# From Evolution to Green Chemistry: Rationalization of Biomimetic Oxygen-Transfer Cascades

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The accumulation of O_2 in the earth's atmosphere began approximately two billion years ago, after the molecular oxygen that was liberated from photosynthetic bacteria had oxidized most of the iron(II) resources in the oceans to ferric minerals.[1] Although a powerful oxidant had become available, the low reactivity of O_2 to typical organic fuel molecules was a major obstacle in evolution. Nature circumvented the unfavorable kinetics of direct oxidations by designing the aerobic respiratory chain, which proceeds in the inner mitochondrial membrane of eukariotic cells.[2] The feasibility of each electron-transfer step in respiration depends on the difference of the electron-transfer potential, E, for the corresponding pairs of redox couples Ox/Red^-. Electron-transfer potentials are typically measured relative to the $H^+/{}^1\!/_2 H_2$ reference couple and are connected to the reaction free energy ΔG_r of reaction 1.

$$Ox + {}^1\!/_2 H_2 \rightarrow Red^- + H^+ \qquad (1)$$
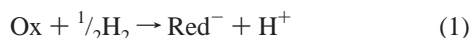
Chemists learned from nature to improve the efficiency of catalytic oxidation processes.[3] Protocols using the green terminal oxidant hydrogen peroxide are of particular interest because water is the only waste product. The Beller[4] and Bäckvall[5] laboratories recently reported environmentally benign oxygen-transfer chains for the Sharpless dihydroxylation,[6,7] where the oxidation of the five-membered metallacycle of osmium(VI) (dioxoosma-2,5-dioxolane) to the osmium(VIII) species is a crucial step (Figure 1). Whereas experimental electron-transfer potentials from textbooks[1,2] reflect the electron flow in the redox reactions of respiration (see Supporting Information), a quantitative rationalization of the design of oxygen-transfer chains has not been achieved. In this work, we define and predict the thermodynamic oxygen-transfer potential (TOP, in kcal/mol) for a couple XO/X as the reaction free energy ΔG_r of reaction 2.

$$X + H_2O_2 \rightarrow XO + H_2O \qquad (2)$$

The oxidation of X is thermodynamically more favorable than that of Z (or X may be oxidized by ZO) if TOP (XO/X) < TOP (ZO/Z). Figure 2 displays TOP values for a variety of oxidants and substrates calculated using density functional theory (DFT) at the B3LYP level.[8] The results provide a unified view of oxygen-transfer pathways, for example, in osmium-catalyzed olefin di-hydroxylation methods developed in the last nine decades.[4–7] The oxidation of dioxoosma-2,5-dioxolane to the trioxo species requires an oxidant with a higher TOP than that of trioxo-/dioxoosma-2,5-dioxolane (TOP = −36).[9] Perchlorate (TOP = −24) was used in Hofmann's pioneering work[6a] and N-methylmorpholine N-oxide (TOP = −17 for Me_3NO/NMe_3) is the terminal oxidant in the Upjohn process.[6c] For Bäckvall's recent method[5c] of olefin dihydroxylation with H_2O_2 in the presence of methyltrioxo-rhenium(VII) (MTO),[10] the chiral tertiary amine (DHQD)₂PHAL, and osmium tetraoxide, the TOPs in Figure 2 demonstrate the likely
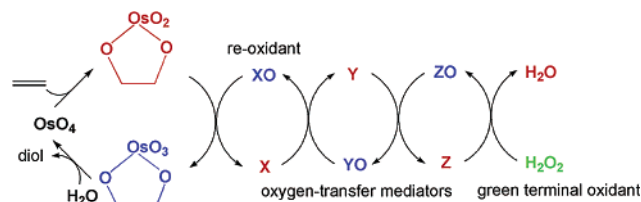

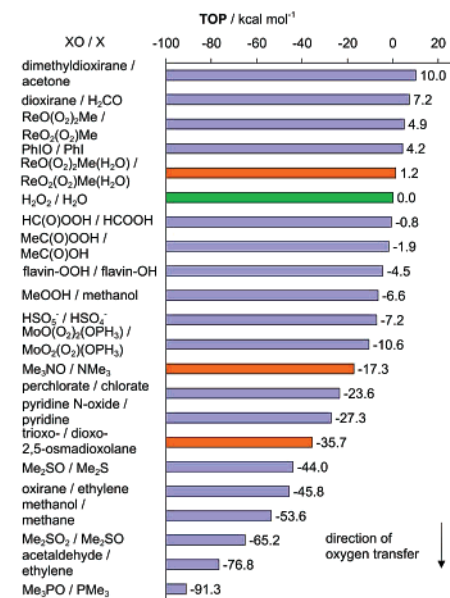**Figure 1.** "Green" Sharpless dihydroxylation.

