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Origins of Selectivities in Proline-Catalyzed α-Aminoxylations

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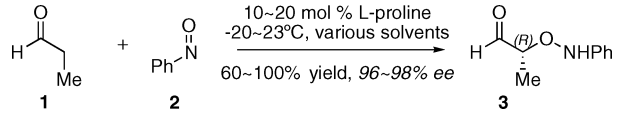
Three groups in southern California and Japan have recently discovered that proline catalysis promotes stereoselective α-aminoxylation of aldehydes and ketones by nitrosobenzene. MacMillan, Hayashi, and Zhong independently reported the direct proline-catalyzed α-aminoxylation of aldehydes,[1] while Hayashi and Córdova reported the analogous α-aminoxylation of ketones[2] (Scheme 1). Previous α-oxidation methodologies involved the preparation of enol ether intermediates.[3]

Scheme 1 [1,2]



The greater electrophilicity of oxygen than that of nitrogen in the reaction is surprising, in light of the opposite behavior often exhibited by nitrosobenzene in related reactions.[4] Three different variations of the mechanism have been proposed (Figure 1).[1,5] We have performed a quantum mechanical computational study that establishes the mechanism as well as the origins of the regioselectivity and stereoselectivity of these reactions.[6]

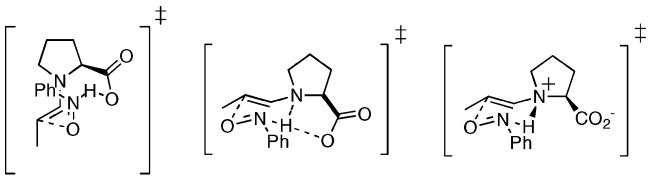


Figure 1. Mechanisms proposed for the proline-catalyzed α-aminoxylation of aldehydes.

The proposed mechanisms shown in Figure 1 all feature a pseudo-six-membered transition structure, but differ by the degree to which the carboxylic acid or the proline amine participates in the proton-transfer process. Hayashi preferred transition state **4a**, which is analogous to the transition structures we have found computationally for proline-catalyzed aldol and Mannich reactions[7] in that the proton transfer occurs from the carboxylic acid. Zhong proposed transition structure **4b** in which both the carboxylic acid and the proline amine facilitate the proton transfer, while MacMillan proposed an enaminium-mediated ene-like zwitterionic transition state **4c**.

The above pathways do not exhaust the mechanistic possibilities. Nitrosobenzene dimerizes readily,[8] and analogous pathways involving the nitrosobenzene dimer **7** as the electrophile are possible.[9]

We explored quantum mechanically[10] the reactions of the proline enamine of propionaldehyde, which exists as conformers ***(E)*-Anti-5** and ***(E)*-Syn-6**, with nitrosobenzene **2** and its dimer **7** (Scheme 2). In all cases, transition structures lacking the intermolecular proton transfer[11] or involving the *(Z)*-enamines were found to be much higher in energy and therefore are not reported here.

Scheme 2

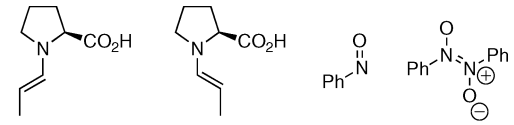


Figure 2 shows the lowest-energy transition structures for this reaction. The most stable aminoxylation transition structure ***(R)*-O-Anti-8** involves an *(E)*-anti enamine **5** attack[12] on the oxygen of the nitrosobenzene **2**. The phenyl group adopts the axial position, anti to the carboxylic acid group (Figure 2), akin to the proline-catalyzed Mannich reaction transition structure previously reported by our group.[7]

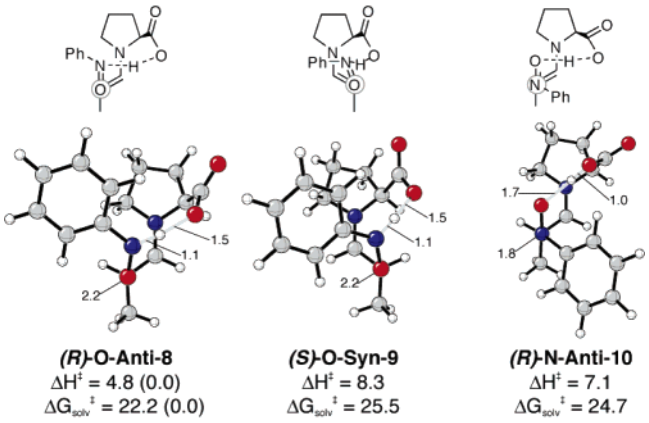


Figure 2. Proline-catalyzed α-aminoxylation and α-hydroxyamination transition structures of the proline enamine of propionaldehyde **1** with nitrosobenzene **2**.[13]

Transition structure ***(S)*-O-Syn-9** gives the minor enantiomer product; it is 3.3 kcal/mol higher in energy.[14] The syn enamine transition states are uniformly higher in energy due to the energetic cost in distorting the molecular geometry to accommodate proton transfer to a more proximal nitrogen. These calculations predict an enantiomeric excess of *99%* of the product favored experimentally, in reasonable agreement with the experimentally reported ee of *97%*.

