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Dimerization of myrcene to form the camphorenes: A density functional theory investigation

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Abstract
Dimers of myrcene, *p*-camphorene and *m*-camphorene, are sometimes detected as minor components in essential oils of members of the Burseraceae and other myrcene-rich essential oils. The compounds likely arise from Diels-Alder dimerization of myrcene. In order to provide some insight into the dimerization of myrcene to form camphorenes, a computational investigation using density functional theory (DFT) was carried out at the B3LYP/6-31G* level of theory. The transition-state energy for the formation of *m*-camphorene is lower than the transition-state energy for *p*-camphorene. On the other hand, the energy of the final *p*-camphorene product is lower than the energy of *m*-camphorene.

Keywords: Diels-Alder, [4+2] cyclization, DFT, B3LYP

1. Introduction

We have observed the occurrence of myrcene dimers, *m*-camphorene and *p*-camphorene (Fig 1), in the essential oils of *Boswellia carteri* (unpublished results from our laboratories). Simla Basar had isolated and characterized both *m*-camphorene and *p*-camphorene from *Boswellia serrata* [1]. Both *m*-camphorene and *p*-camphorene have been detected in *Humulus lupulus* (hops) essential oil [2], "breu branco" (white pitch oleoresin, probably from *Protium* spp. [3]) [4], and *Cannabis sativa* (hemp) essential oil [5]. *P-Camphorene* has also been reported in the oleo-gum resin of *Commiphora mukul* [6] and *Commiphora wightii* [7].

Basar found *m*-camphorene to be in higher concentration than *p*-camphorene (62:38 ratio) in *B. serrata* [1]. The Carmagnola variety of hemp essential oil, on the other hand, showed *p*-camphorene to be predominant over *m*-camphorene (ratio of 67% *p*-camphorene, 33% *m*-camphorene) [5]. Our own investigation of *B. carteri* resin essential oils revealed *m*-camphorene (52-73%) to dominate over *p*-camphorene (27-48%) (Unpublished results from our laboratories).

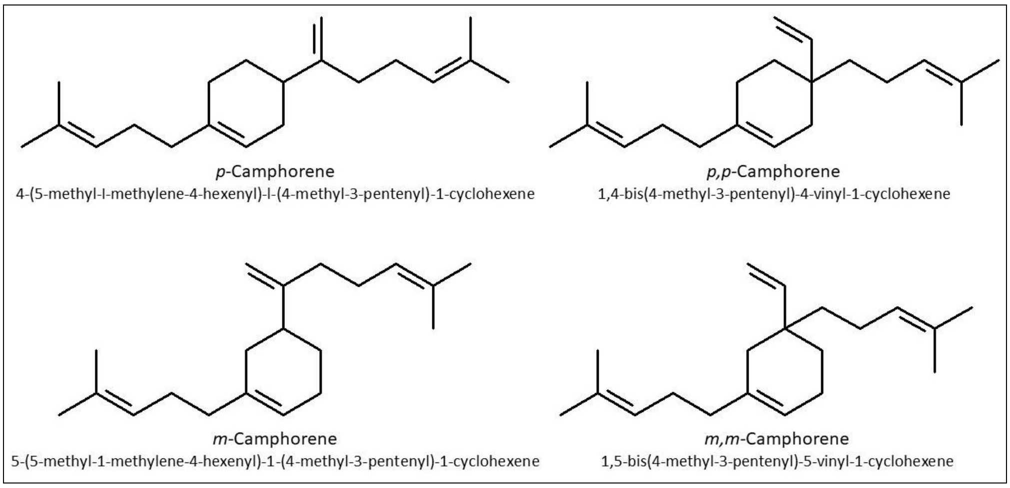

Fig 1: Camphorenes from Diels-Alder dimerization of myrcene

Thermal Diels-Alder dimerization of myrcene led to four products, *m*-camphorene and *p*-camphorene, as well as two minor compounds, *m*, *m*-camphorene and *p*, *p*-camphorene (Figure1) [8, 9].

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The distribution of the camphorenes (*p*-camphorene, *m*-camphorene, *p*, *p*-camphorene, and *m*, *m*-camphorene was approximately 43:28:18:11 [8] and 32:44:11:13 [9]. Photosensitized dimerization of myrcene led to at least seven dimeric products, including camphorenes ([4+2] dimeric products) as well as [2+2] cycloaddition dimers and possibly [4+4] dimers [10]. Unfortunately, the dimerization products were not fully characterized. In order to provide some insight into the energetics of the Diels-Alder dimerization of myrcene, the reactions have been modeled using density functional theory (DFT) at the B3LYP/6-31G* level of theory.

2. Computational Methods

All calculations were carried out using Spartan ’18 for Windows [11]. Initial conformational analyses were carried out on myrcene and each dimeric product using a Monte-Carlo molecular mechanics conformational search using the MMFF force field [12]. For each compound, all conformations from the MMFF conformational analysis were then modeled using density functional theory with the B3LYP functional [13, 14] and the 6-31G* basis set [15]. The lowest-energy conformations for each compound were then used in the analysis. All calculations were carried out in the gas phase.

