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Modeling of the Diels–Alder reaction enantioselectivity by quantum mechanics and molecular mechanics

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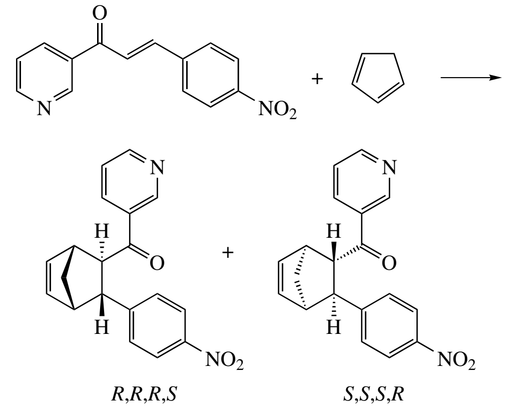
The enantioselectivity of the Diels–Alder reaction between (*E*)-3-(4-nitrophenyl)-1-(pyridin-3-yl)prop-2-en-1-one and cyclopenta-1,3-diene in the chiral ionic liquids 3-butyl-1-methylimidazolium (*S*)-camphorsulfonate and (*S*)-1-methyl-3-(pyrrolidin-2-ylmethyl)-imidazolium tosylate or upon chiral promotion with chiral oxazaborolidine was modeled by molecular and quantum mechanics and then experimentally studied; computations were in good agreement with the experimental data, resulting in no stereoselectivity with a chiral ionic liquid used as a co-solvent and prominent stereoselectivity upon chiral promotion.

Various approaches to asymmetric synthesis have been widely used in fine and industrial reactions, including chiral catalysts,[1–3] chiral solvents,[4,5] in particular, chiral ionic liquids,[6–8] temporary chiral auxiliaries[9] and even spontaneous asymmetric synthesis.[10] Computational chemistry potentially allows achieving desired selectivity without testing all possible reaction conditions. Here, we used molecular mechanics free energy perturbation and quantum mechanics (QM) DFT calculations[†] to optimize Diels–Alder reaction conditions for obtaining the best stereoselectivity.

We studied the Diels–Alder cycloaddition of (*E*)-3-(4-nitrophenyl)-1-(pyridin-3-yl)prop-2-en-1-one to cyclopenta-1,3-diene (Scheme 1), which produces two enantiomeric products (*R*,*R*,*R*,*S* and *S*,*S*,*S*,*R*). To assess the potential of chiral induction in this reaction by a chiral solvent, we calculated the free energy of solvation for each product in a mixture of ethanol with 0.5 mol dm^{-3} chiral ionic liquid 3-butyl-1-methylimidazolium (*S*)-camphorsulfonate (Bmim-CSA)[‡] or (*S*)-1-methyl-3-(pyrrolidin-2-ylmethyl)-imidazolium tosylate (Promim-TSA) (Figure 1) by molecular dynamics free energy perturbation. Resulting solvation free energies were essentially the same for both enantiomers in both systems indicating that the media did not differentiate them, and no chiral induction is expected (Table 1).



Scheme 1

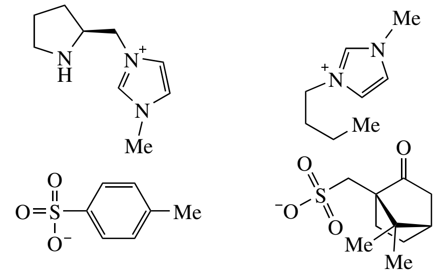


Figure 1 Chiral ionic liquids.

Alternatively, the influence of a chiral oxazaborolidine reagent (Figure 2) was studied by QM DFT. Geometry optimization of the guess-structure of the initial product–oxazaboralidine complex resulted into dissociation of the complex (boron–oxygen distance changed from 1.55 Å in the initial guess to 3.61 Å in the final

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[†] *Computational methods.* Geometry optimization and Gibbs free energies in a vacuum were calculated in Gaussian09[12] with B3LYP DFT functional and 6-31G(d) basis set. Molecular mechanics free energy perturbation (MM-FEP) calculations were performed in Gromacs[13] in OPLS-AA force field.[14] The solute molecule was positioned in a 70 Å cubic box of solvent using the Gromacs utility 'genbox'. Then, FEP was used to switch off the solute–solvent interaction. FEP calculations were performed in 10λ steps (separately for VdW and Coulomb interactions), each step included 100 ps NVT equilibration, 500 ps NPT equilibration and 10 ns NPT production dynamics.

[‡] *Synthesis of Bmim-CSA.* Freshly distilled thionyl chloride (22.0 ml, 0.3 mol) was added dropwise to a boiling solution of (1*S*)-(+)-10-camphorsulfonic acid (58.0 g, 0.25 mol) in 500 ml of dry chloroform. The reaction mixture was refluxed for 15 h; the solvent was evaporated in a vacuum, and the residue was dried in a vacuum desiccator with NaOH to constant weight. The product was dissolved in 400 ml of dry dichloromethane, and a mixture of 42.0 ml (~0.3 mol) of triethylamine and 32.0 ml (0.35 mol) of butan-1-ol was added dropwise. The mixture was stirred at room temperature for 48 h and washed with 1 N aqueous HCl (2×200 ml), saturated $NaHCO_3$ solution (3×200 ml) and water to neutral pH. Organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed. 64.2 g (89%) of butyl (*S*)-camphorsulfonate was obtained.

N-Methylimidazole (17.2 g, 0.21 mol) was added to a solution of butyl (*S*)-camphorsulfonate (60.0 g, 0.21 mol) in 300 ml of anhydrous toluene, and the reaction mixture was refluxed for 30 h. Solvent was removed in a vacuum, and 200 ml of toluene was added to the residue. Solvent was again removed in a vacuum, and the residue was dried for 6 h in a vacuum at 80 °C and 0.2 Torr to give 70.0 g (99%) of the product.

