



### Transition structures for the oxy–ene reaction†

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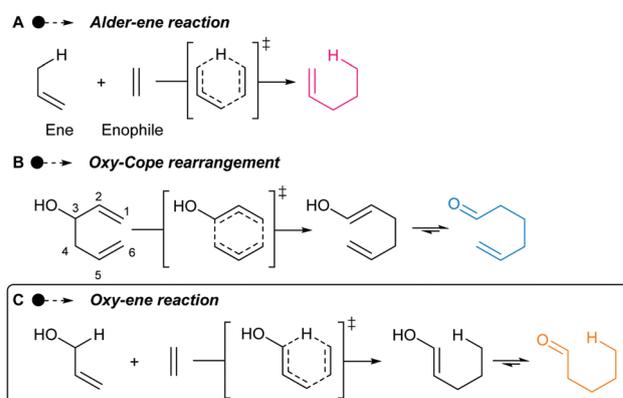
**An overlooked pericyclic reaction between allyl alcohols and alkenes to form carbonyl compounds is analyzed. It combines the characteristic features of the Alder–ene reaction and of the oxy-Cope rearrangement. This oxy–ene reaction could be involved in biosynthetic pathways.**

Discovered in 1943,<sup>1</sup> the Alder–ene reaction is a fundamental organic transformation that keeps receiving considerable attention (Scheme 1A).<sup>2</sup> The computational study of Fernández and Bickelhaupt has explained why it usually requires a high temperature despite its pericyclic nature.<sup>3</sup> The difficult deformation of the reactants to reach the geometry of the aromatic six-membered transition state leads to a high activation strain and consequently a high barrier. However, the use of polarized enes and enophiles greatly reduces the activation energies and allows Alder–ene reactions to take place under gentle heating, or even at room temperature.<sup>4</sup>

Polarized Alder–ene reactions are believed to occur naturally.<sup>5</sup> The first enzyme-catalyzed Alder–ene reaction reported in 2020 by Zhou, Houk, Tang and co-workers<sup>6</sup> supports this hypothesis. This breakthrough could lead to new applications of the Alder–ene reaction and encourages the reconsideration of biosynthetic routes towards some natural products. In that respect, the biogenesis of the aristotelia alkaloid aristone<sup>7</sup> has long been debated (Scheme 2).<sup>8</sup> After ruling out an earlier hypothesis,<sup>8a</sup> Borschberg rationalized the formation of aristone and its stereochemistry by an intramolecular [1,5]-*H* shift from intermediate **1**, which displays an allyl alcohol and an indole moiety.<sup>8b,c</sup> This concerted intramolecular process would lead to enol **2** and then aristone

after keto-enol tautomerism. Because of its similarity with the Alder–ene reaction and with the oxy-Cope rearrangement in terms of reactants and products (Scheme 1B), Borschberg referred to this transformation as “oxyanion-ene” reaction in 1996.<sup>8c</sup>

In fact, such a reaction had been described in 1981 by Klärner and co-workers who named it “oxy-homodienyl hydrogen shift” by analogy with the oxy-Cope rearrangement.<sup>9</sup> The stereoselective thermolysis of (*Z*)-hexa-2,5-dienols like compound **3** into *cis*-cyclopropane **4** was achieved at ca 260 °C, overcoming an experimentally determined Gibbs free energy of activation of 43.5 kcal mol<sup>-1</sup> (Scheme 3). Borschberg designed his own substrates such as **5** and investigated their thermally-induced reaction, coined “oxy–ene” in 2001 (Scheme 1C),<sup>10</sup> pointing out that stereoselective transformations could be achieved at high temperature. It is well-known that the oxy-Cope rearrangement can be accelerated by deprotonation of the hydroxy group.<sup>11</sup> This has been attributed to the bond-weakening effect induced by the alkoxide to the adjacent C3–C4 bond.<sup>12</sup> In a second 2001 paper, Borschberg reported anionic oxy–ene reactions, such as **5** → **8** → **9** → **7**, which proved to be faster than neutral ones.<sup>13</sup> Of note, the first anionic oxy retro–ene reaction was reported by Jung and Davidov the same year.<sup>14</sup>



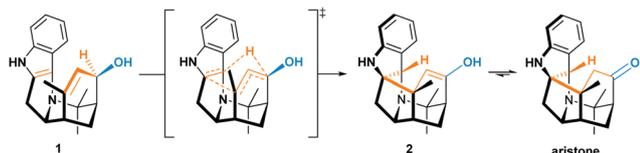
Scheme 1 Some pericyclic reactions.

