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In silico correlation of enantioselectivity for the TADDOL catalyzed asymmetric hetero-Diels–Alder reaction

D. Joseph Harriman, Andreas Lambropoulos and Ghislain Deslongchamps*

Department of Chemistry, University of New Brunswick, Fredericton, NB, Canada E3B 5A3

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Abstract—The reverse-docking of a TADDOL organocatalyst to rigid transition state models of catalyst-free reactions (TS-models) for an asymmetric hetero-Diels–Alder reaction is described. In previous reports, reverse-docking of similar organocatalysts to rigid TS-models showed promise for generating transition state models for the catalyzed reaction, and revealed clear energetic trends favoring the experimentally preferred product enantiomers. Although results indicated a mode of catalysis consistent with experimental data, relative docking energies between TS-model enantiomers were too great to allow for in silico correlation to experimentally observed enantiomeric excesses (ee). Several changes were made to the reverse-docking algorithm, EM-Dock, allowing for the first reported correlation to experimentally reported ee values based solely on reverse-docking and molecular mechanics energies.

Metal-based chiral Lewis acids have played a dominant role in enantioselective catalysis for the last 50 years. However, there has been a recent resurgence in the use of chiral organocatalysts bearing H-bond donors to facilitate enantioselective reactions.[1–3] In 2003, Rawal showed that α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol alcohol (TADDOL) could effectively catalyze asymmetric hetero-Diels–Alder (HDA) reactions (Fig. 1).[4]

The main factor promoting this reaction appears to be H-bonding interactions with the aldehyde dienophiles. Recent publications outline the development of a novel computational procedure, reverse-docking, which has

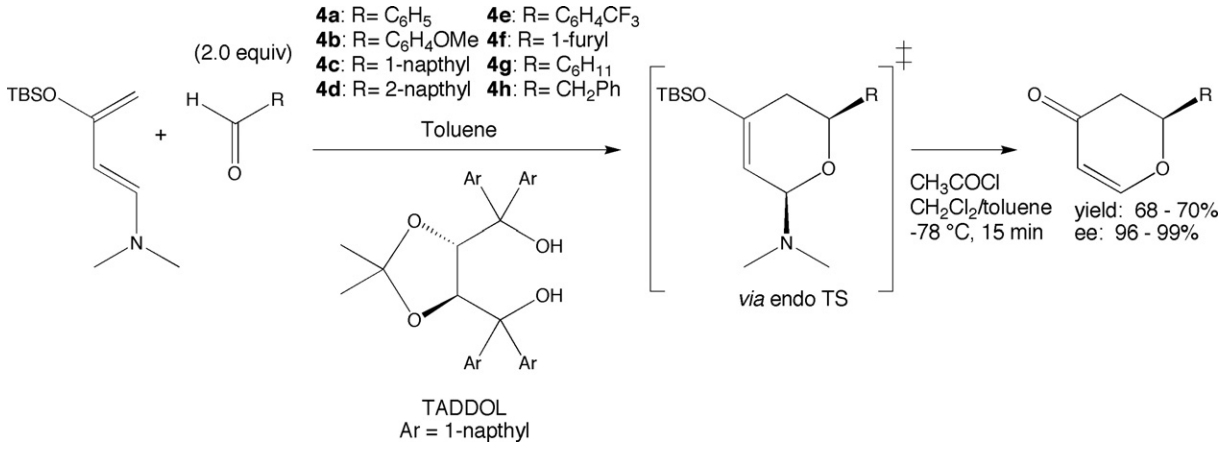

Figure 1. TADDOL catalyzed hetero-Diels–Alder reaction.

Keywords: Reverse-docking; Asymmetric organocatalysis; Enantiomeric excess; Hetero-Diels–Alder; TADDOL.
* Corresponding author. Tel.: +1 506 453 4795; fax: +1 506 453 4981; e-mail: ghislain@unb.ca

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proven to be a useful tool for studying the enantioselectivity of several organocatalyzed reactions.[5,6] In this procedure, a large flexible organocatalyst is docked around rigid transition state models of catalyst-free reactions (TS-models) generated by ab initio transition state optimization (opt = ts) calculations (Fig. 2).

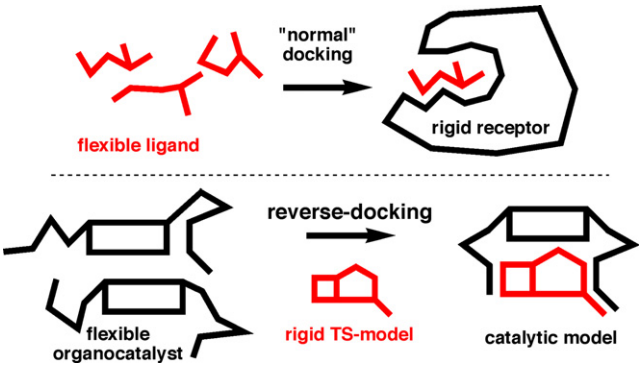

Figure 2. Reverse-docking versus normal docking.

