Origins of regioselectivity in 1,3-dipolar cycloadditions of nitrile oxides with alkynylboronates

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ABSTRACT

Density functional theory (M06-2X) studies of the regioselectivity of 1,3-dipolar cycloaddition reactions of benzo and mesitonitrile oxides with alkynyl pinacol and MIDA boronates are reported. Calculated relative free energies of activation reproduce the experimentally observed product ratios. The electronic energies of activation are found to be mainly controlled by distortion energies required to achieve the transition states. Both electronic and steric effects influence regioselectivities.

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1. Introduction

Isoxazoles are found in a number of drugs such as valdecoxib, a non-steroidal anti-inflammatory agent (Figure 1). The 1,3-dipolar cycloaddition reaction is one of the most useful reactions for the synthesis of isoxazoles.^{1,2} Organoboron reagents have been utilized in the 1,3-dipolar cycloaddition reactions of nitrile oxides and alkynylboronates to form 3,4- and 3,5-substituted isoxazole boronic esters (Figure 2), as reported by Harrity and coworkers.³ The isoxazole boronic esters can be further transformed by Pd-catalyzed cross-coupling reactions. This methodology is promising for the synthesis of a variety of isoxazoles.^{3,4}

Figure 1. Valdecoxib, a non-steroidal anti-inflammatory drug (NSAID) that contains an isoxazole unit.

Figure 2. 1,3-Dipolar cycloaddition reaction of nitrile oxide and alkynyl boronic acid pinacol ester.

Recently, Hamann and coworkers reported the synthesis of 3,5-substituted isoxazole boronic esters by 1,3-dipolar cycloadditions of ethynyl boronic acid MIDA (*N*-methyliminodiacetic acid)⁵ esters and nitrile oxides (Figure 3, reaction (1)).⁶ The reaction between ethynyl boronic acid MIDA ester and benzonitrile oxide only yields the 3,5-substituted product as a single regioisomer, in contrast to the results with the corresponding pinacol esters (Figure 3, reactions (2) and (3)).^{3,6} Hamann and coworkers hypothesized that the complete regioselectivity in the case of the MIDA ester is due to the presence of the sp^3 -hybridized boron center, which is more sterically demanding in the case of the MIDA boronates compared to the sp^2 -hybridized boron of the pinacol esters.⁶ Nitrile oxides in these reactions were generated in situ from the corresponding hydroxamic acid chlorides.^{3,6}

While the pinacol boryl group should be electron-withdrawing due to the partially vacant boron orbital, it is not so clear whether the MIDA boryl is electron-withdrawing or electron-donating.

In reaction (3), the bulkier and electron-rich mesityl group is present on the nitrile oxide. If steric hindrance were governing the regioselectivity of the reaction, then the ratio of 3,5- to 3,4-substituted product in reaction (3) would be larger than the ratio of 3,5- to 3,4-substituted product in reaction (2). However, the

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Figure 3. 1,3-Dipolar cycloaddition reactions of nitrile oxides (generated in situ) with ethynyl boronic acid esters.^{3,6}

ratio of 3,5- to 3,4-substituted product in reaction (3) is much smaller than expected. This unexpectedly lower ratio suggests that steric hindrance is not the only factor governing the regioselectivity of the reaction. We now present detailed computations to explain the regioselectivity of reactions (1)–(3).

2. Computational Methods

Avogadro^{7,8} and *Gaussview*⁹ were used to create initial structures of reactants (nitrile oxides and alkynylboronates) and products (isoxazole boronic esters). All density functional theory calculations were performed using *Gaussian09*.¹⁰ Geometry optimizations and frequency calculations of reactants and transition states were performed at the M06-2X level using the 6-31G(d) basis set.^{11,12} Single point energies were calculated on the optimized structures at the M06-2X level using the 6-311+G(d,p) basis set. Solvation effects in acetonitrile and diethyl ether were computed by a self-consistent reaction field (SCRF) using the SMD solvent model.¹³ The frontier molecular orbitals (FMOs) and their energies were computed at the HF/6-31G level on the M06-2X/6-31G(d) optimized geometries. *CYLVIEW*¹⁴ was used to create images of optimized structures. *Chemcraft*¹⁵ was used to create images of molecular orbitals.