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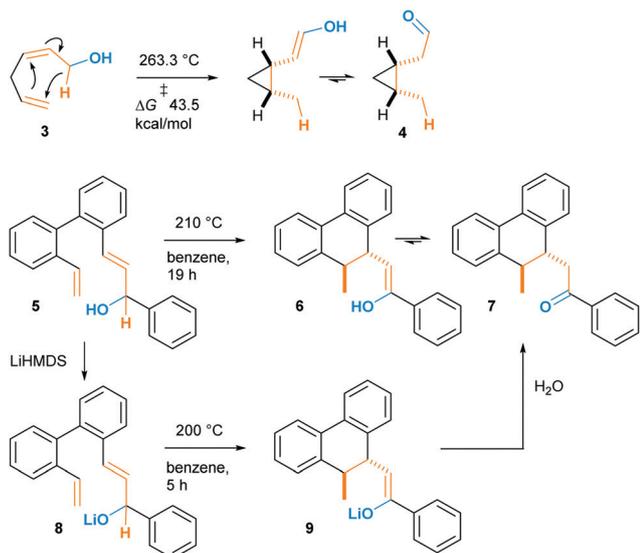
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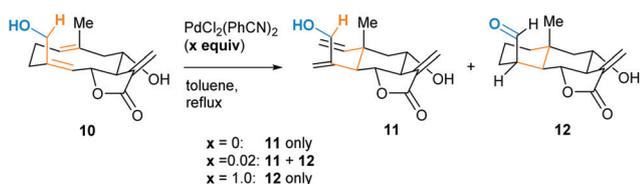


Scheme 2 Borschberg's hypothesis regarding the biosynthesis of aristone.



Scheme 3 Reported neutral and anionic oxy-ene reactions.

The high energy demand of the reported oxy-ene reactions seems to question the viability of such a process in a biological environment. However, the enophilic moiety of compound **1** is quite specific, being both an indole and an enamine double bond. This substrate also presents acidic and basic sites that could form strong hydrogen bonds. In 1998, Barrero and co-workers reported that, when heated in toluene, (+)-salonitenolide **10** undergoes thermal Cope rearrangement into (+)-dehydromelitensin **11** (Scheme 4).<sup>15</sup> In the presence of 0.02 equiv of PdCl<sub>2</sub>(PhCN)<sub>2</sub>, **10** transforms into a mixture of **11** and (+)-stoebenolide **12**. The latter can be obtained selectively when using an equimolar amount of the Pd(II) complex. With a low concentration of Pd(II), ring opening leads to **11** as in a typical Lewis acid catalyzed formal Cope rearrangement.<sup>16</sup> At higher Pd(II) concentration, the ligand acts as a base, leading to **12** as formal oxy-ene product.



Scheme 4 Pd(II)-promoted rearrangement of germacranolides: formal Cope (**11**) and oxy-ene (**12**) reactions.

The capacity of enzymes to catalyze Alder-ene reactions<sup>6</sup> offers a new perspective on biosynthetic pathways. We report herein the first theoretical analysis of the oxy-ene reaction under neutral or basic conditions using parent compounds. We then shed light on its possible role in the biosynthesis of aristone using enzyme residues (theozymes). We started our investigations with the parent system **A** composed of allyl alcohol as ene partner and ethene as enophile (Fig. 1, see the ESI† for computational details). A concerted pathway leading to enol ether **B** was modelled. The Gibbs free energy of activation to reach TS<sub>AB</sub> is 42.1 kcal mol<sup>-1</sup>, which is consistent with the experimental value of 43.5 kcal mol<sup>-1</sup> reported by Klärner *et al.* for the intramolecular cyclization of (*Z*)-hexa-2,5-dienol.<sup>9</sup> Of note, **A** was taken in its *s-cis* conformation, leading to a *cis* enol. With the *s-trans* conformation, a slightly higher barrier of 42.3 kcal mol<sup>-1</sup> was obtained. With substituted allyl alcohols (*vide infra*), the *s-trans* conformation is the one that leads to the lowest barrier.

