Enhancing 2-Iodoxybenzoic Acid Reactivity by Exploiting a Hypervalent Twist

Julius T. Su and William A. Goddard III*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

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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. IBX effects oxidations of functionality beyond simple alcohols, making it an ideal reagent for carrying out a wide range of oxidative transformations. 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.

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Hypervalent twisting is a coordinated motion of ligands driven by the necessity of generating a stable, planar form of the byproduct IBX from an IBX–alcohol intermediate (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.

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

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 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 1,2-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.

We now consider the nature of the hypervallent 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...
Our work has focused on accelerating the overall oxidation rate and unlocking IBX’s reactive potential. 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.

References


(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 Povson–Boltzmann continuum theory (ε = 47.2, rmax = 2.41 Å) using Jaguar 6.0 (Schrödinger Inc.). Thermochromic 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.


(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. 1999, 65, 7272–7276.

(7) ΔGelim < ΔGemuls for all alcoholic 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 deactivated the reagent, while electropositive groups, such as B(OMe)3, activate the reagent, but to a lesser extent than even o-methyl IBX.

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