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Tetrahedron
Tetrahedron 63 (2007) 13032–13038

Reverse-docking study of the organocatalyzed asymmetric Strecker hydrocyanation of aldimines and ketimines

D. Joseph Harriman, Glen F. Deleavey, Andreas Lambropoulos and Ghislain Deslongchamps*

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

Received 26 July 2007; revised 28 September 2007; accepted 2 October 2007
Available online 6 October 2007

Abstract—A methodology for reverse-docking flexible organocatalysts to rigid transition state models of catalyst-free asymmetric reactions has been developed. The investigation of Jacobsen's chiral thiourea-based organocatalyst for the hydrocyanation of aldimines and ketimines (Strecker reaction) via reverse-docking is described. Results from reverse-docking Jacobsen's organocatalyst to both enantiomers of six Strecker TS-models (i.e., rigid transition state models of the catalyst-free asymmetric reaction) indicate a clear energetic preference for binding the organocatalyst to the *R*-enantiomer TS-model, which is in agreement with experimental results. The most favorable docking poses reveal structural features consistent with principles of molecular recognition, catalysis, and NMR data. These poses may represent simplified geometric models of the transition state for the catalyzed reaction.

1. Introduction

The rational design of catalysts for carrying out highly enantioselective reactions is of great interest to the chemical community, especially the pharmaceutical industry. Organocatalysts (metal-free organic catalysts) are especially interesting as they present opportunities for biomimicry, and may fall within the realm of 'green chemistry'.[1] In particular, chiral hydrogen-bond donors have emerged as a broadly applicable class of enantioselective organocatalysts.[2,3]

The hydrocyanation of imines, termed the Strecker reaction, is particularly interesting from an asymmetric catalysis perspective as enantioselectivity is critical for the synthesis of non-natural amino acids.[4] A study published by Jacobsen and Vachal in 2002[5] reports the successful application of a flexible thiourea-based organocatalyst for the asymmetric Strecker reaction, using six different imine substrates (four aldimines and two ketimines, Fig. 1). The exact catalytic mechanism for this system remains unknown but is believed to involve hydrogen bonding of both thiourea hydrogens of the catalyst to the imine nitrogen of the substrate. 3D transition state models of catalysis can be highly useful for rationalizing and predicting the stereochemical outcome of asymmetric reactions, and for the design of new catalysts. Computational studies of asymmetric catalysts have been very useful for in-depth analysis of systems in which the transition state geometries are fairly well defined. However, devising useful transition state models of reactions involving highly flexible organocatalysts presents a particularly daunting challenge; one must explore the vast conformational space of the catalysts as they interact with substrates, approximate their respective transition state geometries and energies, and account for experimental enantioselectivities. For large systems, quantum mechanical (QM) approaches become very computationally demanding, and molecular mechanics (MM) approaches may introduce errors if improperly parameterized force fields are used. However, both QM and MM approaches have enjoyed much success in studying transition state geometries and enantioselectivities of asymmetric reactions.[6–9]

Computational tools are becoming increasingly useful for both understanding and predicting asymmetric synthesis reactions. Several computational approaches for studying molecular interactions exist, many of which are powerful tools for the organic chemist.[10] Due to the computational demands of QM calculations, a number of docking strategies have been developed based on molecular mechanics principles. The advantage is that MM-based docking algorithms can be used to study systems that are too large to reasonably investigate with QM. We have developed a molecular mechanics-based methodology for reverse-docking flexible organocatalysts to rigid transition state models of catalyst-free asymmetric reactions, producing simplified geometric models of the transition state for the organocatalyzed reactions. Reverse-docking a chiral organocatalyst to two enantiomeric TS-models for a particular substrate produces

Keywords: Asymmetric organocatalysis; Thiourea; Reverse-docking; Strecker reaction.
* Corresponding author. Tel.: +1 506 453 4795; fax: +1 506 453 4981; e-mail: ghislain@unb.ca

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doi:10.1016/j.tet.2007.10.009

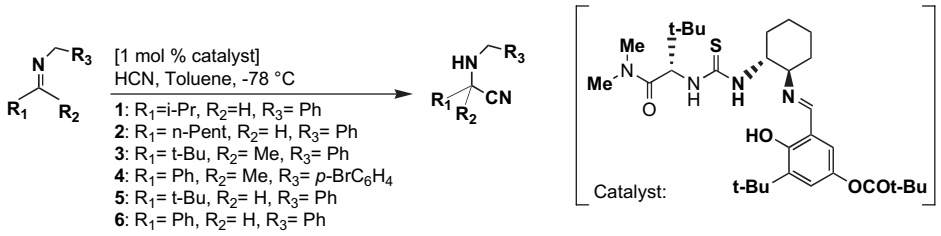

Figure 1. Jacobsen's thiourea-catalyzed Strecker reaction.

approximations of the two enantiomeric transition states, including geometry and relative energy. This reverse-docking approach has predicted the preferred product enantiomer in all cases studied to date.[11–13] Jacobsen's Strecker organocatalyst offers a particularly challenging case for study due to its large number of conformational rotors. Here, we report the successful reverse-docking investigation of this Strecker reaction, and show that the most energetically favorable docking poses are consistent with experimental data, correctly predicting the preferred product enantiomers and providing modest correlation with the experimental enantiomeric excess (ee) values in some cases.

