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Enhancing 2-Iodoxybenzoic Acid Reactivity by Exploiting a Hypervalent Twist

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Among oxidizing agents, 2-iodoxybenzoic acid (IBX) stands out for being mild, selective, and environmentally friendly, as it contains no toxic or expensive heavy metals, and variants exist that operate in aqueous solution.[1] IBX effects oxidations of functionality beyond simple alcohols,[2,3] making it an ideal reagent for carrying out a wide range of oxidative transformations were it possible to tame and enhance its reactive capabilities.

We propose a modification of IBX predicted to increase its oxidizing power while preserving its selectivity, based on a new mechanism in which the rate-limiting step is *hypervalent twisting*. Our mechanism, derived from density functional quantum mechanics (QM) calculations,[4] also explains the native alcohol size-selectivity of unmodified IBX.

Hypervalent twisting is a coordinated motion of ligands driven by the necessity of generating a stable, planar form of the byproduct IBA **4** from an IBX−alcohol intermediate **3** (Figure 1). The proposed modification, substitution of IBX at the *ortho* position, lowers the barrier of this step. Since the rate-accelerating *ortho* position is near the site of substrate binding, it offers a possible route to an oxidant capable of chiral discrimination.[5]

We find that alcohols exchange with the hydroxyl ligand of IBX **1** via a low-barrier (∼9 kcal/mol) acid-catalyzed pathway, producing an IBX−alcohol complex **2** blocked from eliminating IBA (Figure 1). To form the oxidation products, **2** must twist, moving the *oxo* group into the plane and the alcohol out of the plane to form complex **3** (rate-limiting barrier of ∼12 kcal/mol). Only after the twisting barrier has passed can the complex between $\ddagger_{twist}$ and **3** eliminate IBA **4** to produce the oxidation product **5** (∼5 kcal/mol barrier). Intermediates **1**, **2**, **4**, and **5** consistent with our calculations have been observed by NMR.[6]

This hypervalent twist mechanism explains the propensity of IBX to oxidize large alcohols faster than small ones. Larger alcohols have a lower twisting barrier since the twisting is driven forward by a repulsion between the alkoxy ligand and the *ortho* hydrogen that is relieved as the motion is completed (Figure 3). Figure 2 shows that lower twisting barriers correlate well with higher measured oxidation rates over the alcohols examined.

To accelerate the overall reaction, we propose placing a bulky substituent in the *ortho* position to encourage IBX twisting. As a simple test, an *ortho* methyl substituent lowers ΔG_{twist} by >2.4 kcal/mol over a test set of seven alcohols, with a typical rate acceleration of ∼100 times (Figure 2). The rate acceleration is especially pronounced for the secondary alcohols 2-propanol and 2,4-dimethyl-3-pentanol, consistent with increased steric repulsion between the *ortho* methyl and the alcohol.

The optimum size for the *ortho* group is a compromise between being large enough to favor the twisted form and being small enough to allow a favorable equilibrium between **1** and **2** (Ph and *t*-Bu are too large). Medium-sized nonpolar aliphatics, such as methyl, ethyl and isopropyl, provide the best balance of good twisting and ligand exchange thermodynamics.[8]

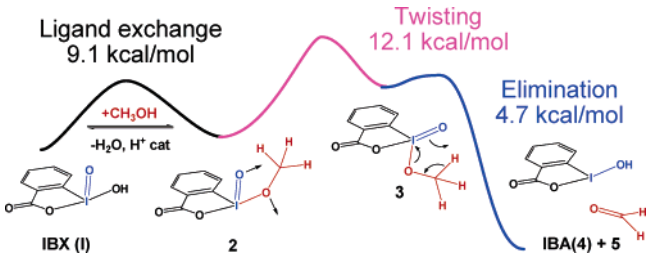

Figure 1. Hypervalent twist (HT) mechanism showing the reaction path and associated barriers for oxidation of alcohols by IBX (barriers relative to reactants at each step). The coordinated motion that converts intermediate **2** to **3** is the rate-limiting step of the reaction.

