–N_5 bond length is close to the C–N bond in the proximal cycloadduct (1.46 Å) while the C_1–O_6 bond remains closer to the sum of the Van der Waals radii for C and O (3.24 Å) than to the final length in the proximal cycloadduct (1.44 Å). This is similar to the situation described by Leach and Houk for the reaction of butadiene and HNO. These authors have