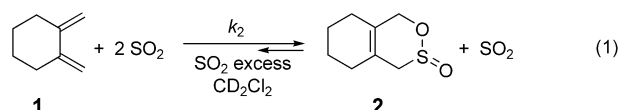


Hetero-Diels–Alder Reaction

Equilibrium and Kinetic Deuterium Isotope Effects on the Hetero-Diels–Alder Addition of Sulfur Dioxide**

Frédéric Monnat, Pierre Vogel,* Rubén Meana, and José A. Sordo*

At room temperature butadiene and alkyl-substituted 1,3-dienes that can adopt the *s-cis* conformation add to sulfur dioxide giving the corresponding sulfones (2,5-dihydrothiophene-1,1-dioxides),^[1] which are about 10 kcal mol^{−1} more stable than the isomeric sultines (3,6-dihydro-1,2-oxathiin-2-oxides).^{[2][3]} In the presence of acid catalysts and at temperatures below −40 °C the latter equilibrate with the 1,3-dienes, which results in hetero-Diels–Alder additions that are much faster than the corresponding cheletropic additions.^[4] The hetero-Diels–Alder addition of 1,2-dimethylenecyclohexane (**1**) to SO₂ does not require promotion by an acid [Eq. (1)]. However, we have demonstrated that the reaction is



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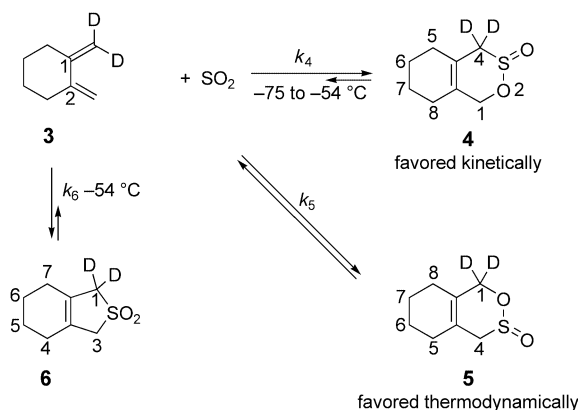
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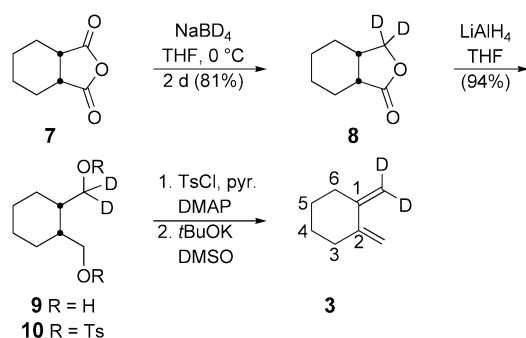
promoted by SO₂ itself (rate law of second order in [SO₂]).^[5] The unstable sultine **2** resulting from that cycloaddition has been crystallized and analyzed by X-ray diffraction studies at –100 °C.^[6] High-level quantum calculations^[6,7] have suggested that the hetero-Diels–Alder addition of SO₂ to 1,2-dimethylidenecyclohexane is concerted and asynchronous, with the C–S bond formed to a greater extent than the C–O bond in the transition state. We confirm this hypothesis by measuring the kinetic deuterium isotope effect^[8] of the reactions of **1** and its dideuterated derivative **3** with SO₂. Diene **3** equilibrates with the two regioisomeric adducts **4** and **5** (Scheme 1). The experimental kinetic isotope effects are



Scheme 1. The reaction of SO₂ with **3**.

compared with those estimated by quantum calculations. We have been able also to measure the deuterium isotope effect on the equilibrium **4** ⇌ **5** and have found that it is opposite to the kinetic deuterium isotope effect on the regioselectivity of the addition. This is the first example of Diels–Alder additions for which kinetic and equilibrium isotope effects are compared.

Diene **3** (98 % D₂) was prepared as outlined in Scheme 2, starting with the reduction of *cis*-cyclohexane-1,2-dicarboxylic anhydride (**7**) with one equivalent of NaBD₄ in THF at 0 °C. The resulting lactone **8** was reduced with LiAlH₄ to give diol **9**. Esterification with 4-toluenesulfonyl chloride (TsCl) gave **10**, which underwent double elimination of toluenesulfonic acid to provide **3** (26 % overall yield based on **7**).



Scheme 2. Synthesis of diene **3**. DMAP = dimethylaminopyridine, DMSO = dimethyl sulfoxide, pyr. = pyridine.

The rate laws $d[4]/dt = k_4[3][SO_2]^2$, $d[5]/dt = k_5[3][SO_2]^2$ (formation of regioisomeric sultines **4**, **5**), and $d[6]/dt = k_6[3][SO_2]^2$ (formation of sulfolene **6**) were followed between –75 and –54 °C and with a 10- to 40-fold excess of SO₂ in CD₂Cl₂. The third-order rate constants k_4 , k_5 , and k_6 are reported in Table 1. One finds a kinetic regioselectivity $k_4/k_5 = 1.11 \pm 0.01$ at –75 °C and 1.0798 ± 0.0003 at –54 °C. The thermodynamic

Table 1. Third-order rate constants [M²s^{–1}] determined by ¹H NMR spectroscopy with toluene as an internal reference.

