

A DFT Study on the Regioselectivity of the Reaction of Dichloropropynylborane with Isoprene

María A. Silva,[†] Silvina C. Pellegrinet,[‡] and Jonathan M. Goodman^{*,†}

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, U.K., and Instituto de Química Orgánica y de Síntesis (CONICET) - Facultad de Ciencias Bioquímicas y Farmacéuticas, U.N.R. Suipacha 531, Rosario (2000), Argentina

j.m.goodman@ch.cam.ac.uk

Received December 9, 2002

This theoretical study deals with the reaction of isoprene and dichloropropynylborane. We report the results of the DFT calculations applied to the two processes involved, Diels–Alder cycloaddition and 1,4-alkynylboration. The boron influences both the chemoselectivity and the regioselectivity of this reaction through secondary orbital interactions (SOI hereafter) that give rise to transition structures with strong [4 atom + 3 atom] character. The “meta” regioselectivity observed experimentally for the reaction between 2-substituted 1,3-dienes and alkynyldihaloboranes has been explained as a result of the higher stabilization of these transition structures with “meta” orientation. Intrinsic reaction coordinate calculations were performed to determine connectivities and established the remarkable result that the geometrically very similar transition structures leading to both regioisomeric 1,4-alkynylboration products correspond to different pathways. For the “meta” orientation a direct alkynylboration of the diene through a concerted transition structure was found.

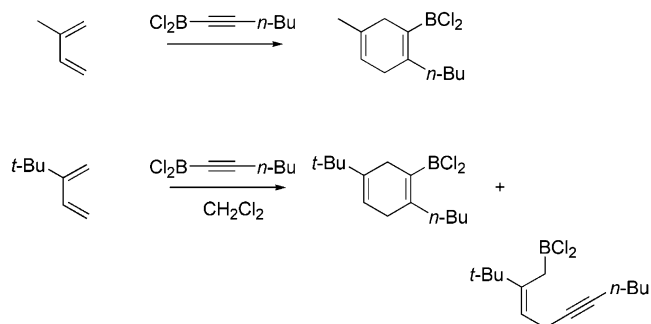
Introduction

In a study by Singleton,^{1,2} a series of alkynylboranes was synthesized and tested as Diels–Alder dienophiles. The experimental outcome of these reactions is a theoretical puzzle. The reaction of *n*-hexynyldichloroborane with isoprene in hexanes or dichloromethane yielded the Diels–Alder cycloadduct as the only product and with complete meta regioselectivity. The reaction of hexynyldichloroborane with 2-*tert*-butylbutadiene in dichloromethane afforded the meta Diels–Alder product, together with the product of the 1,4-alkynylboration (Scheme 1).

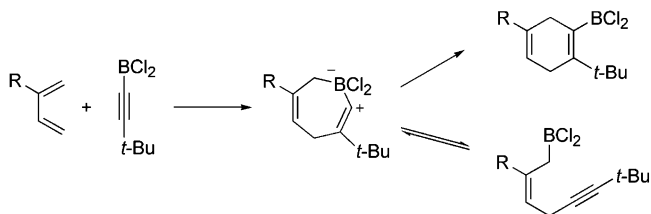
Initially, Singleton and co-workers located a transition structure corresponding to the concerted process for the Diels–Alder reaction of ethynyldichloroborane with butadiene.^{1,2} The computed ab initio RHF/6-31G* geometry for such transition structure showed strong [4 atom + 3 atom] character.² This transition structure shed some light into the origin of the 1,4-alkynylboration of dienes. A unified mechanism for the Diels–Alder reaction and the 1,4-alkynylboration through a zwitterionic seven-membered ring species as shown in Scheme 2 was thus proposed, though this intermediate was not computationally characterized.

More recently, theoretical work from these laboratories provided further insight into the mechanism of this class of reactions.³ Inspection of the potential energy surfaces (PESs) of the reactions of 1,3-butadiene with different

SCHEME 1



SCHEME 2



alkynylboranes at the B3LYP/6-31G* level of theory led to the location of three types of transition structures (Scheme 3). Two different transition structures connecting the reactants with the 1,4-cyclohexadienylborane products were found. The more energetically favored transition structures (TS-I) had classical [4 + 2] geometries and exhibited [4 + 3] C–B secondary orbital

[†] University of Cambridge.

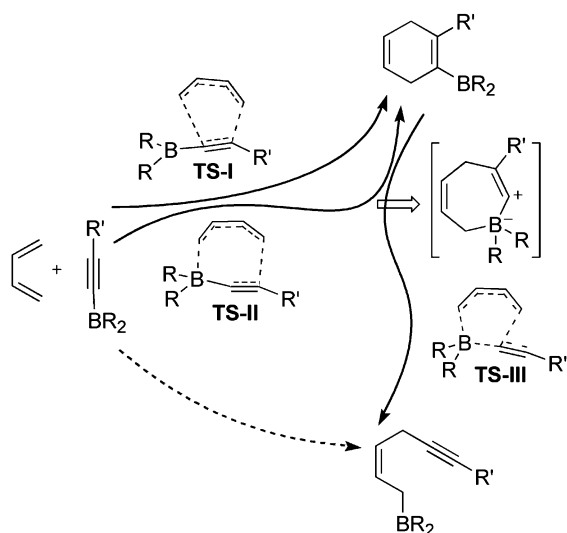
[‡] Instituto de Química Orgánica y de Síntesis (CONICET).