3. Results and discussion

The transition structures (TS) and activation energies for the three reactions are shown in Figure 4. The TS leading to the 3,5-substituted product of a reaction is denoted “TS-Xa”, where X is the number of the reaction being discussed. The transition state leading to the 3,4-substituted product of a reaction is denoted “TS-Xb”, accordingly. The free energy barriers for the 3 reactions are all about 28 kcal/mol. The difference in activation free energies ($\Delta\Delta G^\ddagger$) between the reaction (1) transition states is 5.2 kcal/mol. This difference in activation energies is in good agreement with Hamann’s findings of complete regioselectivity favoring the 3,5-product when the MIDA ester was used.⁶ The relative electronic energy ($\Delta\Delta E^\ddagger$) of the two transition states is slightly smaller, 4.5 kcal/mol. For reaction (2), involving the

Figure 4. Transition structures for the 3 reactions of nitrile oxides with ethynyl boronic esters.

pinacol boronic ester, the calculated $\Delta\Delta G^\ddagger$ is 1.2 kcal/mol. The experimental product ratio is 9 to 1, favoring the 3,5-product.³ This ratio corresponds to a difference in activation energies of 1.3 kcal/mol at room temperature, according to transition state theory. This is in good agreement with the calculated $\Delta\Delta G^\ddagger$ value (1.2 kcal/mol). Interestingly, the calculated $\Delta\Delta E^\ddagger$ is -0.9 kcal/mol, favoring the minor product. For reaction 3, in which the larger mesityl group is present, the calculated $\Delta\Delta G^\ddagger$ further decreases to 0.6 kcal/mol. This is in good agreement with the experimental product ratio of 2.5:1. The $\Delta\Delta E^\ddagger$ is -2.2 kcal/mol, favoring the minor product even more, compared to reaction (2).

To gain more insight into the factors controlling the trends in activation energies, the six transition states were analyzed using the distortion/interaction model,^{16,17} also known as the activation strain model.^{18,19} For each reaction, the transition structure is separated into two fragments (dipole and dipolarophile),

Figure 5. Graph of distortion, interaction, and activation energies for the three reactions discussed previously (green: distortion energy of dipolarophile, blue: distortion energy of dipole, red: interaction energy, black: activation energy).

followed by single-point energy calculations on each distorted fragment. The difference in energy between the distorted fragments and optimized ground-state geometries is the distortion energy of dipole ($E_{\text{dist-}4\pi}$) and dipolarophile ($E_{\text{dist-}2\pi}$), respectively. The difference between the activation energy ($\Delta E^\ddagger$) and the total distortion energy ($E_{\text{dist}} = E_{\text{dist-}4\pi} + E_{\text{dist-}2\pi}$) is the interaction energy (E_{int}). The results are shown in Figure 5. The black arrows correspond to the activation energies ($\Delta E^\ddagger$). The green arrows correspond to the distortion energies of the dipolarophiles ($E_{\text{dist-}2\pi}$). The blue arrows correspond to the distortion energies of the dipoles ($E_{\text{dist-}4\pi}$). The total length of blue and green arrows corresponds to the total distortion energy (E_{dist}). The red arrows correspond to the favorable interaction energies (E_{int}).

For each of the six transition states, the $E_{\text{dist-}4\pi}$ is the main contributor to the E_{dist} . This observation is quite general in 1,3-dipolar cycloadditions and Diels-Alder reactions.^{17,20} The $E_{\text{dist-}2\pi}$ is relatively small and constant, except for **TS-1b**. The dipolarophile distortion is 8.6 kcal/mol for **TS-1b**, whereas the others are 5.2–5.7 kcal/mol. In **TS-1b** (Figure 4), the C-C-B angle is 149°, whereas the same angles in the other 5 TS ranges from 161–174°. This greater deviation from linear structure accounts for the much higher distortion energy of the dipolarophile in **TS-1b** is likely due to the steric repulsion between the nitrile oxide phenyl group and the bulky MIDA group. Comparing the two TSs in reaction (1), $E_{\text{dist-}2\pi}$ of **TS-1b** is 3.0 kcal/mol higher than that of **TS-1a**. The much higher activation energy of **TS-1b** than that of **TS-1a** is mainly attributed to the higher distortion energy arising from steric effects. The larger MIDA substituent on the alkyne strongly disfavors the formation of the 3,4-substituted product.

