



## DFT calculations induced a regiochemical outcome revision of the Diels–Alder reaction between levoglucosenone and isoprene

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### ABSTRACT

An appealing inversion in the regiochemical outcome of Diels–Alder reactions between levoglucosenone (**1**) and its  $\alpha$ -bromo derivative (**5**) with isoprene (**2**) was studied computationally. Based on different DFT calculations we concluded that both reactions should display the same regioselectivity. This result was further validated experimentally.

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The Diels–Alder (DA) reaction is one of the most powerful methods to synthesize, in a regio and stereocontrolled manner, six-membered carbocyclic compounds with up to four stereogenic centers in one step.<sup>1</sup> Its remarkable versatility offers organic chemists an excellent synthetic tool in the construction of complex molecular architectures.<sup>2</sup> One of the main features of this chemical transformation is the regioselective product formation when using unsymmetrical dienes and dienophiles. In simple cases the regiochemistry outcome can be predicted by the *ortho/para* rule, although exceptions have been observed.<sup>1</sup>

Within this context, in 1996 Miftakhov et al.<sup>3</sup> reported an unusually regioselective Diels–Alder reaction between levoglucosenone (**1**), a chiral bicyclic enone obtained as major product of the pyrolysis of cellulose,<sup>4</sup> and isoprene (**2**). As shown in Scheme 1, the reaction between **1** and isoprene (**2**) led to the formation of adducts **3** (*para*) and **4** (*meta*), being compound **4** the major isolated product under both thermal and Lewis acid-promoted reaction conditions.<sup>3</sup> More recently, the group of Isoe described the reaction between bromolevoglucosenone **5** and isoprene as a key step in the total synthesis of optically active (–)-tetrodotoxin, a toxic principle of puffer-fish (tora fugu) poison.<sup>5</sup> In this case, the expected *para* cycloadduct **6** was obtained in good to excellent yields (Scheme 1).

It has been well documented that **1** acts as a ‘normal’ dienophile in DA reaction with other unsymmetrical dienes such as 1-substituted-1,3-butadienes<sup>6</sup> and 9-substituted anthracenes,<sup>7</sup> affording the expected *ortho* adducts as major isomers. For that reason, the

*meta* regioselectivity in the DA reaction between **1** and **2**, along with the clear inversion in the regioselectivity caused by the bromine substitution, resulted in an interesting system to be theoretically treated. Hence, in an effort to address the origins of these puzzling experimental findings, we undertook a computational investigation at the B3LYP/6-31G\* level of theory using GAUSSIAN 09.<sup>8</sup>

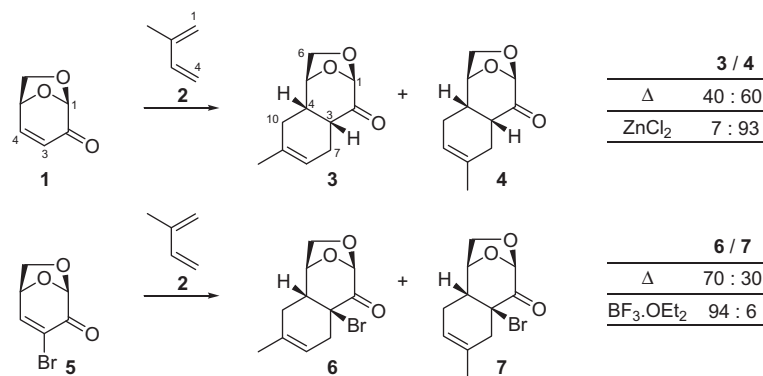
Recent studies devoted to DA reactions have shown that the global and local indexes defined within the context of DFT are helpful to gain insight into the chemical reactivity and selectivity.<sup>9–11</sup> For this reason, selected static global (electronic chemical potential  $\mu$ , chemical hardness  $\eta$ , and global electrophilicity  $\omega$ ) and local (Fukui functions  $f_k^\pm$  and local electrophilicity indices  $\omega_k$ ) descriptors have been computed for **1**, **2** and **5** at the B3LYP/6-31G\* level of theory (Table 1).<sup>12</sup>