(1) Singleton, D. A.; Leung, S.-W. *J. Org. Chem.* **1992**, *57*, 5796.

(2) Leung, S.-W.; Singleton, D. A. *J. Org. Chem.* **1997**, *62*, 1955.

(3) Silva, M. A.; Pellegrinet, S. C.; Goodman, J. M. *J. Org. Chem.* **2002**, *67*, 8203.

SCHEME 3

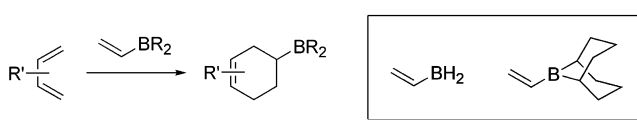


interactions while TS-II showed strong [4 + 3] character. Although we performed a thorough inspection of the PESs, we could not find transition structures corresponding to the concerted pathway for the direct alkynylboration of the diene (dotted line, Scheme 3). Instead, we located transition structures (TS-III) that, when launched toward the reactants, passed through a nearly flat region associated with a zwitterionic structure that led to the cyclohexadienylborane product when minimized. These zwitterionic species represented an inflection on the IRC calculations for both the TS-II and the TS-III pathways and could not be characterized as a minimum, or as a transition structure, but seem to correspond to the intermediate species in Scheme 2.

Very recently, Carreaux, Cossío, and co-workers have computationally and experimentally studied the mechanism of a related reaction, i.e., the dimerization of 2-boryl-1,3-butadienes. This study looks into the origin of the evolution of the [4 + 3] character structures to [4 + 2] cycloadducts and increases understanding to the Diels–Alder reactions of different boron-substituted compounds.⁴

In addition to these mechanistic issues, the regioselectivity of the Diels–Alder reactions of boron-activated dienophiles has aroused considerable attention both from the experimental⁵ and theoretical⁶ points of view. However, only the regioselectivity of the [4 + 2] cycloadditions of vinylboranes with substituted butadienes has been theoretically analyzed (Scheme 4).^{6b} The regioselectivity of such reactions can be rationalized either in terms of electronic or steric effects depending on the substitution

SCHEME 4



pattern on boron. For vinylborane, the regiochemical preferences for the formation of the meta adducts seemed to be founded purely on electronic effects, while for bulky systems, such as vinyl-9-BBN, steric effects were shown to control the outcome of the reactions giving rise to the adducts derived from the less congested transition structures. No reaction analogous to alkynylboration has been found.

Although our earlier study gave us a better understanding on the Diels–Alder and the alkynylboration reaction pathways,³ it became apparent that a more detailed study was required. As far as we know, no computational study on the regioselectivity of the Diels–Alder reactions of alkynylboranes has appeared in the literature. In the present work, we report the results of a density functional theory (DFT) study on the reaction between dichloropropynylborane and isoprene as a model for substituted systems.

Computational Methods

All calculations were carried out using Gaussian 98⁷ and GAMESS.⁸ Density functional theory with the B3LYP functional and the 6-31G* basis set was used. This level of theory has been widely used in computational studies on pericyclic reactions with satisfactory results.⁹ Moreover, the choice of this method for the present investigation was based on our previous results^{6b} and is supported by the recent study by Cossío,⁴ which indicated that B3LYP/6-31G* nicely reproduces experimental results for Diels–Alder reactions of boron-substituted compounds. Geometries for reactants and transition structures were fully optimized and characterized by their vibrational frequencies. All minima and transition structures were confirmed to have none or only one imaginary frequency, respectively. All the B3LYP/6-31G* energies presented in this study include zero-point energies (ZPE) without scaling. Natural bond orbital (NBO) method¹⁰ was used in order to analyze the bond orders (Wiberg indices¹¹) in all the transition structures. Intrinsic reaction coordinate (IRC) calculations, starting at all

(4) Carreaux, F.; Possémé, F.; Carboni, B.; Arrieta, A.; Lecea, B.; Cossío, F. P. *J. Org. Chem.* **2002**, *67*, 9153.

(5) (a) Singleton, D. A.; Martinez, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 7423. (b) Singleton, D. A.; Martinez, J. P. *Tetrahedron Lett.* **1991**, *32*, 7365. (c) Singleton, D. A.; Martinez, J. P.; Watson, J. V. *Tetrahedron Lett.* **1992**, *33*, 1017. (d) Singleton, D. A.; Martinez, J. P.; Ndiip, G. M. *J. Org. Chem.* **1992**, *57*, 5768. (e) Singleton, D. A.; Martinez, J. P.; Watson, J. V.; Ndiip, G. M. *Tetrahedron* **1992**, *48*, 5831. (f) Singleton, D. A.; Leung, S.-W. *J. Org. Chem.* **1992**, *57*, 4796. (g) Singleton, D. A.; Kim, K.; Martinez, J. P. *Tetrahedron Lett.* **1993**, *34*, 3071. (h) Lee, Y.-K.; Singleton, D. A. *J. Org. Chem.* **1997**, *62*, 2255.

(6) (a) Singleton, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 6563. (b) Pellegrinet, S. C.; Silva, M. A.; Goodman, J. M. *J. Am. Chem. Soc.* **2001**, *123*, 8832.

