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Combining Q2MM modeling and kinetic studies for refinement of the osmium-catalyzed asymmetric dihydroxylation (AD) mnemonic

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Abstract

The interactions between the substrate and the ligand in the Sharpless AD reaction have been examined in detail, using a combination of substrate competition experiments and molecular modeling of transition states. There is a good agreement between computational and experimental results, in particular for the stereoselectivity of the reaction. The influence of each moiety in the second-generation ligand $(DHQD)_2PHAL$ on the rate and selectivity of the reaction has been elucidated in detail.

Keywords: Osmium; Asymmetric synthesis; Dihydroxylation; Molecular modeling; Kinetics

1. Introduction

In 1980, Hentges and Sharpless published a seminal paper describing asymmetric induction in the reaction of osmium tetroxide with alkenes [1]. The process required a stoichiometric amount of osmium, and relied on the “pseudoenantiomeric” ligands dihydroquinine acetate and dihydroquinidine acetate, respectively, for induction of chirality in the diol products (25–90% ee). This relatively humble beginning was followed by a major breakthrough in 1988, when the reaction was made catalytic by Sharpless and coworkers by use of *N*-methyl-morpholine-*N*-oxide as a reoxidant [2]. Rapid development of the process then followed, resulting in new ligands for acceleration of the reaction and experimental protocols which are operationally simple, provide excellent chemical yields and enantioselectivities for a wide range of 1,2-diols at low catalyst loadings, and equally easy access to both enantiomers of a given chiral diol [3]. The Sharpless osmium-catalyzed asymmetric dihydroxylation (AD) reaction thus serves as a benchmark for research in the burgeoning field of catalytic asymmetric synthesis, and has found extensive use in target-oriented synthesis [4]. An empirical mnemonic device was introduced (Fig. 1, left) [5] and later refined (Fig. 1, middle) [6] for prediction of absolute stereochemistry, and a number of mechanistic investigations have appeared, including kinetic [6,7], computational [8–11], and isotope effect [12] studies. We recently published an updated version of the AD mnemonic (Fig. 1, right) [13] and in the current paper we describe how a combination of Q2MM modeling [14] and kinetic measurements can be used to further refine our understanding of the factors underlying the selectivity in the AD reaction.

The revised mnemonic by Sharpless and coworkers (Fig. 1, middle) [6], based upon kinetic [6] and modeling [9] studies, importantly identified that an area of the catalytic complex could provide stabilization for the substrate, and thus rationalized the phenomenon of ligand accelerated catalysis (LAC) [15] that had been observed in the AD reaction. Our work on substrate selectivities extended this concept and suggested that two separate areas provide independent stabilization in two different regions of the ligand [13]. The first of these is identical to the one

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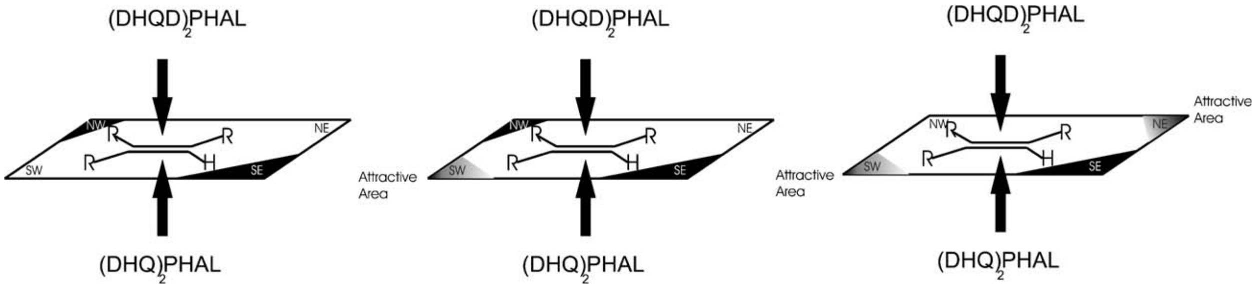

Fig. 1. Left: The original mnemonic device proposed by Sharpless and coworkers [5]. Middle: The revised version of the mnemonic device proposed by Sharpless and coworkers [6]. Right: The modified mnemonic device recently proposed by Norrby and coworkers [13].

identified by Sharpless and coworkers, caused by interactions between alkene substituents and the aromatic linker of the AD-ligand [9], whereas the second corresponds to the interactions with the quinoline moieties first postulated by Corey et al. [16] (Fig. 2).