The electronic chemical potential of **1** and **5** are lower than the electronic chemical potential of isoprene, indicating thereby that along these DA reactions a net charge transfer will take place from diene toward dienophile, as expected in normal electron demand DA reactions. The electrophilicity of enones **1** and **5** are 1.83–2.13 eV, values that fall in the range of strong electrophiles within the  $\omega$  scale.<sup>10</sup> Interestingly, the  $\omega$  value for **5** (2.13 eV) is larger than that for levoglucosenone (1.83 eV), accounting for the net electron-withdrawing effect exerted by the halogen substitution. As a consequence, more polar character should be expected in the reaction between **2** and **5** (vide infra).

Regarding the local indexes, in both dienophiles the C4 is the preferential electrophilic site for nucleophilic attack as measured by both the large  $f_k^+$  and  $\omega_k$  values, whereas the nucleophilic site of isoprene is the C1 atom with largest value of  $f_k^-$ .<sup>11</sup> According to this analysis, the *para* adducts should be favoured regarding

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Scheme 1.

the nature of the dienophile. In addition, the larger  $\Delta\omega$  value in **5** indicates that higher regioselectivity should be expected in this case.<sup>10,11</sup>

We next turned our attention to locate all competing transition structures (TSs) for the thermal cycloaddition processes under study. Although up to four isomeric products can be formed in the Diels–Alder reaction between **2** and **1** or **5**, the transition structures resulting of the attack of diene from the  $\beta$  face of dienophiles were neglected, since it is well known that the steric hindrance produced by the 1,6-anhydro bridge precludes any addition from this side.<sup>4a,6,7</sup> As a consequence, we considered only four reaction channels, depending on the approach and orientation of isoprene towards dienophiles, namely **TS-1-NP**, **TS-1-NM**, **TS-1-XP**, **TS-1-XM**, **TS-5-NP**, **TS-5-NM**, **TS-5-XP** and **TS-5-XM**. The transition structures were named as follows: the first number indicate the dienophile; the N and X were used for endo and exo orientation, the P and M accounts for *para* and *meta* orientation. Each product can be formed from both the endo and exo approaches corresponding to the same regiochemistry. Examination of the reaction surfaces allowed us to locate the transition structures corresponding for each mode of addition, as shown in Figure 1. The concerted nature of these reactions was determined after IRC calculations, yielding all TSs as the only saddle points connecting reagents and products. The lengths of the two C–C forming bonds at these TSs indicate that they also correspond to high asynchronous bond formation process. The shorter distances and higher Wiberg bond indices (WBI) correspond to the C–C bond formation involving the C4 carbon atom of the dienophile, that is, the most electrophilic center. The more polar character of the DA reaction between **5** and **2** is evidenced by the higher asynchronicity of the corresponding TSs. In addition, we found that the charge transfer is higher (0.18–0.23 e) than for the **1** + **2** system (0.14–0.16 e), in perfect agreement with the conceptual DFT analysis discussed above.<sup>12</sup> Calculated activation energies suggests that in both cycloadditions the *para* reaction channels are slightly favoured. Accordingly, the computed *para/meta* ratio for the reaction between **5** and **2** is 77:23, in excellent agreement with the reported value of 70:30.<sup>13</sup>

Table 1

Compd	Global properties			Local properties			
	$\mu$ (au)	$\eta$ (au)	$\omega$ (eV)	Site	$f_k^+$	$f_k^-$	$\omega_k$ (eV)
<b>1</b>	–0.15	0.17	1.83	C3	0.08	0.02	0.15
				C4	0.24	0.09	0.44
<b>5</b>	–0.16	0.17	2.13	C3	0.05	0.00	0.10
				C4	0.24	0.09	0.50
<b>2</b>	–0.12	0.21	0.94	C1	0.23	0.28	0.21
				C4	0.24	0.24	0.22