(7) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

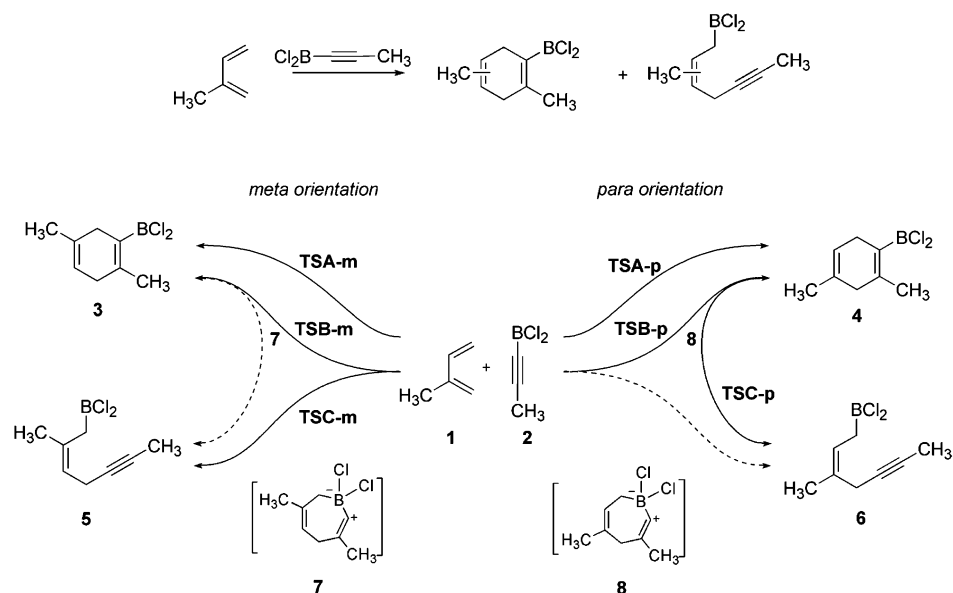
(8) Schmidt, M. W.; Baldrige, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

(9) (a) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036. (b) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Pople, J. A. *J. Chem. Phys.* **1997**, *106*, 1063. (c) Birney, D. M. *J. Am. Chem. Soc.* **2000**, *122*, 10917. (d) Birney, D.; Lim, T. K.; Koh, J. H. P.; Pool, B. R.; White, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 5091.

(10) (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

(11) Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083.

SCHEME 5



the transition structures, were performed to determine the connections between the transition structures and the reactants and products. IRC calculations were obtained using the Gonzalez–Schlegel procedure¹² with GAMESS.

Results and Discussion

To investigate the origin of the experimental regioselectivity for the reaction of 2-substituted 1,3-butadienes with alkynylboranes, we chose as model system the reaction of isoprene (**1**) and dichloropropynylborane (**2**).

Following the same methodology we have previously used in the study of the mechanism for the reaction with butadiene and different alkynylboranes, we searched for the cycloaddition and also the alkynylboration process transition structures. Three different transition structures for each of the two possible regioisomers, meta and para, were found at the B3LYP/6-31G* level (Scheme 5). Transition structures **TSA** and **TSB** correspond to the cycloaddition reaction, while **TSC** corresponds to the alkynylboration process.¹³

Scheme 5 pictures the situation found for the two possible orientations of the diene and dienophile. For the para orientation, the situation matches the previously described results for the case of butadiene.³ The meta orientation is intriguingly different, with a direct pathway from the reactant to the product of alkynylboration, which was not found in the case of butadiene or the para orientation. As suggested in Scheme 5, the pathways with the meta orientation **TSB-m** and **TSC-m** are very close in the first part of the reaction path uphill to the TSs from the reactants. Before reaching the transition structures pathways **TSB-m** and **TSC-m** diverge, leading to the cycloadduct **3** and the enyne **5**, respectively. For the

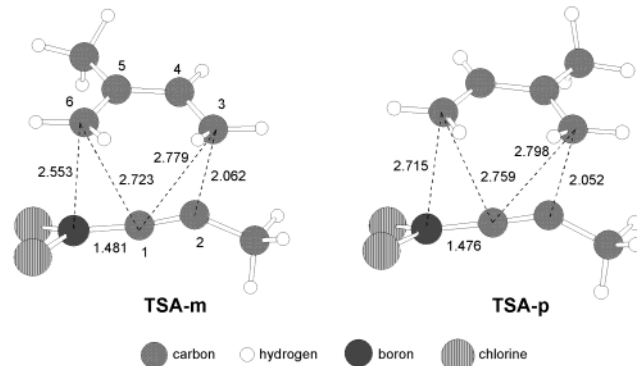


FIGURE 1. B3LYP/6-31G*-optimized geometries of the transition structures corresponding to the cycloaddition reaction between isoprene (**1**) and dichloropropynylborane (**2**) (path TSA). All distances are in Å.

para orientation, we found that the reaction paths leading to the cycloadduct, i.e., **TSB-p** pathway from the reactants and **TSC-p** pathway from enyne **6**, merge at intermediate species **8**, and after that point they are practically the same.¹⁴

Diels–Alder Reaction. As in our previous studies with butadiene, two different transition structures for the Diels–Alder reaction were found (**TSA** and **TSB**). The optimized geometries of these transition structures are different. In the case of **TSA-m** and **TSA-p**,¹⁵ concerted but asynchronous structures were found with forming C2–C3 bonds being shorter than C1–C6 distances, and the degree of synchronicity was similar for both TSAs (Figure 1). In relation to the C6–B distances, both TSA transition structures showed shorter C6–B distances than the C1–C6 forming bond, giving evidence of significant C–B SOI in these systems, as described previously. Nevertheless, the transition structures on the TSA

(12) (a) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154. (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523. (c) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363.

