Asymmetric Catalysis

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Is Enantioselectivity Predictable in Asymmetric Catalysis?**

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asymmetric catalysis · computer chemistry · enantioselectivity · prediction

The ultimate goals of asymmetric catalysis are to develop reactions that occur with high turnover and enantioselectivity under mild conditions. Meeting those goals is challenging, and focuses mainly on catalyst design. In turn that requires considerable synthetic effort with all the twists and turns of empirical science; much hard work, but immensely satisfying when it succeeds. Traditionally, mechanistic insight has followed rather than led synthesis. The role of computational chemistry had normally been refinement of the understanding at that stage.

Given the enormous experimental demand, covering hundreds of doctoral theses and thousands of postdoctoral years, shortcuts would be highly desirable. Computational chemistry has become so widely accessible that it will indeed play an increasing role in more rational approaches. This Highlight indicates the extent to which it is already happening. So is it possible to predict the enantiomer excess for a defined set of catalysts and reactants? Going beyond that, is it possible to predict the best catalyst for a desired reaction before the experiment is done?

Enzyme catalysts have evolved to near-perfect efficiency, which is associated with an optimum catalytic turnover rate and a minimum binding energy. Intermediate states (I) of comparable energies offer the maximum benefit, as does more than one partly rate-limiting transition state contribution to the turnover (Figure 1 a).[1] Chemical catalysts for asymmetric synthesis are less perfect. Typically, a multistep process will have disparate energies for the individual ground (GS) and transition states (TSs), as shown in Figure 1 b. The enantio-determining step may either coincide with or come after the turnover-limiting transition state. If the ground state

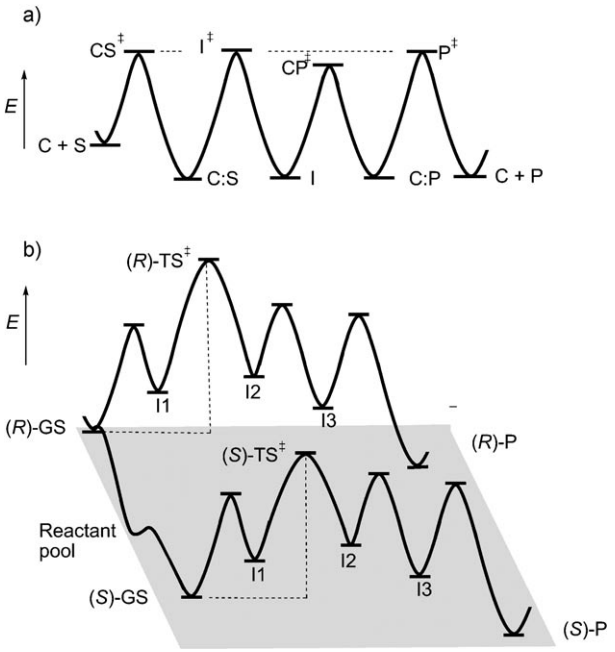

Figure 1. Comparison of the energy surface for an ideal enzyme catalyst (a: C: catalyst; S: substrate; P: product) with an idealized multistep asymmetric catalytic reaction (b), having a low barrier between the pathways leading to the *R*- and *S*-configured products, (*R*)-P and (*S*)-P respectively; the (*S*)-P is preferred. Background reactions are ignored.

is a rapidly interconverting pool of bound prostereogenic reactants directly linked to both diastereomeric pathways, computing the relative energies of the transition states of highest energy ((*R*)-TS versus (*S*)-TS) provides access to the *ee* value of the catalytic reaction. The criteria would need to be modified when considering kinetic resolutions of racemic reactants.

This sequence, involving rapid pre-equilibria, fits the Curtin–Hammett principle.[2] Restated for this context, early intermediates that interconvert rapidly on the timescale of catalytic turnover do not influence the distribution between competing stereo-differentiating pathways. The highest energy TS does not need to be the same step for the pathway that delivers the *R*- or *S*-configured products. Fortunately, they frequently coincide. Not only can mechanistic proposals be placed on a more secure footing, but there is also the potential for prediction.

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Consider the theoretical methodologies available. The bond-making/bond-breaking processes inherent in catalytic pathways appear to demand an explicit quantum mechanical (QM) treatment. The breathtaking developments in computer hardware coupled with the advent of density functional theory (DFT) have made the QM calculation of the energy and structure of GSs and TSs for medium-sized systems more or less routine. Larger systems are amenable to hybrid quantum mechanics/molecular mechanics (QM/MM) where the core "active site" region is handled by QM and the conformationally flexible "outer" regions are treated classically by much more efficient molecular mechanics (MM).[3] Provided these outer regions exert predominantly steric interactions, QM/MM is appropriate. This mix of computational methods is exploited in, for example, the ONIOM and IMOMM methods.[4]

However, despite these enormous advances, as the systems grow in size and complexity, QM methods rapidly become too expensive for comprehensive conformational searching or dynamics simulations. In contrast, MM is efficient enough to sample conformational space adequately, but until recently it has been adapted only to the analysis of GSs.