The transition state of a pericyclic reaction is expected to be aromatic. To confirm this property, we computed the nuclear independent chemical shift (NICS(0)) value<sup>17</sup> at the center of the six-membered ring, using the GIAO method<sup>18</sup> at the ωB97XD/6-311+G(d,p) level of theory (Table 1). We obtained -24.7 ppm for TS<sub>AB</sub>, which is very close from the parent aromatic Alder-ene transition state (-24.2 ppm at our level of theory).<sup>3</sup>

We then performed an activation-strain analysis of the transition state according to the general equation  $\Delta E^\ddagger = \Delta E_{\text{strain}}^\ddagger + \Delta E_{\text{int}}^\ddagger$ , where  $\Delta E_{\text{strain}}$  is the strain energy and  $\Delta E_{\text{int}}$  the instantaneous interaction energy (Table 2).<sup>19</sup> The results are very close from the parent Alder-ene reaction for which the barrier mostly stems from the activation strain of the ene partner.<sup>3</sup> To reach the geometry of the aromatic transition state, an energy of 32.1 kcal mol<sup>-1</sup> is required to deform allyl alcohol but only 11.6 kcal mol<sup>-1</sup> to deform

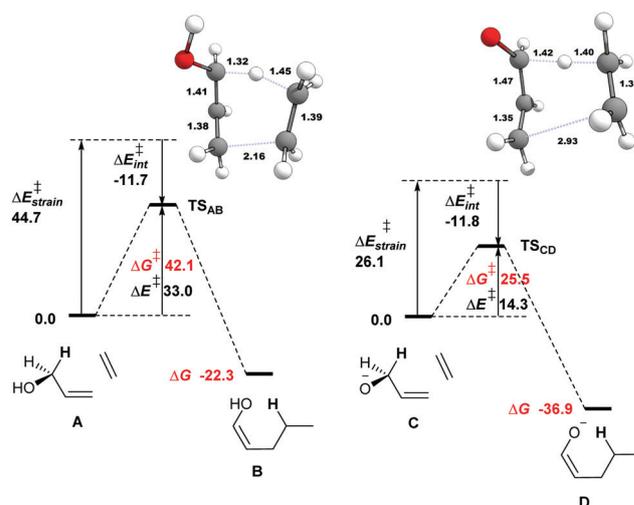


Fig. 1 Energy profiles at 483.15 K (kcal mol<sup>-1</sup>) and transition state geometries (selected distances in Å) of the neutral (**A** to **B**) and anionic (**C** to **D**) oxy-ene reactions of allyl alcohol with ethene computed at the ωB97XD/def2-QZVPP//ωB97XD/6-311+G(d,p) level.



Table 1 NICS(0) values of the transition states (ppm)

TS	NICS(0)	TS	NICS(0)	TS	NICS(0)
TS <sub>AB</sub>	-24.7	TS <sub>GH</sub>	-13.4	TS <sub>12</sub>	-20.5
TS <sub>CD</sub>	-16.6	TS <sub>MN</sub>	-13.6	TS <sub>1-2</sub> <sup>a</sup>	-20.1

<sup>a</sup> With all additives.Table 2 Activation-strain analysis ( $\Delta E^\ddagger = \Delta E_{\text{strain}}^\ddagger + \Delta E_{\text{int}}^\ddagger$ )<sup>a</sup>

Step	$\Delta E^\ddagger$	$\Delta E_{\text{strain}}^\ddagger$	total <sup>b</sup>	$\Delta E_{\text{strain}}^\ddagger$ ene	$\Delta E_{\text{strain}}^\ddagger$ enophile <sup>e</sup>	$\Delta E_{\text{int}}^\ddagger$
A → TS <sub>AB</sub>	33.0	44.7	32.1 <sup>c</sup>	11.6		-11.7
C → TS <sub>CD</sub>	14.3	26.1	18.3 <sup>d</sup>	7.8		-11.8