(13) The transition structures are named as follows: TSA, TSB for the transition structures in the cycloaddition pathways; TSC for the transition structures related to the alkynylboration process. We then added **m** and **p** for meta and para regiochemistry.

(14) For a representation of the reaction pathways on the PES, see the Supporting Information.

(15) Meta and para refer to the boryl group and the methyl substituent from the diene.

TABLE 1. Relative Energies (kcal mol⁻¹) Including Zero-Point Vibrational Energy (ZPE) Corrections, ZPE Corrections (kcal mol⁻¹), and Imaginary Frequencies (cm⁻¹) for the Stationary Points Corresponding to the Reaction between Isoprene (1) and Dichloropropynylborane (2), Computed at the B3LYP/6-31G* Theory Level

	ΔE^{\ddagger}_0	ZPE	imaginary frequency
1		71.61	
2		33.97	
TSA-m	20.60	106.77	415.7i
TSA-p	20.16	106.72	406.4i
TSB-m	18.03	107.26	252.0i
TSB-p	21.53	106.95	259.5i
TSC-m	18.84	106.96	215.1i
TSC-p	23.05	107.16	238.5i
3	-40.44	110.10	
4	-40.52	110.07	
5	-6.06	107.84	
6	-6.45	108.14	

pathway can still be considered as classical concerted [4 + 2] cycloaddition transition structures.

The activation energies computed, including ZPE, for all the transition structures studied are collected in Table 1. In relation to the energies of both TSA regioisomers, we found that there is little difference between the para and meta regioisomers: 0.44 kcal/mol, favoring **TSA-p**. With this small difference in the calculated activation energy, the total regioselectivity found experimentally for the reaction of 2-substituted 1,3-butadienes and alkyndihaloboranes could not be explained. We inferred from this observation that the cycloaddition reaction could follow a different pathway where the meta regioisomer would be preferred.

The search for a different pathway was not an easy task, as the new transition structures would vary only slightly from the classical Diels–Alder ones. The electrophilicity of the boron atom in the dienophile is expected to influence the electronic effects controlling the outcome of the reaction. A strong stabilization due to the interaction between the boron atom and C6 in the diene would be expected, which means that C6–B distances will be shorter than in the case of the classical Diels–Alder cycloaddition (TSA). In other words, strong [4 + 3] SOI are anticipated for these transition structures. On the other hand, a new cycloaddition pathway that favors the meta over the para regioisomer, as observed experimentally, indicates that electronic stabilization is larger in the meta transition structure over the para. As previously suggested by Singleton, a donating group in the diene will stabilize the incipient positive charge in C5 after the “boron attack” to the diene in the first stage of the [4 + 3] cycloaddition.

The geometries found for these transition structures (TSBs) adopting strong [4 + 3] character are depicted in Figure 2. Unlike in the case of TSAs, where both transition structures exhibit a similar degree of asynchronicity, we observed that the energetically preferred **TSB-m** is more asynchronous than **TSB-p**, a trend that has been observed for a diverse number of transition structures on Diels–Alder cycloadditions.¹⁶ The lengths of the forming bonds show that the more favorable **TSB-m** is more advanced than **TSB-p**. Moreover, as in our study with butadiene, the geometries confirmed strong carbon–boron interactions with distances C6–B

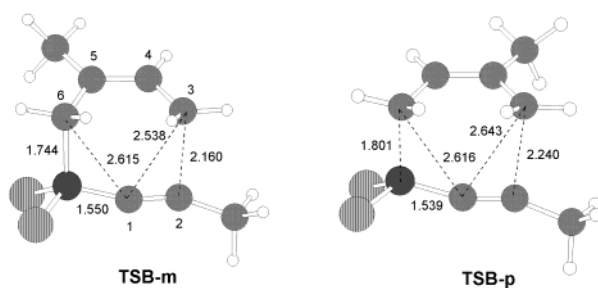


FIGURE 2. B3LYP/6-31G*-optimized geometries of the transition structures corresponding to the cycloaddition reaction between isoprene (1) and dichloropropynylborane (2) (path TSB). All distances are in Å.

being 1.74 and 1.81 Å for the **TSB-m** and **TSB-p**, respectively. These distances are significantly shorter than the ones corresponding to TSAs and also contrast with the distances found for the forming bonds C1–C6, 2.62 Å for both TSBs. At first sight, the geometry of TSBs suggests that the cycloaddition could occur through a stepwise pathway, where the first step would be the [4 atom + 3 atom] cycloaddition to form a seven-membered ring intermediate, as reported for allylic cations¹⁷ that in the second step would lead to the cycloaddition product. An IRC study to determine whether an intermediate was present in this cycloaddition pathway was performed. Although our previous experience with butadiene showed us that no intermediate was found during the cycloaddition, we could observe a flat region in the reaction path corresponding to a seven-membered ring structure. With isoprene, a similar result was expected, or else that the surface could be flat enough to be localized as a minimum or a transition structure. Following precedent, there is no difficulty with the IRC having two transition structures directly connected without intervening intermediates.¹⁸ Dynamics of molecular systems having PESs that show flat areas associated with valley-ridge inflection points might give rise to nonstatistical product distributions by following non-steepest descent trajectories. The IRCs for both **TSB-m** and **TSB-p** pathway exhibited rather flat areas that corresponded with a seven-membered ring structure (Figure 3). This plateau in the PES has an energy value very close to the reactants (around 8 kcal/mol, compared to the 62–66 kcal/mol energy gap to the product) and leads to the cycloaddition products.