Nevertheless, with such an appealing target, the effort is intensifying. Since organocatalysts lack heavy atoms, notably transition-metal atoms, the computational load is lightened there. Houk and Cheong have summarized their own work and the work of others in the area based mainly on DFT calculations, a highlight being the delineation of the reaction pathway in proline-catalyzed aldol condensations. This delineation led on to the computational prediction of an effective catalyst for an *anti*-selective asymmetric Mannich reaction; the *syn* product is the normal outcome of this type of reaction.[5]

An interesting MM-based approach (ACE) treats the approximate transition state as a "real" species with partial bonding between the reacting centers [Eq. (1)].[6] This

$$\mathrm{TS} = (1-\lambda)\mathrm{reactant} + (\lambda)\mathrm{product} \qquad (1)$$

method works well in predicting the *ee* value of stoichiometric Diels–Alder reactions involving a chiral auxiliary, having an early TS ($\lambda = 0.2$). In 41 out of 44 samples of the meta analysis the correct diastereomer of product was predicted, the failures being associated with structurally complex auxiliaries. For the organocatalyzed aldol condensation, 38 out of 40 reactions sampled by ACE using a variation of the catalyst, aldehyde, and ketone gave the correct handedness of the product, close to that from state of the art DFT calculations in terms of the accuracy of the *ee* value prediction, but far more rapidly.

Metal-complex-based asymmetric catalysis has also been reviewed by Maseras together with Balcells, and in a separate broader review with Bo.[7] These commentaries include asymmetric dihydroxylation and vanadium-catalyzed epoxidation, as well as enantioselective hydroboration, hydroformylation, and cyclopropanation. Rhodium-catalyzed asymmetric hydrogenation, a focus of this Highlight, is also covered. Alkylzinc additions to aldehydes catalyzed by chiral β-amino alcohols provide an additional area of notable progress. The mechanism is reasonably well understood in that the catalyst reacts with the zinc reagent to form a chelated zinc alkoxide. The monomeric form of this product acts as a template for both the aldehyde and the dialkylzinc, and a combination of steric and stereoelectronic factors controls the Zn–R addition to one prostereogenic C=O face. The defined positions of the three reactive components make this an excellent candidate for TS computation.[8]

The scope of the analysis was enhanced by the MM approach of Norrby and Rasmussen, in which a specific Zn force field parameterization allowed concurrent evaluation of several catalysts.[9] The employment of quantitative structure selectivity relations (QSSRs)[10] permits a prediction of enantioselectivity based on knowledge of the ligand structure. The approach requires a "training set" that teaches the system about intercomplex forces which are responsible for the observed stereoselection. The catalyst parameters were derived from semi-empirical PM3 computations, initially of the TS and subsequently of the GS of the zinc alkoxide dimers, which turn out to have structures reasonably close to the previously determined TSs and where a number of corroborative X-ray structures were available (Figure 2).[11a,b]

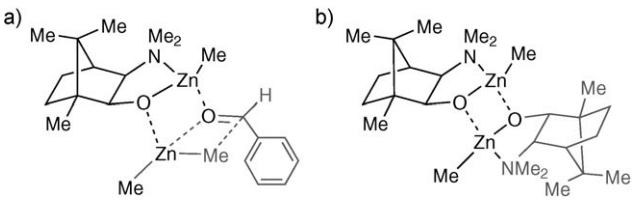
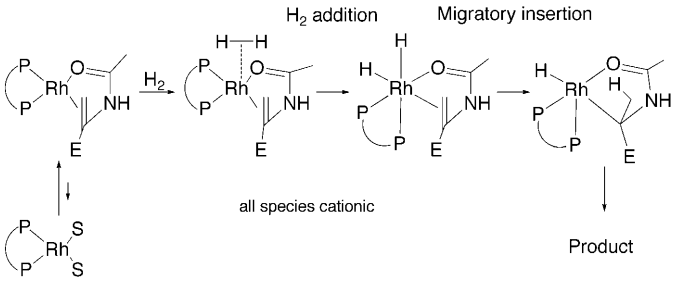


Figure 2. a) The predicted TS for Zn alkylation. b) The homochiral dimer used as "tutor". The example is from Noyori's 3-*exo*-dimethylaminoisoborneol (DAIB) ligand.

The procedures were validated by the prediction of a new catalyst for the alkylation of aldehydes, with the computed enantioselectivity being closely matched by experiment.[11c] A variant on the QSSR approach using a molecular shape field (MSF) gave specific information on the enantio-determining regions of the catalyst.[12]

Rhodium-catalyzed asymmetric hydrogenation is probably the most heavily studied of all relevant reactions. The standard mechanism is based on kinetics, and the structural characterization of reactive intermediates, particularly by NMR methods.[13,14] The bar for future computational work was set high through the comprehensive study by Feldgus and Landis; they carried out an ONIOM analysis of the "classical" mechanism (Scheme 1) using Me-duphos (=(*R*,*R*)- or (*S*,*S*)-1,2-bis(2,5-dimethylphospholano)benzene) as the ligand. They correctly demonstrated the reversal of enantiomer preference between the GS and the TS, with approximately 4 kcal mol^{-1} energy difference between the enantiomers in each case. For both diastereomeric paths the turnover-limiting TS is the H_2 addition step, but it is close in energy to that for the migratory insertion step. There are four additional pairs of stereoisomers introduced in the H_2 addition step; computing all of them defines the energetically preferred in silico