Promim-TSA was synthesized as described elsewhere.[15]

Table 1 Solvation free energy of enantiomeric adducts of (*E*)-3-(4-nitrophenyl)-1-(pyridin-3-yl)prop-2-en-1-one and cyclopenta-1,3-diene in ethanol + 0.5 M ionic liquid and 0.02 M $CuCl_2$ calculated using an MM FEP approach.

Product	Ionic liquid	Coulomb ΔG/kJ mol^{-1}	VdW ΔG/ kJ mol^{-1}	Total solvation ΔG/kJ mol^{-1}
R,*R*,*R*,*S*	Bmim-CSA	–24.34±0.99	–58.66±0.19	–83.00±1.00
S,*S*,*S*,*R*	Bmim-CSA	–25.55±1.71	–58.28±0.22	–83.83±1.71
R,*R*,*R*,*S*	Promim-TSA	–25.31±0.62	–57.39±0.40	–82.70±0.74
S,*S*,*S*,*R*	Promim-TSA	–24.97±0.16	–57.07±0.46	–82.04±0.49

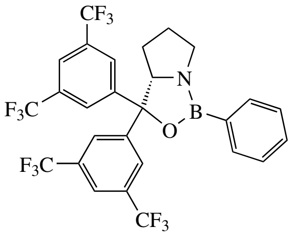

Figure 2 Oxazaborolidine reagent for the Diels–Alder reaction.

structure). However, when the nitrogen atom of oxazaborolidine was protonated, geometry optimization smoothly converged to the tetrahedral boron complex with a B–O bond length of 1.42 Å (Figure 3). Free energy of this boron complex for *R*,*R*,*R*,*S* product was 5.75 kJ mol^{-1} lower than that for *S*,*S*,*S*,*R* product, indicating that the reaction should occur in enantioselective fashion.

The model reaction enantioselectivity was further experimentally studied in a chiral ionic liquid or with chiral promotion.[§] As expected, the addition of 0.5 M chiral ionic liquid to ethanol led to the formation of racemic product (*ee* 0.04% for Promim-TSA and 3.26% for Bmim-CSA). The addition of a chiral reagent resulted in moderate but distinguishable enantioselectivity (*ee* 11% in Bmim-CSA and 16% in Promim-TSA), which corresponded to the modeled preference towards *R*,*R*,*R*,*S*-enantiomer.

Note that the protonation of nitrogen in oxazaborolidine was strongly required for binding with the products; this fact was described recently[11] and independently demonstrated here.

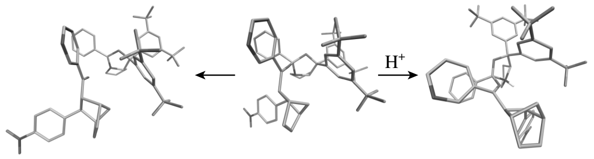

Figure 3 Protonation is required for the binding of oxazaborolidine to reaction products.

In summary, we have successfully applied state-of-the-art computational chemistry methods to study factors affecting the enantioselectivity of the Diels–Alder reaction. Our work supports extensive application of molecular modeling techniques to the optimization of organic reaction conditions.

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[§] *Diels-Alder reaction without chiral oxazaborolidine.* (*E*)-3-(4-Nitrophenyl)-1-(pyridin-3-yl)prop-2-en-1-one (10 mmol) was dissolved in 100 ml of a 0.5 mM ionic liquid solution in 70% (v/v) aqueous ethanol, and a solution of copper(II) chloride (1 mmol) in 5 ml of water was added. The reaction mixture was stirred for 10 min at room temperature, and freshly distilled cyclopentadiene (1.0 ml, 12 mmol) was added. The resulting mixture was stirred at 30 °C until complete disappearance of the starting chalcone. The solution was filtered through silica gel; ethanol was evaporated in a vacuum; the residue was dissolved in 100 ml of dichloromethane and washed with water (4×50 ml), dried with Na_2SO_4 and separated chromatographically (to remove 1,3-diaryl-1,2-dihydropentalene). A white crystalline product was obtained, yield 79%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.71 (d, 1H), 1.98 (d, 1H), 3.15 (s, 1H), 3.43 (s, 1H), 3.61 (d, 1H), 3.82 (d, 1H), 5.85 (d, 1H), 6.45 (d, 1H), 7.41 (m, 3H), 8.12 (m, 2H), 8.18 (d, 1H), 8.76 (d, 1H), 9.13 (s, 1H).

Diels–Alder reaction with chiral oxazaborolidine. (*E*)-3-(4-Nitrophenyl)-1-(pyridin-3-yl)prop-2-en-1-one (10 mmol) was dissolved in 100 ml of a 0.5 mM ionic liquid solution in 70% (v/v) aqueous ethanol, and a solution of copper(II) chloride (1 mmol) in 5 ml of water and chiral oxazaborolidine (61 mg, 0.1 mmol) were added. The reaction mixture was stirred for 10 min at room temperature, and freshly distilled cyclopentadiene (1.0 ml, 12 mmol) was added. The mixture was stirred at 30 °C until complete disappearance of the starting chalcone. The solution was filtered through silica gel, ethanol was evaporated in a vacuum, the residue was dissolved in 100 ml of dichloromethane and washed with water (4×50 ml), dried with Na_2SO_4 and separated chromatographically (to remove 1,3-diaryl-1,2-dihydropentalene) to give 83% of a white crystalline product.

Chiral chromatography. Chiral chromatography was performed on a Lux Cellulose-3 column (4.6×150 mm) using isocratic elution with a hexane–isopropanol (90:10) mixture. Analytes were detected by UV at $\lambda = 220$ nm.