Origins of Contrasteric \( \pi \)-Facial Selectivity in Epoxidations of Encumbered Tetrahydropyridines by a Bifunctional Peracid

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Nitrogen heterocycles are prevalent motifs in natural products and pharmaceutical agents that constitute important synthetic targets for drug discovery.\(^1,2\) Efficient methods of accessing functionalized nitrogen heterocycles with high levels of stereocontrol are therefore highly sought after.\(^3\) The ability of hydroxyl groups to direct the stereoselectivity of alkene epoxidations through hydrogen-bonding interactions has been well-documented and investigated.\(^4,5\) The role of torsional effects (‘torsional steering’) has also been established for epoxidations and related oxidations.\(^6\) Although examples of stereoselective epoxidations have been reported that are hypothesized to be directed by nitrogen-containing groups,\(^7\) no computational studies have aimed to elucidate the origins of these selectivities.\(^8\)

In an effort to access multiple functionalized piperidines, the Ellman group\(^9\) sought to exploit the hydrogen-bonding ability of nitrogen-containing groups to enforce the diastereoselective epoxidation of tetrahydropyridines \(3\) (Scheme 1, a). The experimental protocol involves the treatment of tetrafluorophthalic anhydride \(1\) with hydrogen peroxide to yield bifunctional epoxidation agent \(2\). In addition to the oxidizing peracid functionality, \(2\) also possesses a carboxylic acid group capable of forming strong hydrogen bonds with the basic amine nitrogen in \(3\) either before or after proton transfer. It was hypothesized that the tetrafluoroarene portion serves as a rigid covalent tether, forcing the epoxidation event to occur at the hydrogen-bonded \(\pi\)-face of the molecule. Interestingly, for tetrahydropyridines \(3\), contrasteric delivery of the epoxide oxygen to the more hindered \(\pi\)-face is observed (Scheme 1, b). Epoxidation agents without the tether feature, such as \(m\)-CPBA and trifluoperacetic acid, resulted in low diastereoselectivities (Scheme 1, a).

Given this remarkable ability of this transformation to override steric bias, we undertook a computational investigation into the origins of diastereoselectivity for the epoxidation of tetrahydropyridines shown in Scheme 1 (a).

Computations were performed with Gaussian 09.\(^{10}\) Molecular geometries were optimized using the M06-2X\(^{11}\) functional and the 6-31+G(d) basis set. The effect of solvation on molecular geometries was accounted for during optimizations using the SMD\(^{12}\) solvation model with tetrahydrofuran as the solvent. Frequency calculations were carried out at the same level of theory as that used for geometry optimization to characterize the stationary points as either minima (no imaginary frequencies) or saddle points (one imaginary frequency) on the potential energy surface and to obtain thermal corrections to the Gibbs free energies. Intrinsic reaction coordinate (IRC) calculations were performed to ensure that the saddle points found were true transition states connecting the reactants and the products. Single-point energies were calculated with the M06-2X functional and the 6-311++G(3df,2pd) basis set, and solvation effects were modeled using the SMD solvation model with tetrahydrofuran as the solvent. For fragment distortion analysis, single-point energies of the
molecular fragments were computed at the M06-2X/6-311++G(3df,2pd) level using the M06-2X/6-31+G(d) geometries obtained in solution. Molecular structures were visualized using CYLview.\textsuperscript{13} Monte Carlo conformational search-es were performed with the Merck molecular force field (MMFF) implemented in Spartan ’16 to ensure that the low-est energy conformations of intermediates and transition states are presented in the manuscript. Geometries and energies of alternative conformers explored in this study can be found in the Supporting Information.

We first calculated the hydrogen-bonded and nonhy- drogen-bonded epoxidation transition states for the epo-xidation of unsubstituted 1,2,5,6-tetrahydropyrindine 3a by 2 (Scheme 2, a). A free energy preference of 3.8 kcal/mol was found in favor of the hydrogen-bonded transition state TS-1, in which the O–H···N distance is 1.73 Å (Scheme 2, b). The strong preference for a hydrogen-bonded TS is particularly striking considering that the hydrogen bond has the effect of deactivating the alkene double bond toward electrophilic epoxidation by making the alkene moiety less nucleophilic.