In terms of energy for the TSBs, we found a noticeable change on the energy barriers, particularly in the case of the meta regioisomer, **TSB-m**, with respect to the

(16) (a) Jorgensen, W. L.; Lim, D.; Blake, J. F. *J. Am. Chem. Soc.* **1993**, *115*, 2936. (b) García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415. (c) Morao, I.; Lecea, B.; Cossío, F. P. *J. Org. Chem.* **1997**, *62*, 7033. (d) Domingo, L. R.; Arnó, M.; Andrés, J. *J. Am. Chem. Soc.* **1998**, *120*, 1617. (e) Domingo, L. R.; Picher, M. T.; Zaragoza, R. J. *J. Org. Chem.* **1998**, *63*, 9183. (f) Domingo, L. R. *J. Org. Chem.* **1999**, *64*, 3922.

(17) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 819.

(18) (a) Bartsch, R. A.; Chae, Y. M.; Ham, S.; Birney, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 7479. (b) Caramella, P.; Quadrelli, P.; Toma, L. *J. Am. Chem. Soc.* **2002**, *124*, 1130. (c) Debbert, S. L.; Carpenter, B. K.; Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **2002**, *124*, 7896. (d) Reyes, M. B.; Lobkovsky, E. B.; Carpenter, B. K. *J. Am. Chem. Soc.* **2002**, *124*, 641. (e) Yamataka, H.; Aida, M.; Dupuis, M. *Chem. Phys. Lett.* **2002**, *353*, 310. (f) Zhou, C.; Birney, D. M. *Org. Lett.* **2002**, *4*, 3279.

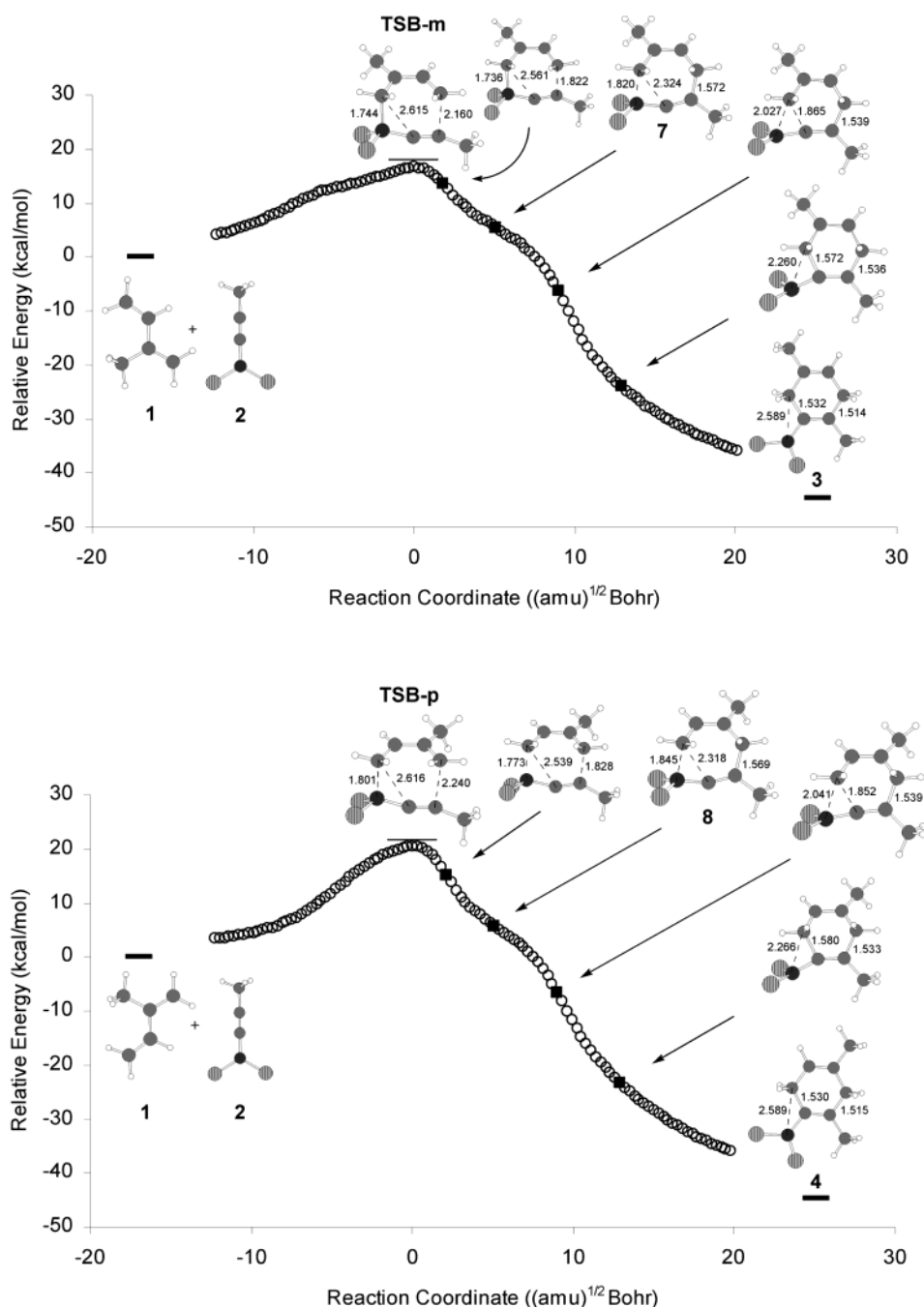


FIGURE 3. Energy profile (B3LYP/6-31G*) along the intrinsic reaction coordinate for the cycloaddition reaction between isoprene (**1**) and dichloropropynylborane (**2**) (path TSB), including the geometries of selected points with the distances of the bonds forming and breaking in this path. Structures **7** and **8** do not correspond to stationary points.