1.1. Strecker organocatalysis

Jacobsen's organocatalyzed Strecker reaction is believed to involve hydrogen bonding of the thiourea component of the catalyst to the imine nitrogen of the substrates, thus enhancing its electrophilicity toward cyanide addition. NMR data suggests that the system shows an energetic preference for a bifurcated H-bonding pattern, with the imine nitrogen of the substrate hydrogen-bonded to both thiourea hydrogens of the catalyst. Isotope shift experiments also provided evidence that the imine substrate interacts solely with the thiourea hydrogens. Overall the work suggests that: (1) the large group on the imine carbon is directed away from the catalyst and into the solvent; (2) the small group (H or Me) on the imine carbon is aimed directly into the catalyst; (3) the *N*-substituent on the imine is directed away from the catalyst; and (4) HCN addition takes place over the diaminocyclohexane portion of the catalyst.[5] Herein, we use the term 'catalytic pose' in reference to a catalyst/TS-model that presents two intermolecular H-bonds between the two thiourea NH groups of the catalyst and the imino nitrogen of the TS-model. This distinction is based not only from the Jacobsen experiments but also from the general role of thioureas in organocatalysis.[14]

1.2. Reverse-docking

Traditional docking approaches dock flexible guest molecules within a rigid representation of the host receptor. As one can imagine, host rigidity can be a major source of error, especially in systems demonstrating induced-fit type host–guest interactions. To avoid some of the inherit pitfalls encountered in traditional docking, techniques for reverse-docking are becoming increasingly common.[11,15,16] The development and preliminary applications of the novel reverse-docking paradigm for studying asymmetric organocatalysis have been previously reported by our group.[11–13] As shown in Figure 2, typical docking explores the configurational space of a small flexible ligand within the confines

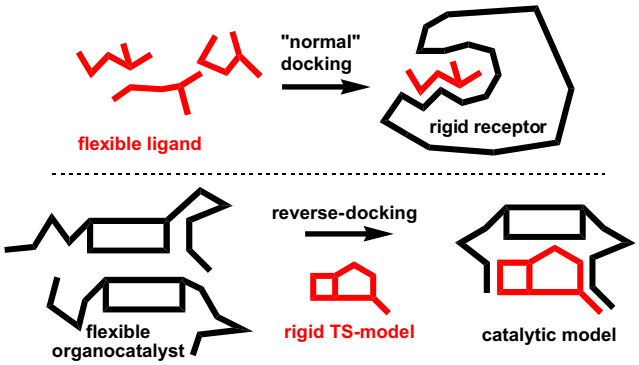

Figure 2. Reverse-docking vs normal docking.

of a large rigid receptor, whereas reverse-docking explores the configurational space of a flexible organocatalyst around rigid transition state models of the catalyst-free asymmetric reaction (referred to as 'TS-models').

This computational approach requires a powerful docking algorithm for adequately sampling the conformational space of flexible organocatalysts around TS-models. Previously, we reported the development of an Energy Minimization-based Docking algorithm, EM-Dock, designed specifically for reverse-docking applications.[17] Written in the Scientific Vector Language (SVL), EM-Dock was implemented in the Molecular Operating Environment (MOE) for rapid prototyping and convenient methodology development.[18] The latest version, EM-Dock 3, performs a systematic conformational search of an organocatalyst using molecular mechanics (MM with energy minimization), and stochastically selects conformers for subsequent reverse-docking to the rigid TS-models. The rigid TS-model geometries are obtained by ab initio calculations, and RESP charges are derived for subsequent MM treatment. As a simple local search strategy, EM-Dock energy minimizes the catalyst/TS-model poses by MM, keeping the TS-model rigid, and a docking score is computed. The chiral organocatalyst is reverse-docked to the two enantiomeric TS-models, and reverse-docking energies are compared.

2. Results and discussion

2.1. Reverse-docking energies

The lowest reverse-docking pose energies, ranks, and calculated enantiomeric excesses (ee) are reported in Table 1 (for information on docking, scoring, and ranking methods, refer to Section 4). In the Jacobsen study, the *R*-enantiomer products were obtained preferentially for both aldimines and