Examination of TS-1 and TS-2 reveals several important geometrical consequences of the hydrogen bonding. In the absence of a hydrogen bond, the peracid and the alkene in TS-2 assumes the expected spiro geometry (Scheme 2, c), which maximizes the stabilizing secondary orbital interaction between the oxygen lone pair and the alkene π* orbital.\textsuperscript{14} This interaction is weaker in TS-1, presumably because
a spiro geometry cannot be achieved due to geometrical constraints imposed by the hydrogen bond. The same geometrical constraints also force the peracid moiety to adopt a nonplanar arrangement. This nonplanarity weakens the hydrogen bond between O1 and the peracid proton (2.12 Å, compared to 1.84 Å in TS-2). In TS-2, the formation of the two C–O bonds is only slightly asynchronous at 2.16 and 2.22 Å, respectively, whereas TS-1 is much more unsymmetrical (2.20 and 2.02 Å).

Having established the favorability of the hydrogen-bonded TS, we next investigated the epoxidation of hexa-substituted tetrahydropyridine scaffolds, represented by tetrahydropyridine 1b. These tetrahydropyridines are observed to undergo epoxidation at the more sterically encumbered π-face.

Computed transition states for the epoxidation of 3b by 2 are shown in Scheme 3. For each product diastereomer, a hydrogen-bonded TS and a nonhydrogen-bonded TS can be envisioned. For TS-4 and TS-6, the two transition states without OH–N hydrogen bonding, calculated free energies of activation indicate that the reaction should be 2.0 kcal/mol in favor of epoxidation at the less sterically hindered face. With OH–N hydrogen bonding, however, the preference is 7.1 kcal/mol in favor of contrasteric epoxidation (TS-3 and TS-5). Geometrically, the undirected transition states TS-4 and TS-6 are spiro and highly symmetrical, similar to TS-2. The hydrogen-bonded TS-3 and TS-5 are both distorted away from a spiro geometry, with highly asynchronous formation of the two C–O bonds. Overall, the hydrogen-bonded TS-3 is 1.7 kcal/mol lower in energy than TS-6, which explains the experimentally observed selectivity for diastereomer 4b-A. This result confirms that the OH–N hydrogen bond is strong enough to override the effects of steric congestion. Considering that the amine moiety is likely to be partially protonated under reaction conditions, which would deactivate the C=C bond toward electrophilic epoxidation, undirected epoxidation is likely to have barriers that are higher than those calculated for TS-4 and TS-6, as these transition states do not take the effect of amine protonation into account.

To further explain the severe energetic unfavorability of TS-5, we calculated the distortion energies (E_{dist}^4) of the tetrahydropyridine fragment in epoxidation transition states TS 3–6 (Figure 1). These E_{dist}^4 values are obtained by comparing gas-phase electronic energies of transition-state geometries of the tetrahydropyridine to that of the corresponding ground-state geometry.\textsuperscript{15} The tetrahydropyridine fragment in TS-5 has a high E_{dist}^4 value of 13.6 kcal/mol, which is 8.8 kcal/mol higher than the corresponding E_{dist}^4 value in TS-3. This difference in distortion energy is comparable in magnitude to the ΔΔG^‡ value of 7.1 kcal/mol between TS-3 and TS-5, indicating that the free energy distinction can be mostly attributed to the distortion of the tetrahydropyridine substrate. Geometrically, the tetrahydropyridine fragment in TS-5 is deformed into a twist-boat-like structure to allow the nitrogen lone pair to occupy the pseudo-axial position needed for hydrogen bonding. Unfavorable near-eclipsing interactions in the twist-boat-like structure (Figure 1) result in a high E_{dist}^4 value.

In conclusion, we used DFT calculations to reveal the origins of the contrasteric π-facial stereoselectivity in the epoxidation of densely substituted tetrahydropyridines by a bifunctional peracid reagent 2. We show that epoxidation of 1,2,3,6-tetrahydropyridines with 2 have a strong preference to proceed through OH–N hydrogen-bonded transition states. Even for hexa-substituted tetrahydropyridines that are highly congested at one π-face, the OH–N hydrogen-bonding interaction is strong enough to overcome the steric disadvantage and deliver the contrasteric epoxide product.

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Scheme 3 Four calculated transition states for the epoxidation of 3b by 2. Energies are denoted in kcal/mol, and interatomic distances are shown in Ångströms. Hydrogen atoms attached to carbons are omitted for clarity.
References and Notes


(8) For kinetic studies on stereoselective oxidations of olefins directed by nitrogen-containing moieties, see ref. 7c