corresponding **TSA-m**. **TSB-m** lowered its energy by ca. 3 kcal/mol, while **TSB-p** increased its energy by ca. 1 kcal/mol, with regard to its TSA counterparts, respectively. The favored **TSB-m** perfectly predicts the complete regioselectivity observed experimentally for similar systems.

In our earlier study, we observed that for the reaction between dichloropropynylborane and butadiene the classical transition structure with [4 + 2] character was more stable than the [4 + 3] structure. This study shows that the presence of a donating alkyl substituent in C-2 of butadiene favors the meta regioselectivity and the system

switches the trajectory so that the reaction path through the non classical [4 + 3] transition structure is followed.

Alkynylboration. Along with the cycloaddition transition structures, the reaction path concerning the 1,4-alkynylboration of the diene has been investigated. Experimentally, enynes were obtained together with the cycloadducts in the reaction of 2-substituted 1,3-butadienes with different alkynyldihaloboranes. Furthermore, only the meta regioisomer of the two possible regioisomers was observed. From our earlier studies on the same system with butadiene, no direct route from the reactants to the alkynylboration product was found and only the

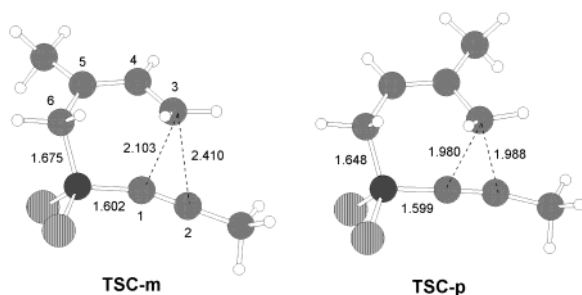


FIGURE 4. B3LYP/6-31G*-optimized geometries of the transition structures corresponding to the alkyneborane reaction between isoprene (**1**) and dichloropropynylborane (**2**) (path TSC). All distances are in Å.

transition structure connecting the cycloadduct and the alkyneborane product were found. However, a different behavior for isoprene would not only explain the experimentally observed enynes but their formation in a regioselective manner.

Figure 4 shows the computed geometries for the transition structures in the alkyneborane process for the two possible regioisomers. The principal feature of these transition structures is the advanced formation of the C6–B bond, as it has been described, with the B atom significantly pyramidalized. In addition, when compared with TSAs and TSBs, in these transition structures the dienophile portion is shifted with respect to the diene so that C1 is farther away from C6 and closer to C3. TSCs also show C1–B distances that are longer than the ones corresponding to TSAs and TSBs, which is consistent with the breaking of this bond during alkyneborane. The similar geometries computed for **TSC-m** and **TSC-p** might lead one to expect that they both correspond to the same reaction pathway. However, to our surprise, the IRC studies for these two transition structures showed very different results. The IRC calculation on **TSC-m** indicates that this transition structure connects the starting materials with the alkyneborane product. By contrast, the IRC carried out on **TSC-p** regioisomer clearly showed that this transition structure connects the alkyneborane and Diels–Alder product. From this important result, the experimental findings for the reaction with similar dienes and alkyneboranes are nicely reproduced since the observed “meta” alkyneborane product is predicted to come from the direct 1,4-alkyneborane of the isoprene, and hence, the only one formed. Closer examination of the geometries of the two TSC allowed us to observe some differences between them. The C2–C3 distance in **TSC-m** is 2.41 Å, while in **TSC-p** this distance is much shorter, 1.99 Å. Similarly, the C1–C3 forming bond in **TSC-m** is 2.10 Å, whereas in **TSC-p** is more advanced, 1.98 Å. This implies that for **TSC-p** the C3 atom is basically equidistant to C1 and C2, in agreement with a transition structure where these bonds are being formed in each side of the reaction coordinate, toward the cyclohexadiene or the alkyneborane product. The activation energy barrier for **TSC-m**, being 18.84 kcal/mol, only 0.81 kcal/mol higher than the **TSB-m**, predicts the formation of a 80:20 mixture of the meta cycloadduct and meta enyne products. However, in the reactions between isoprene and different alkyneboranes, only the cycloadducts are ob-

served experimentally. One possible explanation to account for this discrepancy between the calculations on the model system and the experiments could be that, once the enyne is formed, it undergoes conversion to the Diels–Alder cycloadduct. We have calculated the energies of the products of the reaction studied. We observed that the cycloaddition products are about 34 kcal/mol favored over the alkyneborane products. Moreover, both regioisomeric cycloadducts have the same energy, supporting the idea that the cycloaddition reaction is kinetically controlled, as no para cycloadduct has been observed experimentally. This suggests that the cycloadducts would be both kinetically and thermodynamically favored.