Scheme 1. The sequence of steps in rhodium-catalyzed asymmetric hydrogenation in MeOH, which was used as the model for the computation.

route.[15] Related computations have been published from other laboratories.[16]

Such comprehensive DFT analyses of complete catalytic cycles are impractical on two counts, both of which relate to the computation time. Firstly, since the energetic balance in selectivity is so subtle—that is, of the order of 2–20 kJ mol^{-1}—a thorough search of conformation space in and around the TSs is required. Secondly, we really need to be able to screen a large number of catalyst/substrate combinations. Clearly a faster and more general approach is needed for wider application. One particularly promising method is quantum-guided MM. Wiest and co-workers first carried out the Feldgus–Landis type computation at full DFT level with two achiral ligands and Me-duphos, and also with its relative ethylenebis[(2*R*,6*R*)-dimethyloxaphosphorinane] (tmbop). Now the dihydrogen addition step ($\eta^2 \rightarrow \eta^1,\eta^1$) and migratory insertion to form the alkylhydride were of comparable computed energy.[17a] The same group, now augmented by Norrby, developed a specifically tailored force field that employs QM data, including the TS structure for the migratory insertion step and the computed second derivatives of the representative process, to ensure that the MM model faithfully models the transition-state region (Q2MM). In addition, the negative eigenvalue corresponding to the TS vector is assigned an arbitrarily large positive value which turns the "TS" optimization into a minimization (Figure 3). Although this model TS will not behave correctly with respect to perturbations from other catalyst/substrate combinations, there is substantial error cancelation for selectivities. Whereas the force field development is somewhat time consuming, the huge advantage of Q2MM is: it is computationally efficient, permitting comprehensive conformational searches of the

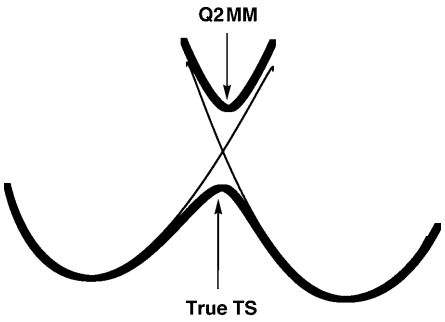


Figure 3. Schematic representation of the Q2MM TS force-field approach.

"TSs". When this is carried out with exclusive focus on the H_2 addition step, the experimental *ee* values for a wide range of symmetrical tetrasubstituted enamides can be simulated.[17b]

This approach was additionally tested using a full set of known ligands having varying efficiency in asymmetric hydrogenation, and a range of substrates. An impressive correlation was obtained with only 3 serious anomalies in a set of 29 trials (6 outriders in 47 overall, including data from the ESI of Ref. [17b]). All calculations predicted the correct handedness of the product (Figure 4).[17c] Of course, exper-

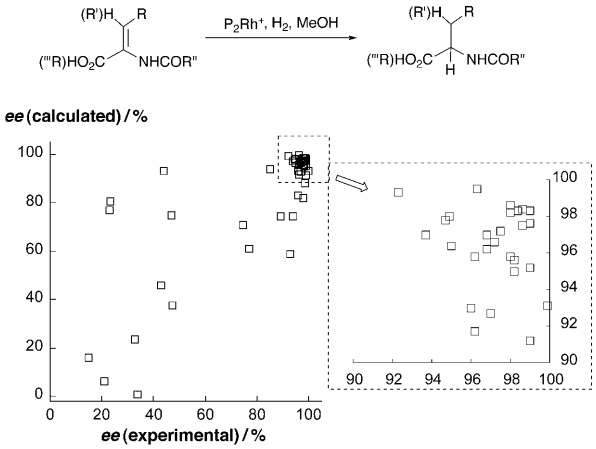


Figure 4. The comparison between computed and experimental *ee* values in enamide hydrogenation. Dipamp and Phanephos, as well as members of the Binap, Duphos, and Bis-PP* ligand families were used, together with a varieaty of dehydroamino acids and esters. using different phosphanes and dehydroamino acids and esters as ligands.

imental *ee* values can depend significantly on the experimental conditions (temperature, pressure, ionic strength, etc.), and experimenters do not always quantify their results. Hence perfect agreement with computational methods, which often do not take such factors properly into account, would be unrealistic.[18]

In summary, therefore, while no computational technique is absolutely perfect, using good-quality QM results on a model system to train a classical MM force field offers a powerful method for catalyst design and refinement. The energetic subtlety of asymmetric catalysis demands good conformational sampling. QM methods including DFT are too expensive and will remain so for the foreseeable future. Therefore, provided one can identify the enantioselective step and is then prepared to invest in the initial QM-guided force-field development, methods like Q2MM offer a real possibility of predicting enantioselectivities computationally. An encouragement towards this goal should be noted.[19]

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