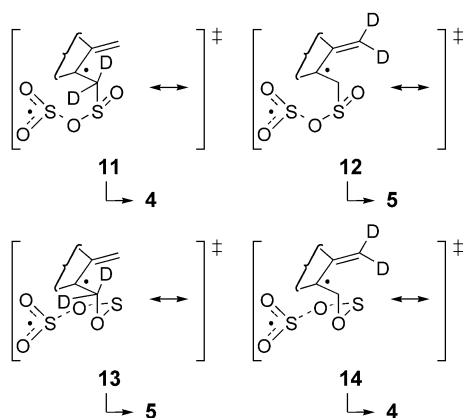
T [K]	$k_4 \times 10^6$	$k_5 \times 10^6$	$k_6 \times 10^9$	k_4/k_5
198	2.13 ± 0.15	1.91 ± 0.13	76.9 ± 0.5	1.11 ± 0.001
219.1	4.03 ± 0.16	3.73 ± 0.15	338 ± 3	1.0798 ± 0.003

regioselectivity given by $[4]/[5]$ could not be measured at –75 °C because equilibrium was reached too slowly. At –54 °C, however, it amounts to $[4]/[5] = 0.73 \pm 0.04$ (no change in this product ratio after more than 300 h at –54 °C).

We have also measured the relative rate constants for the disappearance of dienes **1** and **3**. The ratio of rate constants $k_2/2k_4$ and $k_2/2k_5$ give the kinetic deuterium isotope effect for the formation of sultines **4** and **5**, respectively, where k_2 is the rate constant for the appearance of non-deuterated sultine **2**. This was done by following the reactions of a 1:1 mixture of dienes **1** and **3** ($[1+3] < 0.2$ M, 2.5–3 M SO₂ in CD₂Cl₂) at –75 °C by ¹³C NMR spectroscopy (toluene as internal reference; because of the vicinal deuteration, the chemical shifts of C1 in **1** and **2** are different). The ratio $k_4/k_5 = 1.11 \pm 0.01$ (Table 1) led to $k_2/2k_4 = 0.89 \pm 0.04$ (k_H/k_D for the formation of **4**) and $k_2/2k_5 = 0.99 \pm 0.05$ (k_H/k_D for the formation of **5**) at –75 °C.

Equilibrium deuterium isotope effects have shown that C–D bonds at sp³(C) centers are lower in energy than those at sp²(C) centers.^[9] It was thus expected that the transition structure **11** (in which the C–S bond is formed to a greater extent than the C–O bond) should be more stable than **12** and the corresponding transition structure arising from the non-deuterated dienes. On the contrary, if the C–O bond should be formed first, transition structure **13** is expected to be more stable than **14** and the transition structures of the SO₂ addition to **1** (Scheme 3). Our experimental data ($k_4/k_5 = 1.1$, $k_2/2k_4 = 0.89$, and $k_2/2k_5 = 0.99$ at –75 °C) are consistent only with transition structure **11**, as predicted by quantum calculations.^[2] Although the calculations did not locate any intermediates along the reaction hypersurface of the hetero-Diels–Alder addition of butadiene + 2SO₂,^[5] we cannot exclude formally that **11** and **12** equilibrate with diradical or zwitterionic intermediates before the formation of sultines **4** and **5**, respectively.

Isotope effects were computed by means of the QUIVER program,^[10] which employs the Bigeleisen–Mayer formulation^[11] within the transition-state-theory approximation.^[12] Scaling factors of 0.943 [MP2/6-31G(d)] and 0.9614 [B3LYP6-31G(d)] were used in the calculations.^[13] The kinetic deuterium isotope effects calculated are reported in Table 2 for the hetero-Diels–Alder addition of **1/3** + 2SO₂ and of butadiene (**15**)/1,1-dideuterobutadiene (**16**) + 2SO₂ following concerted mechanisms.



Scheme 3. Transition structures leading to products **4** and **5**.

Calculations predict smaller k_H/k_D values than those found experimentally, but the calculated kinetic regioselectivities k_4/k_5 are similar to the experimental values. This confirms that the C–S bond is formed to a greater extent than the C–O bond in the transition state of the hetero-Diels–Alder additions of sulfur dioxide (see Figure 1). Calculations made for the butadiene + SO₂ reaction predict the C–O bond to be formed to a greater extent in the transition state of the concerted mechanism. For the reaction involving a diradical intermediate ‘OSOCH₂CH=CH₂CH₂’ calculations lead to k_4/k_5 values much smaller than those observed (Table 3). Furthermore, the “energy of concert”^[14] (the difference between the activation energies of the concerted and diradical transition states) is ca. 13 kcal mol^{–1} in favor of the concerted mechanism.

The theoretical prediction for the thermodynamic regioselectivity at the B3LYP6-31G(d) level of theory (0.758 and 0.718 for equilibria involving one and two molecules of SO₂,

Table 2: Calculated kinetic deuterium isotope effects for concerted hetero-Diels–Alder additions.

