Hessisches Kompetenzzentrum
für Hochleistungsrechnen

Synthesis and Conformational Analysis of Parent Perhydroazulenes

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Clusters
Goethe-HLR Frankfurt

Software
GAUSSIAN

Additional Software
CFOUR

Institute
Institute of Organic Chemistry

University
Justus Liebig University Giessen



cis-perhydroazulene (*cis*-**1**) *trans*-perhydroazulene (*trans*-**1**)

Fig. 1: Structures of parent perhydroazulenes *cis*- and *trans*-1.

Introduction

Perhydroazulenes are common structural motifs in a variety of terpene natural products. Despite of their structural importance, studies on parent perhydroazulenes, *cis*- and *trans*-**1** (Fig. 1), have been scarce. In this project, we aim to establish short synthetic routes to both diastereomers *cis*- and *trans*-**1** and carry out their thorough conformational analysis to study the relative stability between them.

Methods

The project consists of experimental and computational parts. In the experimental part, we synthesize the two diastereomers *cis*- and *trans*-**1** through multistep organic synthesis using a cheap, readily available starting material. In the computational part, we perform density functional theory (DFT) and MP2 geometry optimizations and frequency computations for conformations of *cis*- and *trans*-**1**.The relevant conformers are subsequently subjected to single point energy computations using the coupled cluster method.

Results

The synthesis of *cis*-**1** was carried out using cycloheptanone as a starting material. The key step enroute to *cis*-**1** was the stereoselective (and chemoselective) reduction of α,β-unsaturated ketone to establish the *cis* ring fusion. On the other hand, the synthesis of *trans*-**1** involved 1,4-addition of an organocopper reagent to the cycloheptenone starting material followed by electrophilic trapping of the enolate as the key stereoselective step. We obtained both *cis*- and *trans*-**1** in

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diastereomerically pure form.

Next, we performed geometry optimizations and frequency calculations for conformations of *cis*- and *trans*-**1** at the B3LYP, B3LYP-D3(BJ), M06-2X, B2PLYP, B2PLYP-D3 functionals and the MP2 method with a cc-pVTZ basis set. For the MP2/cc-pVTZ optimized structures, we also performed CCSD(T)/cc-pVTZ single point energy computations. These computations revealed that *cis*-**1** is 0.7–1.0 kcal mol^{-1} more stable than *trans*-**1**.

Discussion

After careful analysis of steric and torsional strain in *cis*- and *trans*-**1**, we reason that an additional gauche interaction present in *trans*-**1** accounts for the computed energy difference of 0.7–1.0 kcal mol^{-1}. This result was unexpected and at the first sight, seemed contradictory to previously reported experimental data where the Pd/C-catalyzed isomerization between *cis*- and *trans*-**1** at high temperature (550 K) resulted in a *trans*/*cis* ratio of 1.6. However, by taking the Boltzmann distribution into account, all DFT and MP2 computations listed in Methods provided a *trans*/*cis* ratio of ca. 2 (1.6 at the MP2/cc-pVTZ level of theory), thus an excellent agreement with the experimental data. We conclude that the most stable conformer of *cis*-**1** is energetically lower-lying than that of *trans*-**1**, but at equilibrium at high temperature, the conformers of *trans*-**1** become more populated than those of *cis*-**1**.

Publications

Saito, F.; Becker, J.; Schreiner, P. R. Synthesis and conformational analysis of parent perhydroazulenes reveals an energetically preferred cis ring fusion. J. Org. Chem. 2020.
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