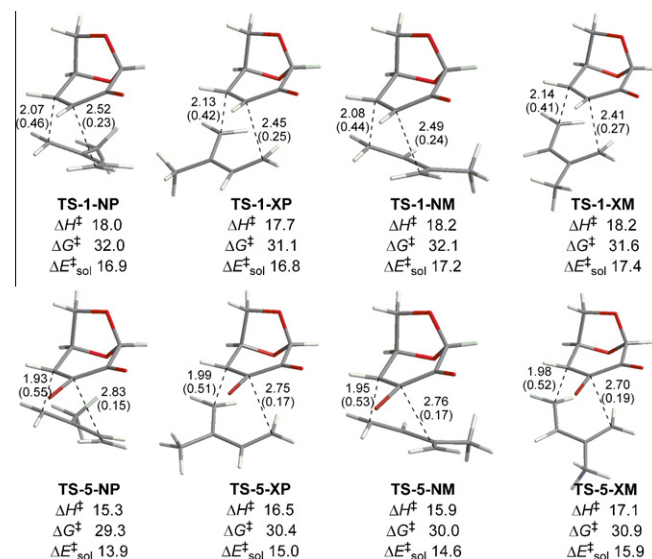
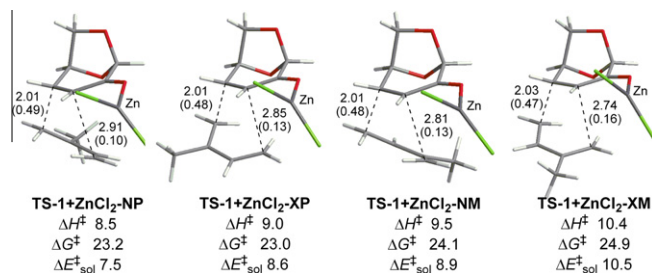


Figure 1. Optimized geometries for the TSs of the cycloaddition reaction of isoprene with **1** and **5** with selected distances in Å and Wiberg bond indices (in parentheses). Computed activation energies in the gas phase and in solution are shown in kcal mol<sup>–1</sup>.

In the case of the reaction between **1** and **2** the calculated *para/meta* ratio is 60:40,<sup>13</sup> in contrast to the 40:60 ratio determined experimentally.<sup>3</sup> One possible explanation to account for this discrepancy between our calculations and the experimental results could be that the reaction is under thermodynamic control, although no cycloreversion was observed experimentally.<sup>3</sup> In good agreement, we found that the retro-DA path should be strongly disfavoured (~21 kcal/mol) clearly indicating that the reaction should be kinetically controlled.

At this point of the study it was clear that the regioselectivity displayed by **5** could be nicely predicted by our calculations. For this reason, we turned our efforts to rationalize the unusual *meta* regiochemical outcome observed when using levoglucosenone as dienophile under ZnCl<sub>2</sub> catalysis. As depicted in Scheme 1, the use of this Lewis acid produced a dramatic effect on both reactivity and regioselectivity.<sup>3</sup> Coordination of ZnCl<sub>2</sub> to the carbonyl oxygen of levoglucosenone increases the electrophilicity of **1** from 1.83 to 3.56 eV, indicating higher polar character in the DA reaction with isoprene.<sup>10</sup> In addition, the local electrophilicity indices computed for the C3 (0.07 eV) and C4 (0.81 eV) atoms suggest that upon complexation the *para* regioselectivity should be higher.<sup>11</sup> After extensive exploration of the potential energy surfaces, we were able to locate all TSs corresponding to the [4 + 2] cycloaddition process