Figure 2. Thermodynamic oxygen-transfer potentials (TOP).

oxygen-transfer cascade from the rhenium peroxide (TOP = 1) via the amine (TOP = −17 for Me_3NO/NMe_3) to the osmium metallacycle (TOP = −36; see orange bars in Figure 2).

Since the TOP values provide only thermodynamic information, one may define the *kinetic* oxygen-transfer potential (KOP, in kcal/mol) of an XO/X couple as the activation free energy ΔG_a of reaction 3[11–13] and then predict the activation free energy ΔG_a of reaction 4 from KOPs using Marcus theory.[14] However, this approach fails entirely in case of Bäckvall's protocol (see Supporting Information).

$$X + XO \rightarrow XO + X \qquad (3)$$

$$X + ZO \rightarrow XO + Z \qquad (4)$$
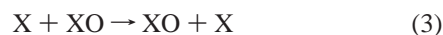
A rigorous investigation of the transition states (TS) for mutual oxygen-transfer events among tertiary amines, osma-2,5-dioxolanes, and rhenium peroxides at the B3LYP level predicts aquamethyl-oxodiperoxo rhenium(VII) (MTO*aq) to oxidize trimethylamine with an activation free energy ΔG_a of 17 kcal/mol. From first sight, the
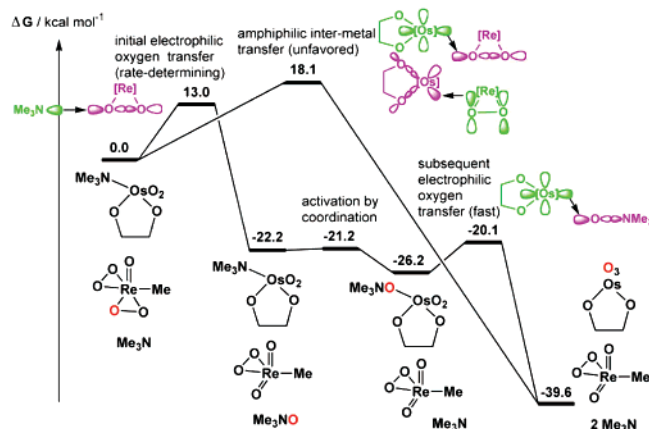
Figure 3. Calculated free energy profile ΔG for the intermetal oxygen transfer from MTO* to DOD and for the amine-mediated oxygen-transfer chain. Electrophilic (magenta) and nucleophilic (green) orbital interactions in the TS.

intermetal oxidation of dioxoosma-2,5-dioxolane (DOD) with MTO*$_{aq}$ seems slightly more favorable ($\Delta G_a = 16$ kcal/mol). However, the dissociation of the aqua ligand from MTO*$_{aq}$ leads to methyloxodiperoxo rhenium(VII) (MTO*),[15] which is significantly more reactive to trimethylamine than to DOD ($\Delta G_a = 13$ vs 18 kcal/mol). Figure 3 displays the calculated free energy profile ΔG for the MTO* species. The activation free energy ΔG_a for the reaction of DOD with Me$_3$NO appears to be extremely small: only 2 kcal/mol relative to DOD and Me$_3$NO. However, exploring the intrinsic reaction coordinate (IRC) reveals a Michaelis−Menten-like coordination of Me$_3$NO to DOD (with a reaction free energy ΔG_r of -4 kcal/mol) and subsequent *intramolecular* oxygen transfer (with an activation free energy ΔG_a of 6 kcal/mol). In contrast, the calculations show that the rhenium peroxides do not form a stable adduct with DOD. This rigorous investigation indicates the potential dual role of the amine oxide in catalytic dihydroxylation both as a carrier of stereochemical information and as an efficient oxygen-transfer mediator due to a unique mechanistic pattern.

Investigation of the transition states for Bäckvall's protocol[5c] using an energy decomposition scheme[16] reveals the TS for the intermetal oxidation, which is paradoxically the TS with the highest activation free energy ΔG_a, to be most strongly stabilized by orbital interactions. This stabilization is caused by the chameleon nature of MTO*, which attacks DOD in both an electrophilic and nucleophilic manner (Figure 3). The analysis elucidates the rather high activation free energy ΔG_a by (i) a substantial Pauli repulsion between MTO* and DOD in the TS and (ii) a strong deformation of the oxo ligands in DOD before reaching the transition state, whereas the amine readily reacts with MTO* without a considerable deformation.

Supporting Information Available: Computational details, methodological evaluation for iodine compounds, TOPs in aqueous solution, reactivity prediction from KOPs, and transition structures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The KOP of Me$_2$SO/Me$_2$S (54.1 kcal/mol) is smaller than that of Me$_2$SO$_2$/Me$_2$SO (68.4 kcal/mol). Therefore, the KOP values may explain the observation that the oxidation of Me$_2$S to Me$_2$SO is easier than the oxidation of Me$_2$SO to Me$_2$SO$_2$, whereas the TOP values would have suggested the opposite.

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