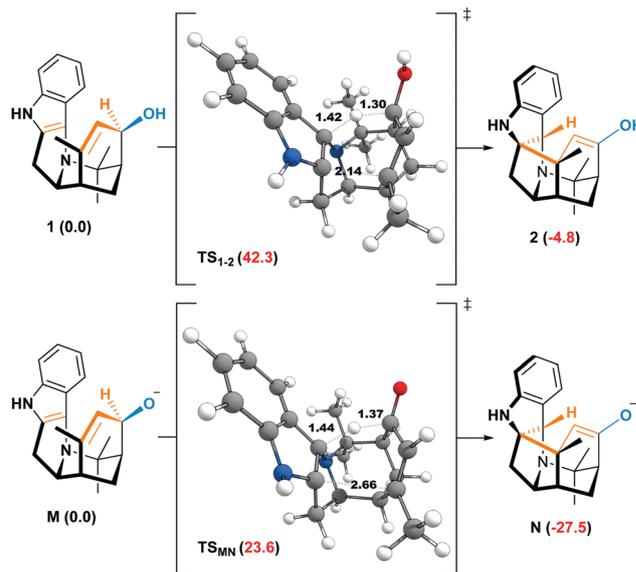
<sup>a</sup> kcal mol<sup>-1</sup>. <sup>b</sup>  $\Delta E_{\text{strain}}^\ddagger$  total =  $\Delta E_{\text{strain}}^\ddagger$  ene +  $\Delta E_{\text{strain}}^\ddagger$  enophile. <sup>c</sup> ene = allyl alcohol. <sup>d</sup> ene = allyl alkoxide. <sup>e</sup> enophile = ethene.

ethene. As the electronic interaction between the strained reactants is just  $-11.7$  kcal mol<sup>-1</sup>, the energy of activation remains as high as 33.0 kcal mol<sup>-1</sup>.

Thus, with simple substrates, the oxy-ene reaction has the same characteristic as the Alder-ene reaction. However, the presence of the OH group allows the formation of an alkoxy anion by deprotonation, which could have a dramatic impact on the reaction barrier by analogy with the oxy-Cope rearrangement. The free energy of activation indeed drops to 25.5 kcal mol<sup>-1</sup> in the alkoxide series (Fig. 1, C to D). The striking geometrical difference between TS<sub>CD</sub> and TS<sub>AB</sub> is the much longer distance of the forming C-C bond (2.93 vs. 2.16 Å). The aromatic character of the transition state is also less pronounced (Table 1, NICS(0)  $-16.6$  ppm). Compared to the alcohol, the alkoxide is easier to deform to reach the geometry of the transition state, as shown by the activation-strain analysis (Tables 2, 18.3 vs. 32.1 kcal mol<sup>-1</sup>). Thus, the transition state is more reactant-like. This phenomenon can be explained by the weakening of the allylic C-H bond in the alkoxide series. The homolytic bond dissociation energy (BDE) of this bond in allyl alcohol is  $\Delta E$  83.4 kcal mol<sup>-1</sup>. In the corresponding alkoxide, the BDE becomes  $\Delta E$  57.2 kcal mol<sup>-1</sup> only. This effect is consistent with that reported for the oxy-Cope rearrangement.<sup>12a</sup>

Intramolecular reactions corresponding to Klärner's and Borschberg's substrates were then studied, which confirmed their pericyclic nature and the lowering of the cyclization barrier after deprotonation of the alcohol (see the ESI,† Fig S1, compounds E to L'), although there is a striking difference between the naked alkoxide and the metallated one.

The weakening of the allylic C-H bond by deprotonation is a good lead to rationalize the formation of aristone under biological conditions (Scheme 2). So far, all barriers computed with neutral substrates (38.3–42.1 kcal mol<sup>-1</sup>) are incompatible with natural processes, and the calculated route to aristone makes no exception (Fig. 2). The transition state connecting **1** to **2** lies 42.3 kcal mol<sup>-1</sup> above the former. On the other hand, if the hydroxy group is deprotonated, the transition state is located only 23.6 kcal mol<sup>-1</sup> above the allyl alkoxide (**M**).

Fig. 2 Free energies at 298.15 K ( $\Delta G$  kcal mol<sup>-1</sup>) of the neutral and anionic oxy-ene reactions corresponding to Scheme 2.

*In vivo*, biocatalysts are able to stabilize transition states or intermediates and to reduce the activation energy.<sup>20</sup> For example, the accepted mechanism for zinc-dependent alcohol dehydrogenase enzymes first supposes that the alcohol substrate binds to the active site by coordination to the zinc ion. Then, deprotonation of the hydroxy group through a proton transfer to the solvent *via* a serine-NAD(P)<sup>+</sup> cofactor-histidine triad allows for the formation of a Zn<sup>2+</sup>-stabilized alkoxide intermediate.<sup>21</sup> Finally, a hydride transfer from the carbon of the alkoxide to the cofactor completes the reaction and releases the corresponding aldehyde or ketone.<sup>22</sup> In such scenario, the *in vivo* deprotonation of a secondary alcohol such as **1** could be effective.