In reaction (2), the -0.9 kcal/mol difference in $\Delta E^\ddagger$ favoring **TS-2b** mainly originates from the distortion of the dipole ($E_{\text{dist-}4\pi}$). $E_{\text{dist-}4\pi}$ of **TS-2b** is 1.0 kcal/mol lower than that of **TS-2a**. In the TS structures, the N-C-C angle of **TS-2b** is 147° compared to that of 143° in **TS-2a**. This is an unusual example in which the $\Delta\Delta E^\ddagger$ and $\Delta\Delta G^\ddagger$ have opposite signs. It is likely due to the fact that the more crowded TS, **TS-2b**, has less vibrational freedom and, therefore, less favorable entropy. In reaction (3), the -2.2 kcal/mol difference in $\Delta E^\ddagger$ favoring **TS-3b** mainly originates

from the distortion of the dipole ($E_{\text{dist-}4\pi}$). $E_{\text{dist-}4\pi}$ of **TS-3b** is 2.3 kcal/mol lower than that of **TS-3a**. In the TS structures, both the N-C-C angle (145°) and the O-N-C angle (141°) of **TS-3a** are smaller (more distorted) compared to those of **TS-3b**.

Figure 6. Frontier molecular orbitals (FMO) involved in the 1,3-dipolar cycloaddition of nitrile oxides and alkynylboronates. From left to right: the HOMO and LUMO of the benzonitrile oxide generated in situ in reaction (1) and (2) (denoted **1a**), the HOMO and LUMO of the mesitonitrile oxide generated in situ in reaction (3) (denoted **8a**), the HOMO and LUMO of the pinacol boronic ester used in both reactions (2) and (3), and the HOMO and LUMO+2 of the MIDA boronate used in reaction (1).

Replacing the phenyl group with a mesityl group generally increases the favorable interaction energies (more negative), as

found in going from reaction (2) to (3). This is due to the electron-donating nature of methyl groups on the phenyl ring. To explore this observation, we computed the energies of the frontier molecular orbitals (FMO) of the two dipoles and two dipolarophiles.^{21, 22} The results are shown in Figure 6.

In reactions (2) and (3), the HOMOs of the dipoles (**1a** and **8a**, respectively) interact with the LUMO of the dipolarophile (**5**). The HOMO of **8a** is 0.4 eV higher in energy than that of **1a**, due to the electron-donating methyl groups present in the latter structure.²³ As a result, the HOMO of **8a** interacts more strongly with the LUMO of **5**. This is in agreement with the more favorable interaction energy of reaction (3) compared to that of reaction (2). In reaction (1), the dominating interaction is between the LUMO of **1a** and the HOMO of **2**. This is an example of inverse-electron-demand 1,3-dipolar cycloadditions.

4. Conclusions

The regioselectivities of three 1,3-dipolar cycloadditions of nitrile oxides with alkynylboronates have been elucidated using density functional theory (M06-2X). The calculated free energy barriers of reaction reproduce the experimentally observed product ratios. Distortion/interaction analyses reveal that the regioselectivity is mainly governed by the distortion energies. With ethynyl boronic acid MIDA ester, the reaction does not afford the 3,4-substituted isoxazole product, due to the large distortion energy required to achieve the corresponding transition state. With ethynyl pinacol boronic ester, the reaction produces a mixture of two regioisomeric products. The electronic energies of activation favor the minor products, due to smaller distortion energies required to achieve the minor transition states. When benzonitrile oxide is replaced with mesitonitrile oxide, the favorable interaction energies increase. This can be explained by the electron-donating nature of the methyl groups present on the mesityl group.

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Supplementary Material

Coordinates and energies of stationary points can be found in the supplementary material.

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Graphical Abstract

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