3. Results and Discussion

The energetics of the Diels-Alder dimerization of myrcene are summarized in Table 1. The Diels-Alder dimerization of myrcene is an exothermic process. Both the *p*-camphorene and *m*-camphorene are lower in energy than the *p*,*p*-camphorene or the *m*, *m*-camphorene, and *p*-camphorene is slightly lower in energy than the *m*-camphorene. These energies would suggest that at equilibrium the distribution of isomers should be 55.9% *p*-camphorene, 44.0% *m*-camphorene, 0.1% *p*, *p*-camphorene, and 0.0% *m*,*m*-camphorene (Fig 2).

Table 1: Density functional theory (DFT) energies (B3LYP/6-31G*, kcal/mol) for the dimerization of myrcene.

Dimer	ΔE_{ts}	ΔE_{dimer}
p-Camphorene	25.7	–35.2
m-Camphorene	24.6	–35.0
p, *p*-Camphorene	26.0	–31.4
m, *m*-Camphorene	26.6	–31.0

ΔE_{ts} = Energy of the Diels-Alder transition states compared to the starting compounds. ΔE_{dimer} = Energy of the dimeric products compared to the starting compounds.

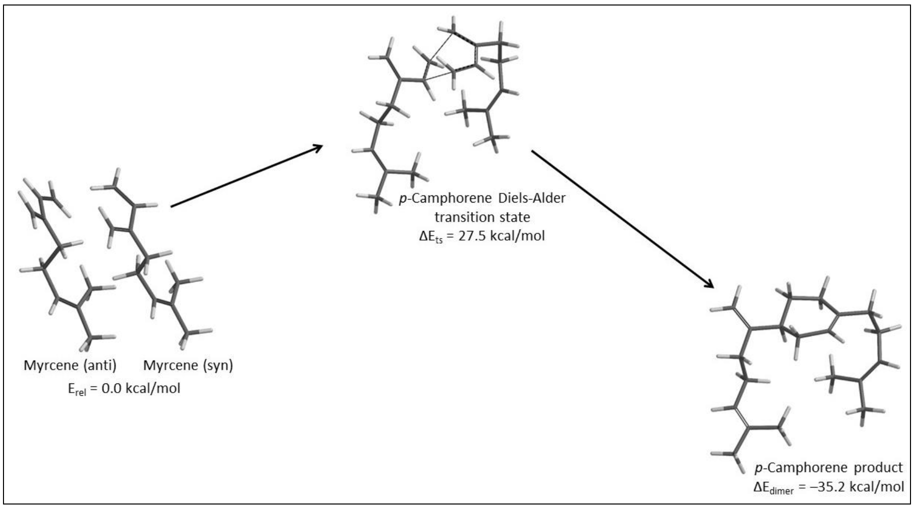

Fig 2: Reaction profile for the Diels-Alder dimerization of myrcene to form *p*-camphorene

The lowest-energy transition structure observed was for the production of *m*-camphorene (24.6 kcal/mol), followed by *p*-camphorene (25.7 kcal/mol), *p*, *p*-camphorene (26.0 kcal/mol) and *m*, *m*-camphorene (26.6 kcal/mol). Thus, the calculated energy barriers are consistent with preferential formation of *m*-camphorene (79.3%), *p*-camphorene (11.5%), *p*, *p*-camphorene (6.8%), and *m*,*m*-camphorene (2.4%). The transition-state energy differences are roughly consistent with the product distributions from the Diels-Alder dimerization of myrcene reported by Staples and co-workers [9] with *m*-camphorene (44%), *p*-camphorene (32%), *m*,*m*-camphorene (13%) and *p*,*p*-camphorene (11%). It is not clear why the product distribution of Diels-Alder dimers reported by Eisfelder and Weyerstahl [8] are different, but the reactions were carried out under different conditions (225 °C for 3.5 h in the case of Eisfelder and Weyerstahl and 200 °C for 15 h in the presence of a free-radical scavenger in the case of Staples *et al.*). Interestingly, *m*-camphorene was the major camphorene observed in the essential oils of *Boswellia serrata* [1] and *Boswellia carteri* (unpublished results from our laboratories).

It is not clear exactly how the camphorenes are formed in the plant resins of *Boswellia* species. The dimerization of myrcene may be thermal and/or photochemical under the sunny and hot conditions of their environments. *Boswellia serrata* is native to India while *B. carteri* is found in the horn of Africa [16]. The presence of camphorenes does not rule out enzyme-mediated formation, however.

4. Conclusions

Density functional theory (DFT) calculations on the thermal Diels-Alder dimerization of myrcene predict the preferred formation of *m*-camphorene over *p*-camphorene under kinetic-control conditions; *m*-camphorene has a lower transition-state energy. On the other hand, under equilibrium-controlled conditions, the *p*-camphorene product is lower in energy and should be the preferred product.

5. Acknowledgments

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