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AMADAR: a python-based package for large scale prediction of Diels-Alder transition state geometries and IRC path analysis

The Diels-Alder (DA) reaction is one of the most important reactions in organic chemistry, which has found so many applications in a variety of domains such as in the total synthesis of natural products, in polymer chemistry as well as in the industrial preparation of agrochemicals and fragrances. Over the past few years, numerous computational studies have been investigating the mechanism of the DA reaction in the framework of the reaction force theory, the activation strain model, and the bond evolution theory. However, all of these theories require that the reaction transition states (TSs) be first predicted. Unfortunately, predicting TSs geometries is one of the most challenging tasks in computational chemistry, which often requires expert-based knowledge and constant human intervention. The main reason is that existing codes require that the search is initiated from a good starting (guess) geometry that is structurally very similar to the actual TS. With the double aim of contributing to solving the challenge of TS prediction and the understanding of the DA reaction mechanism, we have built the "AMADAR" program (Automated workflow for Mechanistic Analysis of Diels-Alder Reactions). The AMADAR tool is designed to generate an unlimited number of Diels-Alder (DA) TS geometries, before carrying out subsequent analyses based on the intrinsic reaction coordinate (IRC) paths. The TSs are predicted sequentially, from a constrainted optimization in internal coordinates to the refinement at a quantum mechanical level using the single-ended Berny algorithm. Two special modules of the package are devoted to executing the numerical calculations concerning the reaction force analysis and the atomic resolution of energy derivatives. The AMADAR package does not need any training step as it is the case in deep learning-based approaches, and uses only SMILES strings of the cycloadducts as inputs. Two of the key features of AMADAR are its high customizability and the ability to handle particular cases such as intramolecular reactions and situations resulting in competing paths. The performance of the protocol has been assessed using a dataset of 2000 likely DA cycloadducts retrieved from the ZINC database. A satisfactory prediction rate of 95% was obtained, corresponding to 1912 TSs successfully located with a unique imaginary frequency lower than 400i. The AMADAR package is projected to be very beneficial to a large community of researchers working on the mechanism of the DA reaction and its applications. The source code of the AMADAR tool is available on GitHub (CMCDD/AMADAR (github.com)) and can be used at the price of some minor customizations, mostly regarding the local working environment of the user.
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