The resulting reverse-docking poses represent simplified models for the transition states of the organocatalyzed HDA reaction. The conformational space of the catalyst in proximity to the TS models is sampled stochastically using a recently reported docking method, EM-Dock,[7] and the energetically favored poses are analyzed to highlight structures having H-bonding attributes compatible with organocatalysis (aldehyde oxygen—TADDOL oxygen distance $\leqslant$4 Å, angle between 100° and 180°).

Docking energies are calculated as the sum of the intermolecular interactions (coulombic + van der Waals) plus the conformational energy of the organocatalyst determined by molecular mechanics (MMFF94x forcefield). Although TS-models for several asymmetric reactions were developed and studied, the enantioselectivity assessments were purely qualitative, predicting the preferred enantiomer in 100% of cases but far from correlating the experimental ee values (docking energy differences to the enantiomer TS-models ranging from 4 to 10 kcal/mol). With this in mind, modifications to the method for calculating docking energy yielded EM-Dock v.2, resulting in much more accurate results.

Table 1. Reverse-docking energies and predicted enantiomeric excess values

Substrate[a]		'S' TS-model[g]		'R' TS-model[g]		ee (%)		
		E[b] (Rank)	E_{Boltz}[c]	E[b] (Rank)	E_{Boltz}[c]	Global[d]	Weighted[e]	Exptl[f]
1	A	207.90 (1)	208.03	209.66 (1)	210.00	98.95	99.46	99
	B	207.90 (1)	207.90	209.60 (1)	210.06			
	C	207.89 (1)	207.94	209.66 (1)	209.91			
2	A	207.44 (1)	207.55	209.78 (1)	210.26	99.62	99.77	97
	B	207.44 (1)	207.44	209.55 (1)	210.14			
	C	207.44 (1)	207.75	209.54 (1)	209.82			
3	A	207.68 (1)	208.10	209.68 (1)	209.70	99.53	99.25	99
	B	207.68 (1)	208.01	209.68 (1)	210.16			
	C	207.68 (1)	208.30	209.99 (1)	210.32			
4	A	207.27 (1)	207.74	208.99 (1)	209.15	98.77	97.46	97
	B	207.27 (1)	207.76	208.96 (1)	209.16			
	C	207.27 (1)	207.71	208.97 (1)	209.15			
5	A	209.65 (1)	210.15	211.70 (1)	212.32	99.47	99.53	97
	B	209.57 (1)	210.15	211.77 (1)	212.14			
	C	209.65 (1)	210.09	211.56 (1)	212.20			
6	A	208.89 (1)	209.26	211.03 (1)	211.30	99.60	99.58	96
	B	208.89 (1)	209.08	211.03 (1)	211.24			
	C	208.89 (1)	209.03	211.03 (1)	211.24			
7	A	208.96 (1)	209.35	210.49 (1)	210.90	98.09	97.97	93
	B	208.96 (1)	209.45	210.48 (1)	210.80			
	C	208.96 (1)	209.52	210.49 (1)	211.07			
8	A	211.27 (1)	211.91	212.37 (1)	212.95	95.28	94.89	97
	B	211.14 (1)	211.41	212.37 (1)	212.96			
	C	211.14 (1)	211.59	212.33 (1)	212.59			

[a] Substrates according to Figure 1; rows A–C refer to triplicate reverse-docking runs.
[b] Docking energy of lowest-energy database entry (kcal/mol); pose rank in parentheses (1 = best rank).
[c] Boltzmann-weighted docking energy average, after removing duplicate entries and poses representing less than 5% of the Boltzmann population.
[d] ee values calculated from the R/S docking energy differences at −78 °C using the averaged lowest energies.
[e] ee values calculated from the R/S docking energy differences at −78 °C using the Boltzmann-weighted energy averages enantiomeric excess values calculated at −78 °C, calculated from the average energies of the global lowest energy catalytic poses.
[f] Experimental values as reported in Ref. 4.
[g] Denotes the endo TS-model leading to the S and R dihydropyrone product enantiomers.