The transition structures for attack at nitrogen (hydroxyamination) were generally higher in energy than those for attack at oxygen. The attack at nitrogen to give the *(R)*-hydroxyamination product via transition structure ***(R)*-N-Anti-10** is disfavored by 2.6 kcal/mol (Figure 2). The heteroatom selectivity can be explained by the higher basicity of the nitrogen than that of oxygen, which leads to the preferential protonation of the nitrogen, allowing the oxygen to become electrophilic. This difference in basicity is reflected in the degree of proton transfer in the respective transition structures. The aminoxylation transition structures all feature a nearly complete

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proton transfer to the nitrogen of the nitrosobenzene (1.1−1.2 Å). This is in contrast to the corresponding hydroxyamination transition structures in which the oxygen proton distances are 1.1−1.7 Å.

In the absence of acidic protons, a reversal in heteroatom selectivity is expected. The hydroxyamination reaction between the dimethyl enamine of propionaldehyde with nitrosobenzene is predicted to be favored over aminoxylation (Figure 3).[2c]

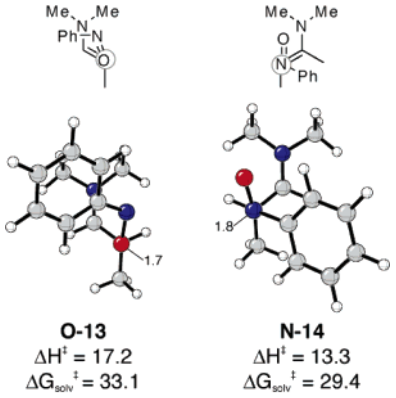

Figure 3. Dimethyl-amine catalyzed α-aminoxylation and α-hydroxyamination transition structures of propionaldehyde **1** with nitrosobenzene **2**.[13]

The Zhong-proposed transition structure **4b** in which the proline amine assists in the proton transfer from the carboxylic acid to the nitrogen anion could not be located. Such transition structures spontaneously decompose to the neutral, more stable transition structure ***(R)*-O-Anti-8** in which only the carboxylate mediates the proton transfer. The proline amine−proton distance was 2.7 Å, and there is no evidence of proline amine pyramidalization.

Enaminium-mediated zwitterionic ene-like transition structures **4c**, with the carboxylate group syn to the proton-transfer face, could not be located. The lowest-energy enaminium transition structure is ***(R)*-O-13**, in which the carboxylate group is anti to the proton transfer face. Zwitterionic transition structures are extremely disfavored due to the poor nucleophilicity of the enaminium olefin and the high energetic penalty accrued by the charge separation. It is 32.4 kcal/mol higher in energy than the most stable transition structure.

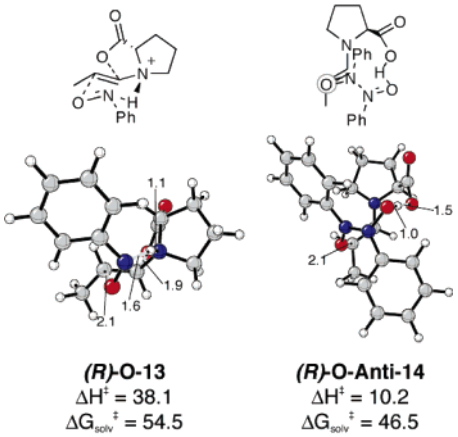

Figure 4. Proline-catalyzed α-aminoxylation transition structures of propionaldehyde **1** with nitrosobenzene **2** or nitrosobenzene dimer **7**.[13]

The transition structures involving the nitrosobenzene dimer **7** are disfavored due to the entropic cost of dimerization and the difficulty of a nucleophilic attack on the partially negatively charged oxygen of the nitrosobenzene dimer. The lowest-energy transition structure ***(R)*-O-Anti-14** (Figure 4) involving the nitrosobenzene dimer **7** is 24.4 kcal/mol higher than the most stable aminoxylation pathway involving the nitrosobenzene monomer. The aminoxylation transition structures involving the nitrosobenzene dimer exhibit almost complete proton transfer to the oxygen due to the anionic character of the oxygen in the nitrosobenzene dimer **7**.

Proline catalysis occurs via a proline enamine attack on the oxygen of the nitrosobenzene monomer with a simultaneous proton transfer from the carboxylic acid. Computational evidence shows that the observed heteroatom selectivity materializes through the difference in basicities of the oxygen and the nitrogen atoms.

Acknowledgment. We are grateful to the National Institute of General Medical Sciences, National Institutes of Health for financial support of this research. We thank the National Computational Science Alliance, the National Science Foundation, and UCLA Academic Technology Services for computer resources.

Supporting Information Available: Full Gaussian references, Cartesian coordinates, electronic and zero-point vibrational energies of all reported structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) In the Lewis acid-catalyzed enol ether-mediated aminoxylation, Yamamoto states that the presence of Lewis acids promote the dimerization of nitrosobenzene and forces the nucleophilic attack to occur on the oxygen of the nitrosobenzene dimer. See ref 3h.

(10) (a) The stationary points (reactants and transition structures) were optimized and characterized by frequency analysis using hybrid density functional theory (B3LYP) and the 6-31G(d) basis set as implemented in the Gaussian 98 and 03 series of programs (see Supporting Information for a complete list of authors of these programs). (b) Solvation free energies were calculated for DMSO with the PCM solvation model and UAKS radii using the HF/6-31+G(d, p) level of theory, as implemented in Gaussian 03. (c) Transition state theory was used to predict the stereoselectivity.

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(13) Figures prepared with *Houkmol*, version 2.6.3; Nakamura, K.; Houk, K. N. NAIST: UCLA, 2004.

(14) Energies presented in the text are the sums of Gibbs free energy and solvation energy.

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