For simple systems, it has been shown that fair predictions of experimental selectivity can be obtained by manual selection of a few transition state structures followed by computational optimization to the transition states and comparison of the energies thus calculated [10]. However, to obtain quantitative predictions for flexible systems, it is necessary to sample the space of all possible transition states, either by regular conformational searching or molecular dynamics [11,13], followed by Boltzmann population analysis. The number of conformations to be sampled calls for a relatively simple and fast computational method. At the present level of computer technology, this requires the use of molecular mechanics force fields, either in conjunction with a DFT representation for the reaction center (QM/MM), or by employing force fields designed to represent the transition states accurately. In the current work, we have chosen the latter approach, utilizing TS force fields based on our own Q2MM methodology [14], which has previously been shown to give highly accurate results for the AD reaction [11].

2. Experimental results

Recently, we have published a limited study of selectivity and reactivity of two groups of tri-substituted alkenes [13]. This study led to the development of a modified mnemonic device, which is able to predict the absolute configuration of the diol product (Fig. 1, right).

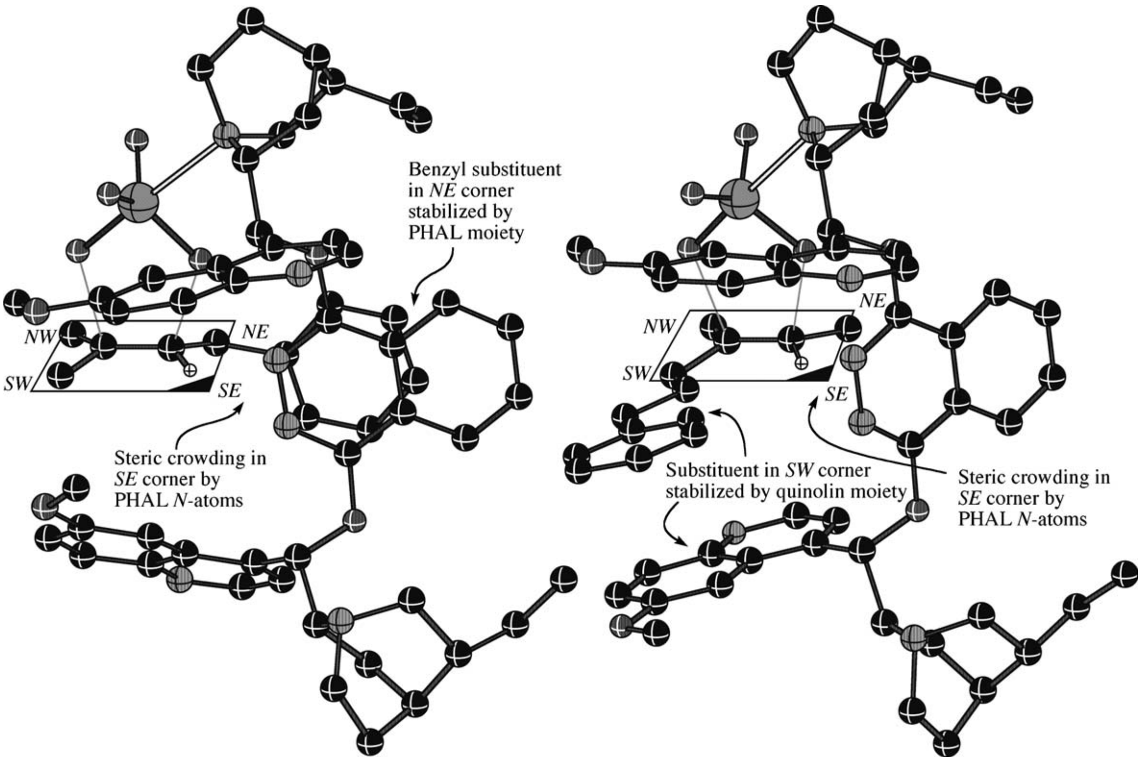

Fig. 2. Illustration of the two attractive pockets described by Sharpless (left) and Corey (right). The TS structures of **2a** (left) and **4b** (right) have been oriented in accordance with the Sharpless mnemonic device.