Singleton et al. enhanced the alkyneborane process over the Diels–Alder reaction by using hindered alkyneboranes.² Under these reaction conditions, the enynes were obtained as the major products in short reaction times. This shows that the steric clashes between the bulky substituent on C2 of the alkyneborane and the atoms of the diene destabilizes the Diels–Alder transition structures, kinetically favoring the alkyneborane process. The geometries of the transition structures located in this study are in accordance with these experimental results since the methyl on C2 of the dienophile is farther away from the diene in **TSC-m** compared with its cycloaddition counterparts **TSA-m** and **TSB-m**. From this observation, it could be inferred that when the bulkiness of the group on C2 increases, the alkyneborane becomes the preferred path because steric hindrance is minimized.

Although the formation of the meta alkyneborane product **5** involves the breaking of the bond between the boron atom and a sp carbon (C1), kinetics show that this process is almost as easy as the Diels–Alder reaction. The IRC calculation demonstrated that the meta alkyneborane has a concerted mechanism with a highly asynchronous transition structure where the C6–B bond is nearly formed and leaves a propargyl system with some degree of anion character coordinated to the boron. Since propargyl anions are reasonably stable, it can be deduced that this migrating group is not very tightly bound to the boron atom and consequently facilitates the alkyneborane process.

Regioselectivity. Although the frontier molecular orbital (FMO) theory has been shown to be a valuable approach in the understanding of the regioselectivity in a vast number of reactions,¹⁹ this is not the case for the system under study. The reactions with isoprene (**1**) and dichloropropynylborane (**2**) are controlled by the HOMO of the diene and the LUMO of the dienophile. As observed previously with vinylboranes,^{6b} the dienophile studied here, dichloropropynylborane (**2**), showed highly polarized orbitals with LUMO coefficients of ~ 0.1 for C1, attached to the boron group, and ~ 0.3 for C2. However, the HOMO coefficients for isoprene are ~ 0.3 for both terminal carbons (C3 and C6). Based on these coefficients, FMO theory incorrectly predicts no regioselectivity for the reaction under study.

The limitations of FMO theory have prompted the development of a number of alternative approaches in

(19) (a) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley & Sons: New York, 1976. (c) Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81.

TABLE 2. B3LYP/6-31G* Dipole Moments and Charge Transfer for the Reaction between Isoprene (1) and Dichloropropynylborane (2) in the Transition Structures

	dipole moment (D)	charge transfer (au)
TSA-m	5.0	+0.17
TSA-p	5.3	+0.17
TSB-m	8.0	+0.23
TSB-p	8.2	+0.24
TSC-m	8.0	+0.20
TSC-p	9.1	+0.09

order to better predict the regiochemical outcome of Diels–Alder reactions.²⁰ To understand the origin of the intriguing regio- and chemoselectivity that this class of reaction exhibits, we decided to look into the electronic effects that are involved in the transition structures found. Two factors are predicted to account for the regioselectivity and chemoselectivity observed. First, the electrophilicity of the boron atom allows strong C–B interactions, leading to transition structures with strong [4 + 3] character like TSBs, on the cycloaddition pathway, and transition structures such as TSCs, on the alkynylboration pathway, where the C–B bond is nearly formed. Second, the charge delocalization, due to the methyl substituent in isoprene, when situated in meta position permits a special stabilization of the transition structures. The greater the charge transfer from isoprene to the dienophile, the more positive charge is left on the isoprene, and so the greater the stabilizing contribution of the methyl.

We studied the charges that are being transferred from isoprene to the dienophile as well as the dipole moments in all the transition structures, as illustrated in Table 2. The values of the charge transferred in both TSA are 0.17 au, while much higher values are calculated for **TSB-m** and **TSB-p**, 0.23 and 0.24 au, respectively. The same significant increase is observed for the dipole moments, 5.0 and 5.3 D for **TSA-m** and **TSA-p**, compared to 8.0 and 8.2 D to **TSB-m** and **TSB-p**, respectively. More interesting are the high differences of these data for both TSCs, as one can expect for transition structures belonging to different pathways. The value of the charge transferred in **TSC-m** is 0.20 while in **TSC-p** is 0.09. Likewise, the value of the dipole moments for **TSC-m** and **TSC-p** are 8.0 and 9.1 D, respectively. The noticeable difference on the charge that is being transferred from isoprene to the dienophile for TSCs can be rationalized assuming that **TSC-m** results from the approach of the two starting materials, and therefore, the charge donated from the diene is expected to be larger than in the case of **TSC-p**, for which the nucleophilic attack of isoprene to the dienophile has taken place, and hence, the two components of the reaction are already bonded.