Even if not deprotonated, the formation of a H-bond network between the hydroxy group and amino acid residues of the active site of a biocatalyst might also weaken the allylic C-H bond. Besides, H-bonding at the tertiary amine moiety of the transition state could influence the reaction rate. In the case of the enzyme-catalyzed Alder-ene reaction, Zhou, Houk, Tang and co-workers<sup>6</sup> used the theozyme<sup>23</sup> computational approach to rationalize the acceleration. A lysine residue was simplified as MeNH<sub>3</sub><sup>+</sup> and histidine as imidazole. While in our case the biocatalyst is not known, we wanted to verify whether typical H-bond donors or acceptors used in theozyme computations could influence the reaction barrier (Fig. 3). With MeNH<sub>3</sub><sup>+</sup>, we observed the protonation of the tertiary amine during optimization. Methylamine remained H-bonded to the newly formed ammonium 2\*. This protonation lowered the energy of the oxy-ene transition state TS<sub>1-2</sub><sup>\*</sup> by 4.4 kcal mol<sup>-1</sup> compared to TS<sub>1-2</sub> (from 42.3 to 37.9 kcal mol<sup>-1</sup>). Further 5.2 kcal mol<sup>-1</sup> were gained with imidazole H-bonded to the hydroxy group (32.7 kcal mol<sup>-1</sup>). Of note, activation of the two sites is important, as using only imidazole raised the barrier to 38.7 kcal mol<sup>-1</sup>. As typical abzyme model,<sup>23</sup> we then used



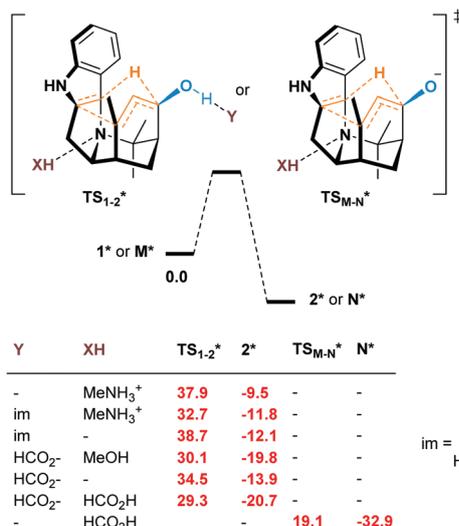


Fig. 3 Free energies at 298.15 K ( $\Delta G$  kcal mol<sup>-1</sup>) of the oxy-ene reaction of **1**\* or **M**\* in the presence of theozyme residues (\* = in the presence of Y and/or XH).

HCO<sub>2</sub><sup>-</sup> and MeOH as H-bond acceptor and donor respectively.<sup>24</sup> This combination had a dramatic impact on the barrier, which was lowered to 30.1 kcal mol<sup>-1</sup>, i.e. 12.2 kcal mol<sup>-1</sup> less than the initial value. Interestingly, the carboxylate bridges the OH and NH groups. As witnessed by the removal of MeOH, activation of the two sites was again more efficient. Replacing MeOH by HCO<sub>2</sub>H further reduced the energy of the transition state to 29.3 kcal mol<sup>-1</sup>. Thus, addition of amino acid residues strongly decreases the oxy-ene barrier. This effect is still valid if the OH group is fully deprotonated. In this case, the barrier becomes 19.1 kcal mol<sup>-1</sup> (vs. 23.6 kcal mol<sup>-1</sup> in Fig. 2) with one H-bonded HCO<sub>2</sub>H (TS<sub>M-N</sub>\*). Although this low value of 19.1 kcal mol<sup>-1</sup> represents a lower limit as it is obtained with a naked alkoxide (see the discussion in the ESI† regarding the deprotonation), it seems conceivable that an oxy-ene reaction occurs *in vivo* in the presence of many H-bond donor or acceptor residues.

Having much in common with the Alder-ene reaction and some similarities with the oxy-Cope rearrangement, the oxy-ene is an overlooked pericyclic reaction. Just like the Alder-ene, the oxy-ene could play a significant role in biological processes and become a useful tool in synthetic organic chemistry. Until now, information about the oxy-ene reaction has remained scattered in the literature. This study puts together the pieces of the puzzle and provides the theoretical background of this underexplored subfield of pericyclic group transfer reactions.

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## Conflicts of interest

There are no conflicts of interest to declare.

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