Reaction	Ratio	T [°C]		
		–75	–54	+25
1/3 + 2 SO ₂ → [11] → 4 + SO ₂	k_H/k_D ^[a]	0.692	0.725	0.816 ^[b]
	(0.714)	(0.746)	(0.830) ^[c]	
1/3 + 2 SO ₂ → [12] → 5 + SO ₂	k'_H/k'_D ^[d]	0.776	0.801	0.869 ^[b]
	(0.734)	(0.763)	(0.841) ^[c]	
Kinetic regioselectivity ^[e] :		1.12	1.10	1.06
15/16 + 2 SO ₂ → [11'] → 4' + SO ₂	k_H/k_D ^[e]	0.707	0.741	0.829 ^[b, j]
	(0.673)	(0.709)	(0.806) ^[c]	
	0.658	0.695	0.796 ^[f]	
	(0.755)	(0.785)	(0.865) ^[g]	
15/16 + 2 SO ₂ → [12'] → 5' + SO ₂	k'_H/k'_D ^[h]	0.693	0.729	0.824 ^[b]
	(0.721)	(0.754)	(0.842) ^[c, k]	
	0.748	0.780	0.861 ^[f]	
	(0.647)	(0.685)	(0.789) ^[g]	

[a] $k_H/k_D \approx k_1/2k_4$. [b] B3LYP6-31G(d). [c] B3LYP6-31G(d) for the reaction with only one equivalent of SO₂. [d] $k'_H/k'_D \approx k_1/2k_5$. [e] $k_H/k_D \approx$ butadiene + 2 SO₂ vs. 1,1-D₂-butadiene + 2 SO₂ giving a sultine analogous to **4**. [f] MP2/6-31G(d). [g] MP2/6-31G(d) for reaction with only one equivalent of SO₂. [h] $k'_H/k'_D \approx$ butadiene + 2 SO₂ vs. 1,1-D₂-butadiene + 2 SO₂ giving sultine analogous to **5**. [i] $k'_H/k'_D(5)/k_H/k_D(4)$ and $k'_H/k'_D(5')/k_H/k_D(4')$; calculated (B3LYP6-31G(d) including zero-point energy). [j] Energy barrier: 4.8 kcal mol^{–1}. [k] Energy barrier: 12.2 kcal mol^{–1}.

Table 3: Calculated kinetic deuterium isotope effects for nonconcerted hetero-Diels–Alder addition of SO₂ + butadiene → [‘OSOCH₂CH=CH₂CH₂’]^[a].

Reaction	Ratio	T [°C]		
		–75	–54	+25
15, 16 + SO ₂ → 4'	k_H/k_D ^[b]	1.086	1.075	1.046 ^[c]
15, 16 + SO ₂ → 5'	k'_H/k'_D ^[d]	0.568	0.610	0.727 ^[c]
Kinetic regioselectivity ^[e] :		0.52	0.56	0.69

[a] Calculated (B3LYP6-31G(d)) energy barrier: 25.3 kcal mol^{–1}, relative stability of the diradical intermediate: 18.5 kcal mol^{–1}, second energy barrier: 19.1 kcal mol^{–1}. [b] $k_H/k_D = k(15 + SO_2)/k(16 + SO_2 \rightarrow 4')$. [c] B3LYP6-31G(d). [d] $k'_H/k'_D = k(15 + SO_2)/k(16 + SO_2 \rightarrow 5')$. [e] Ratio $(k'_H/k'_D)/(k_H/k_D)$.

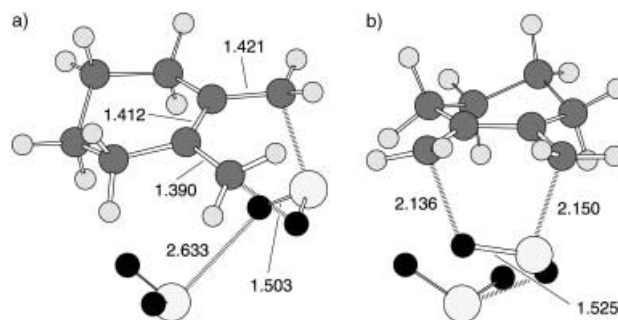


Figure 1. Calculated transition structure for the hetero-Diels–Alder addition **1** + 2 SO₂. a) Top view, b) side view. Large pale balls = sulfur, small black balls = oxygen, medium gray balls = carbon, small pale balls = hydrogen. Distances in Å.

respectively) agrees rather well with the experimental measurements (0.73 ± 0.04).

The equilibrium deuterium isotope effect that renders **5** more stable than **4** can be interpreted in terms of the preference for deuterium to substitute at C–H moieties with the highest stretching vibration energy. In sultines **4** and **5** the acidifying effect of the S=O moiety makes the C4–H bond weaker than the C1–H bond. Thus deuterium prefers C1, rendering **5** more stable than **4**. The kinetic isotope effects (Dimroth principle: $\Delta H^\ddagger = \alpha \Delta H + \beta$), thus reinforcing the validity of the experimental test used here to define the asynchronous character of the concerted hetero-Diels–Alder additions of SO₂.^[14]

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