The natural bond order (NBO) analysis can give us a further insight regarding the extent in the bond-breaking and bond-forming processes. The results are collected in Table 3. The bond orders (BOs) found for the TSAs confirmed that these transition states are very asynchronous, with values for the C2–C3 bond of 0.41, for **TSA-m**, and 0.42 for **TSA-p**, while the values of the

C1–C6 BOs are 0.14 for **TSA-m** and 0.13 for **TSA-p**. Smaller values of the C6–B BOs, in both **TSA-m** and **TSA-p**, were observed, 0.16 and 0.11, respectively. More interesting results were observed in the data obtained in the case of TSB and TSC. In **TSB-m** and **TSB-p**, the high BO values for C6–B, 0.68 and 0.62, respectively, reveal the [4 + 3] character, due to the strong C–B interaction, observed in these transition structures. Besides, the BOs values for the C3–C4 and C4–C5 bonds for both TSBs are in the range 1.40–1.49, which indicates that the double bond is delocalized between C3, C4, and C5. For the TSCs, corresponding to the alkynylboration process, the BO values clearly confirm the differences between the **TSC-m** and **TSC-p**, as expected for transition structures that are in different pathways. While for **TSC-m**, the BO value of C2–C3 is 0.18, **TSC-p** shows a higher value, 0.41. This suggests that in the latter transition structure (**TSC-p**) this bond participates in the bond formation process (from cycloadduct to enyne), whereas in the **TSC-m**, this bond is not being formed (from reactants to enyne). Furthermore, the BO value for C6–B in **TSC-m** is slightly lower, 0.77, compared to the corresponding value in **TSC-p**, 0.82. Finally, the BO values for C1–B in **TSC-m** and **TSC-p** are 0.82 and 0.81, respectively, significantly lower than the values for the same bond in their TSA and TSB counterparts (varying in the range of 1.09–0.91), showing that this bond is breaking.

Although the IRC studies clearly showed that the two TSC found were actually in different pathways, and only **TSC-m** is connecting the starting material with the alkynylboration product, previous analysis of the frequencies suggested that this was the case, despite the similarity between the geometries of both transition structures. The components of the transition vector corresponding to the imaginary frequency allowed us to observe the motion of the atoms in the transition structure. This way, we observed that for **TSC-m**, the imaginary frequency corresponds to the motion of the C1 and C3 carbon atoms along the C–C bond formation. Nevertheless, in the case of **TSC-p**, it can be observed that the imaginary frequency corresponds to the motion of C3 that swings between C1 and C2, as well as the motion of these atoms toward or away from C3.

Conclusion

A DFT study has been carried out to investigate the regioselectivity of the reaction between isoprene and dichloropropynylborane. The Diels–Alder cycloaddition and 1,4-alkynylboration processes competing in this reaction have been characterized through their transition structures. For the cycloaddition, two different pathways have been found: the first one corresponds to the classic [4 + 2] cycloaddition, with some degree of [4 + 3] character due to SOI; the second one corresponds with a transition structure with a large [4 + 3] character because of the strong C–B interaction. The latter reaction pathway is energetically favored when the orientation between the diene and dienophile is meta, explaining the experimental findings for similar systems. There is no difference in energy between the two possible orientations (meta and para) in the case of the classical [4 + 2] transition structure. This suggests that the starting

(20) (a) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381. (b) Domingo, L. R.; Aurell, M. J.; Pérez, P.; Contreras, R. *J. Phys. Chem. A* **2002**, *206*, 6871. (c) Robiette, R.; Marchand-Brynaert, J.; Peeters, D. *J. Org. Chem.* **2002**, *67*, 6823.

TABLE 3. B3LYP/6-31G* Bond Orders for the Transition Structures in the Reaction between Isoprene (1) and Dichloropropynylborane (2)

	C1–C6	C2–C3	C1–C3	C6–B	C1–B	C3–C4	C4–C5	C5–C6	C1–C2
TSA-m	0.14	0.41	0.01	0.16	1.07	1.48	1.31	1.55	2.34
TSA-p	0.13	0.42	0.01	0.11	1.09	1.44	1.28	1.64	2.32
TSB-m	0.06	0.34	0.12	0.68	0.91	1.39	1.49	1.17	2.40
TSB-p	0.07	0.30	0.09	0.62	0.93	1.41	1.46	1.25	2.44
TSC-m	0.01	0.18	0.35	0.77	0.82	1.32	1.54	1.12	2.41
TSC-p	0.02	0.41	0.40	0.82	0.81	1.11	1.75	1.07	2.25

materials follow the pathway of the transition structures showing high [4 + 3] character. The reaction coordinate profile for this cycloaddition pathway showed a nearly flat region in the reaction coordinate that corresponds to a seven-membered ring structure that was not quite a stationary point, as found previously for the same type of systems with butadiene. For the 1,4-alkynylboration process, IRC calculations confirmed that the transition structure with meta orientation corresponds to the concerted direct alkynylboration of the 2-substituted 1,3-butadiene, and, therefore, explains the regioselectivity found experimentally for similar systems, whereas the para orientation transition structure, when launched toward the reactants, leads to the cyclohexadienylborane product, as in the case of butadiene.

Acknowledgment. We are grateful to the Royal Society. S.C.P. thanks Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) and Fundación

Antorchas for postdoctoral fellowships. M.A.S. thanks the European Community for a Marie Curie fellowship. We thank the Departamento de Química Orgánica, Universidad de Extremadura, for providing us with computer facilities.

Supporting Information Available: Cartesian coordinates and absolute energies (in hartrees), including ZPE, and number of imaginary frequencies of all stationary points reported in the paper; values of imaginary frequencies of all transition structures. Plots of the relative energy (kcal/mol) versus reaction coordinate (in atomic units, (amu)^{1/2} Bohr), from B3LYP/6-31G* intrinsic reaction coordinate calculations, for all the transition structures. Representation of the reaction pathways TSB and TSC on the PES for the meta and para orientations. Energies and atomic coefficients of the frontier molecular orbitals of the reactants. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO026821Z