DFT Analysis of Diels-Alder Reactions for the preparation of forskolin derivatives

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Diels-Alder reactions represent one of the most significant steps in the synthesis of forskolin derivatives. The cycloaddition in question takes place between a structurally invariable diene (tert-butyldimethylsilyloxybuta-1,3-diene) and a dienophile (methyl-p-benzoquinone) characteristically substituted in *meta-position* with respect to the methyl group. Depending on the nature of the substituent, individual stereoisomers of products are formed in various ratios. The presented theoretical study focuses on the calculation of reaction energy profiles for a set of substituted dienophiles. Trends in activation barriers are in good agreement with experimental stereochemical outcomes. Relative energies of transition states are interpreted in terms of orbital interactions between diene HOMO and dienophile LUMO. Both energy differences and frontier orbital compositions within the Mulliken population analysis are considered, with a straightforward correlation to the heights of activation barriers in the cycloaddition reactions.

Calculations of activation barriers were carried out at the B3LYP/6-31G* or B3LYP/6-31+G* levels of theory using the SMD implicit solvatation model within the Gaussian09 or Gaussian16 implementation. Comparative energy profile calculations and all orbital analyses have been done at the B3LYP/STO-DZ level using the ADF package.
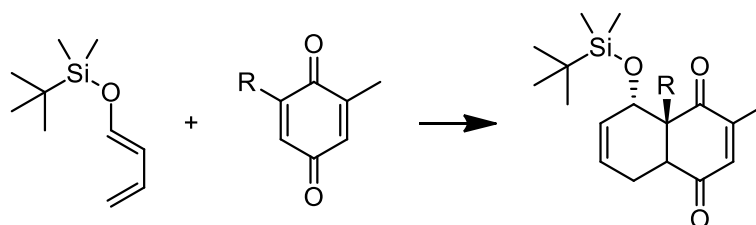

Figure 1. General scheme of Diels-Alder reaction for the preparation of forskolin derivatives.