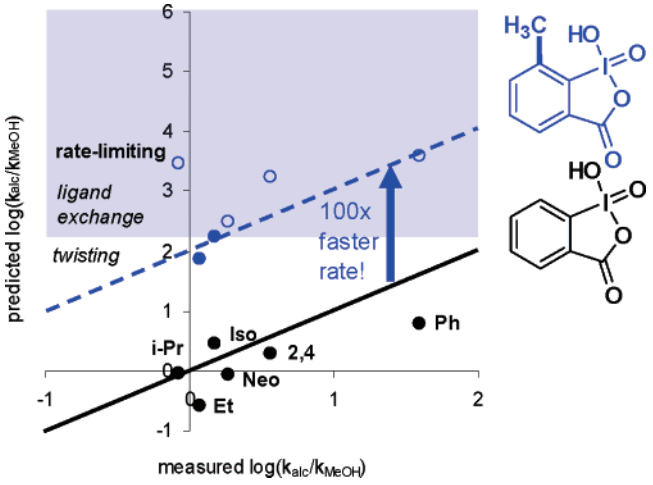

Figure 2. Alcohol oxidation rates estimated from hypervalent twisting barriers show good correlation with experimentally measured rates. We predict that *ortho*-methyl IBX multiplies the twisting rate by a factor of 100, up until ligand exchange becomes the rate-limiting step of the overall oxidation.

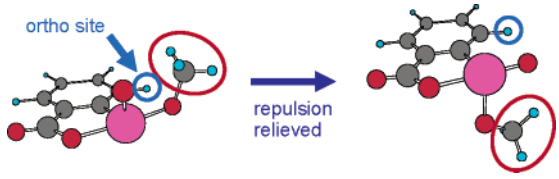

Figure 3. Explanation of IBX−alcohol size-selectivity: large alcohols twist IBX more easily, which makes them oxidize more quickly. The proposed *ortho*-substituted IBX enhances this effect and should be more active.

We now consider the nature of the hypervalent twist. IBX and its alcohol derivatives can exist favorably in untwisted and twisted conformations. In contrast, the byproduct IBA is only stable in a planar form—the form of IBA with hydroxyl and carboxylic acid ligands 90° from each other is destabilized by ∼48 kcal/mol relative to planar IBA.

Figure 4 shows that this stability difference affects the barriers to IBA elimination and product formation: the transition state is

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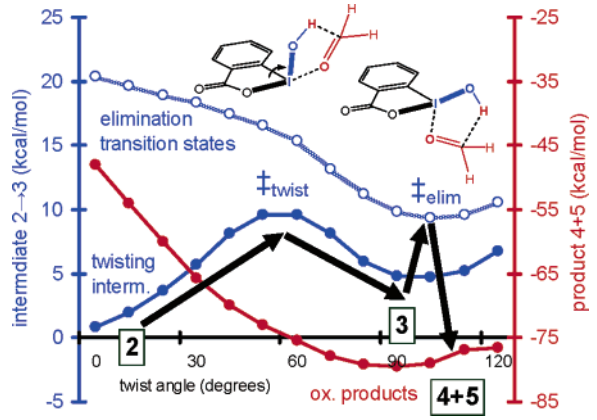


Figure 4. The alcohol−IBX intermediate **2** (blue curve, solid circles) can pass through elimination transition states (blue curve, open circles) to form oxidation products (red curve). The black arrows show the most favorable reaction pathway, where **2** twists past $‡_{twist}$ to form **3**, access $‡_{elim}$, and form oxidation products **4** and **5**.

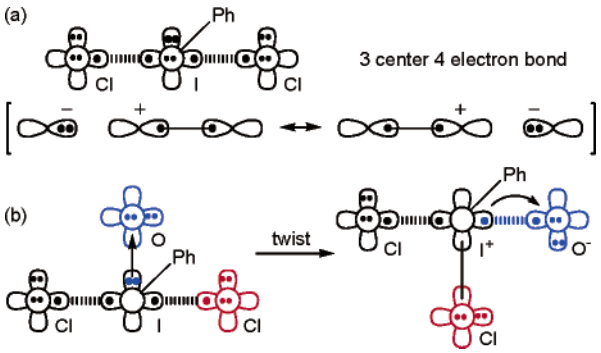


Figure 5. Hypervalent bonding in analogues to IBA **4**, IBX **2**, and twisted IBX. (a) Resonance structures responsible for the half-ionic half-covalent three-center four-electron bond in $PhICl_2$, similar to IBA; (b) structures of $PhIOCl_2$, similar to those of IBX and twisted IBX.