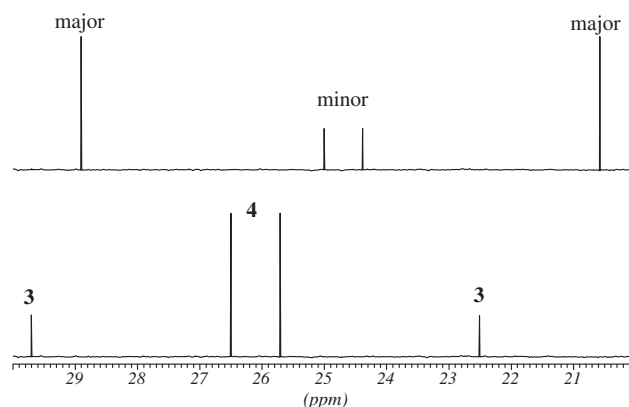
**Figure 2.** Optimized geometries for the TSs of the cycloaddition reaction of isoprene with **1** + ZnCl<sub>2</sub> with selected distances in Å and Wiberg bond indices (in parentheses). Computed activation energies in the gas phase and in solution are shown in kcal mol<sup>-1</sup>.

(Fig. 2). As expected, the **TS-1 + ZnCl<sub>2</sub>** display higher asynchronicity and charge transfer (~0.30 e), indicating the advanced ionicity of the process.<sup>12</sup> As in the thermal reactions, the TSs leading to the *para* adduct are lower in energy. The calculated *para/meta* ratio is 90:10,<sup>13</sup> in clear contrast with the reported 7:93 ratio.<sup>3</sup>

The markedly difference between calculated and reported experimental regiochemical preference in the reaction of **1** and **2** resulted in a intriguing result. Under these circumstances, we envisaged the use of quantum chemical NMR chemical shift prediction to solve this discrepancy in a straightforward manner,<sup>14</sup> since it is not uncommon for structures to be incompletely or incorrectly assigned, even after scrupulous spectroscopic studies.<sup>15</sup>

For that reason, we computed the NMR shifts of both regioisomers **3** and **4**, and compared with the available experimental data reported for both isomers. Among different methods for calculating nuclear magnetic shielding tensors, we used the GIAO (gauge including atomic orbitals)<sup>16</sup> combined with the multi-standard approach (MSTD), that involves the use of methanol and benzene as reference standards for computing NMR shifts of sp<sup>3</sup>- and sp<sup>2</sup>-hybridized carbon atoms, respectively.<sup>17</sup> This approach has been shown to perform much better than TMS as reference standard in terms of accuracy and precision, and also displays lower dependence on the level of theory employed. Accordingly, the <sup>13</sup>C NMR chemical shifts for **3** and **4** were computed at the recommended mPW1PW91/6-31G\*/mPW1PW91/6-31G\* level of theory,<sup>17</sup> and are shown in Table 2 together with the reported experimental values for the major and minor isomers, respectively.<sup>3</sup>

As shown in Table 2, the correlation level was rather low, with high average deviations (2.6–2.7 ppm) and several carbon atoms showed absolute errors higher than 3 ppm. Although most of the computed <sup>13</sup>C NMR signals were in agreement with the literature data, we found that the pairs C7–C10 were calculated in the reverse order.<sup>12</sup> Moreover, the experimental values of those nuclei



**Figure 3.** Experimental (top) and calculated (bottom) <sup>13</sup>C NMR chemical shifts of allylic carbons C7 and C10 for adducts **3** and **4**.

are more differentiated in the major isomer, feature that is better reproduced in the calculated shifts for the *para* isomer (Fig. 3).

To further test the correctness of the original structural assignment, we computed the CP3 parameter recently introduced by Goodman to address the question of assigning two sets of experimental data to two possible structures.<sup>18</sup> After matching up the experimental shifts in order with the calculated shifts, the CP3 parameter calculated for the combination major-**4** and minor-**3** was –0.79, while the CP3 parameter for the system major-**3** and minor-**4** was 0.76. Since a positive value indicates good agreement (assignment likely to be correct),<sup>18</sup> there was a high probability that the adducts **3** and **4** had been incorrectly assigned, confirming the *para* selectivity of the former DA reaction.