The original EM-Dock v.1 used a rapid grid-scoring scheme for calculating intermolecular interactions between organocatalyst conformations and TS-models during the population routine of the docking algorithm. The use of a grid with pre-calculated electrostatic and van der Waals probes saves considerable computational time, especially when docking several ligands to a large protein; non-bonded interactions are quickly obtained by trilinear interpolation on the pre-calculated grid. However, in the reverse-docking paradigm, the docking target is a small TS-model bearing diffuse charges, and presents a limited framework for obtaining grid-based non-bonded interactions with the catalyst. Although this would increase calculation times, we chose to calculate the reverse-docking pose energies using full pair-wise evaluation of the intermolecular coulombic and van der Waals terms. This was deemed reasonable in light of the relatively small size of the organocatalysts and TS-models. In addition, observations made during the algorithm optimization showed that the molecular mechanics-based energies obtained by grid scoring correlated poorly to the explicitly calculated electrostatic interaction energies.

Using EM-Dock v.2, Rawal's asymmetric HDA organocatalyst was re-examined in an effort to correlate the reported experimental ee values. As outlined in Table 1, triplicate reverse-dockings of TADDOL were carried out with each enantiomer of the TS-models (endo addition of aldehydes to silylated aminodiene leading ultimately to *S* and *R* dihydropyrone product enantiomers) derived for the eight HDA aldehyde dienophiles reported by Rawal (number of runs: 1000; population size: 1000; number of generations: 1600). Enantiomeric excess values were calculated based on the reverse-docking energies to the pairs of TS-model enantiomers, using both the global minimum energy poses and the Boltzmann-weighted energies of the pose ensembles.

As shown in Table 1, for all eight HDA aldehyde dienophiles, EM-Dock v.2 gave lower reverse-docking energies to the '*S*' TS-model enantiomers, which correspond, after initial product formation and desilylation, to the experimentally preferred *S*-enantiomer dihydropyrone products.

Structural analysis of the lowest-energy reverse-docking poses reveals a common mode of catalysis that is consistent with principles of molecular recognition, organocatalysis, and all available experimental information. The presence of intramolecular H-bonding within the TADDOL catalyst is believed to enhance the acidity of the free hydroxyl proton and allow for a stronger intermolecular H-bond with the carbonyl oxygen of the incoming dienophile,[8,9] likely another example of a chiral Brønsted acid-assisted Brønsted acid (BBA).[10]

In addition to cooperative H-bonding patterns, π-stacking and/or van der Waals interactions between the aldehydes and the pseudo-equatorial naphthyl ring of the organocatalyst at the transition state may be operative in blocking one of the dienophile faces and contributing to the observed enantioselectivity (Fig. 3).

However, the most interesting aspect of this study is the much closer correlation between calculated enantiomeric excesses (using two different methods) and experimental values. In the original work carried out with EM-Dock v.1, the energy differences between docking to the '*S*' and '*R*' TS-model enantiomers were in the range of 0–10.7 kcal/mol (4 kcal/mol average, 99.99% ee at −78°). In the present work, the energy differences between the lowest-energy docking poses determined by EM-Dock v.2 are in the range of 1.1–2.34 kcal/mol (1.82 kcal/mol average, 98.2% ee at −78°). We view the latter results as being much more realistic in light of the experimental results. Consideration was also given to the fact that each reverse-docking run produces a database of poses with corresponding energies, and that perhaps the Boltzmann-weighted docking energies derived for the ensemble of poses would be more appropriate for predicting ee's instead of just considering the global energy minima. Table 1 shows that the predicted ee's calculated with Boltzmann-weighted docking energy averages still correlate with the experimental ee values.

For 8/8 substrates, the predicted ee's using reverse-docking energies are within 4% of the reported experimental values. To the best of our knowledge, this is the first reported case of enantioselectivity correlation for an asymmetric organocatalyst, based on the reverse-docking paradigm. Using a computationally inexpensive approach, it signifies an important step toward the computer-assisted design of new organocatalysts. Studies on other systems are in progress, including cases where the experimental ee's span a much wider range; these will be reported in due course.

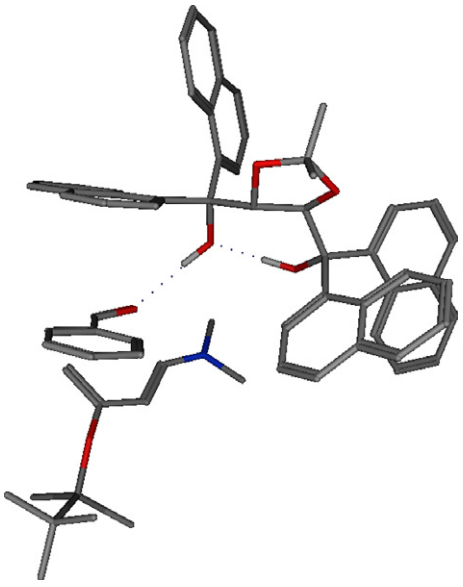

Figure 3. Representative lowest-energy reverse-docking pose to the '*S*' TS-model derived from aldehyde **4a** ($E = 207.90$ kcal/mol), non-polar hydrogens omitted for clarity.

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