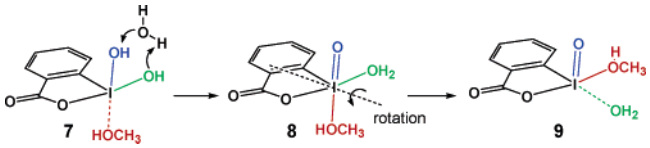
product-like. Intermediate **2** prefers to twist first (12 kcal/mol), then eliminate IBA (5 kcal/mol), rather than eliminate IBA directly without twisting (20 kcal/mol).

To understand why IBX twists readily while IBA prefers so strongly to be planar, consider the bonding of iodine in IBA (Figure 5). Iodine makes a normal covalent bond to the phenyl carbon, leaving two doubly occupied 5p orbitals perpendicular to this bond. In IBA, one doubly occupied orbital is flanked by hydroxyl and carboxylic acid ligands opposite each other, bound by a three-center four-electron bond that is half-ionic and half-covalent. The two anionic ligands must be opposite to each other to gain full stability from resonance.

In IBX and its alcohol derivatives, the other doubly occupied orbital is used to make a dative donor−acceptor bond to the oxo group. Upon twisting, as with IBA, the methoxy ligand loses resonance with the acid ligand, making it less strongly bound, but unlike in IBA, the *oxo* group picks up the resonance with that ligand to compensate. In addition, the *oxo* bond becomes more covalent in character, as the iodine transfers an electron to the oxygen to avoid placing three electrons into one p orbital. These balanced effects make the twisted complex a true intermediate only ~3 kcal/mol less stable than the untwisted complex.

Our work has focused on accelerating the overall oxidation rate by lowering the twisting barrier, but beyond a certain point, ligand exchange becomes the rate-limiting step. For methanol oxidation, this point is reached when the barrier to hypervalent twisting of ~12 kcal/mol is lowered to the ligand exchange barrier of ~9 kcal/mol, a rate acceleration of ~270 times.

Scheme 1. Acid-Catalyzed Water/Alcohol Exchange on IBX, Showing Proton Transfer (6.0 kcal/mol barrier) Followed by Coordinated Ligand Motion (9.1 kcal/mol barrier)



Alcohol/water exchange occurs via two steps: a fast proton transfer and a slower coordinated ligand motion (Scheme 1). The proton transfer starts with protonated IBX complex **7** and preferentially goes in one direction to produce **8** with an out-of-plane *oxo* ligand. Lacking an anionic ligand to twist with, the dative *oxo* ligand ($I^+−O^-$) stays out of plane to maximize charge transfer. Once the alcohol ligand has been deprotonated, IBX−alcohol **9** proceeds to twist and oxidize as described previously.

Our studies show that IBX twisting—the coordinated motion of an *oxo* group and an anionic ligand—acts as a gatekeeper to oxidation. Hypervalent bonding concepts explain why the twisting must occur, how it can occur, and when it occurs. By controlling the twisting through *ortho* group substitution, we control the oxidation pathway and unlock IBX's reactive potential.

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Note Added after ASAP Publication. The title compound was named incorrectly in the version published ASAP September 15, 2005. The corrected version was published September 20, 2005.

Supporting Information Available: Coordinates, energies, and frequency data for compounds referenced (PDF), and crystal structure and NMR shift comparisons. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Method validated by comparing theoretical geometries to a variety of known hypervalent iodine crystal structures; see Supporting Information. Restricted MPW1K/LACV3P**, with single point solvation from Poisson−Boltzmann continuum theory ($\epsilon = 47.2$, $r_{probe} = 2.41$ Å) using Jaguar 6.0 (Schrödinger Inc). Thermochemical corrections (ΔG, ZPE) used calculated vibrational frequencies. Intermediates and transition states were stationary points with the correct number of positive eigenvalues; reactants and products were optimized from transition structures perturbed along a negative eigenvalue path.

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(6) Computed NMR shielding constants correlate well with experimental chemical shifts; see Supporting Information. All comparisons to experiment are to Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272−7276.

(7) $\Delta G_{elim}^{‡} < \Delta G_{twist}^{‡}$ for all alcohols studied; see Supporting Information.

(8) Electronic effects exist but are less significant. Electronegative *ortho* groups, such as fluorine, repel the *oxo* group in intermediate **3**, inhibiting twisting and deactivating the reagent, while electropositive groups, such as $B(OMe)_2$, activate the reagent, but to a lesser extent than even *o*-methyl IBX.

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