In order to validate the result of our calculations, we finally synthesised compounds **3** and **4** according to the published procedure.<sup>3</sup> Treatment of levoglucosenone with freshly distilled isoprene and anhydrous ZnCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C afforded two unseparable products in a 88:12 ratio and 45% overall yield after column chromatography.<sup>12</sup> Recrystallization from hexane/ether furnished pure crystals of the major isomer (mp 104–106 °C [lit.<sup>3</sup> 103–105 °C]; [ $\alpha$ ]<sub>D</sub> –38.7 (c 1.06, CHCl<sub>3</sub>) [lit.<sup>3</sup> –39.1 (c 1.00, CHCl<sub>3</sub>)]. The individual <sup>1</sup>H and <sup>13</sup>C resonances were assigned by using gradient-selected (gs-) COSY, HSQC and HMBC experiments, and are shown in Table 3.

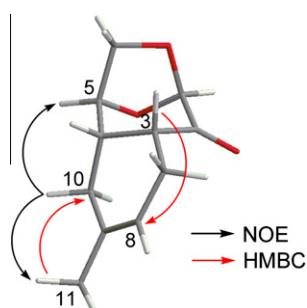
The *para* regiochemistry of this compound was unequivocally determined by HMBC experiments. As depicted in Figure 4, the key interactions are between H-3 (3.12 ppm) with the CH vinylic carbon (117.9 ppm), and between methyl group at 1.64 ppm with the allylic C-10 carbon (28.9 ppm). This assignment was further confirmed by NOE experiments, since signal enhancement between H-10/H-5 and H-10/H-11 was also detected.

**Table 2**

Atom	Experimental (ppm)		Calculated (ppm)		Difference (ppm)	
	Major	Minor	<b>4</b>	<b>3</b>	$\delta_{\text{major}} - \delta_4$	$\delta_{\text{major}} - \delta_3$
C1	101.6	101.6	99.0	99.1	2.6	2.5
C2	202.3	202.3	201.2	201.2	1.1	1.2
C3	41.0	40.3	38.4	37.3	2.6	3.0
C4	37.6	38.7	40.2	41.1	2.6	2.4
C5	77.2	77.2	75.1	75.3	2.1	1.9
C6	67.2	67.2	65.8	65.9	1.4	1.3
C7	28.9	25.0	25.7	22.5	3.2	2.5
=C–H	117.9	118.7	123.0	123.9	5.1	5.2
=C–Me	131.5	130.9	133.7	132.5	2.2	1.6
C10	20.6	24.4	26.5	29.7	5.9	5.3
C11	23.5	23.2	24.8	25.1	1.3	1.9
				Average	2.7	2.6

**Table 3**  
 $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts of compound **3** in  $\text{CDCl}_3$

Position	$^1\text{H}$	$^{13}\text{C}$
1	5.12	101.6
2	—	202.2
3	3.12	37.6
4	2.50	41.1
5	4.48	77.2
6	4.19, 4.03	67.2
7	2.67, 2.01	20.6
8	5.35	117.9
9	—	131.5
10	2.33, 1.89	28.9
11	1.64	23.5



**Figure 4.** Optimized geometry of compound **3** (major adduct) with key HMBC and NOE correlations.

In summary, the regiochemical outcome of the Diels–Alder reaction between levoglucosenone and isoprene has been revised using different DFT theoretical approaches, and was validated experimentally.<sup>19</sup> In addition, the result of this study underscores the value of modern computational chemistry in solving apparent puzzling experimental results.

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### Supplementary data

Supplementary data (computational and spectroscopic data and experimental procedures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.021.

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- Similar experimental and NMR data treatment was performed with compound **5**. The study was found coincident with the results published by Isobe and co-workers.