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An Alternative One-Electron Oxidation Strategy to Access Hypervalent Iodine Reagents

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SUMMARY

In a recent study reported in Chem, Hyun et al. demonstrate that iodanyl radicals are the key oxidants and chain carriers in a proposed open-shell mechanism for the aerobic synthesis of hypervalent iodine compounds.

In nature, molecular oxygen is ubiquitously exploited as an oxidizing reagent and reactant, by oxygenases and oxidases respectively, based on the use of high-valent metal centers to bind and activate the O₂ molecule for a wide scope of substrate functionalizations.¹ In contrast, only few aerobic functionalizations have been developed in synthetic chemistry. This is surprising, as O₂ is arguably one of the most attractive oxidants. It has a strong oxidation potential, is easily obtained and stored, and the byproducts obtained when using oxygen are not harmful to the environment. Nonetheless, reacting with the triplet ground state of O₂ continues to be a major challenge. Therefore, current aerobic oxidizing synthetic methodologies are mostly based on: 1) oxygen as terminal stoichiometric oxidant for a low-valent transition metal catalyst, typically Pd(0),² and 2) O₂ autoxidation-induced radical reactivity with a narrow scope of substrates.³⁻⁵ Because of these limitations, chemists have found ways to synthesize other strong oxidizing reagents, which can then be used in a broader range of oxidations. The synthesis of such reagents often involves several steps, strong oxidants, toxic metals and in many cases high temperature. Hypervalent iodine (HI) compounds, I(III) and I(V), are amongst the most common and versatile of these reagents.⁶ Nevertheless, their synthesis involves several steps and typically the use of peroxides. Recently, important progress has been made in developing I(I)/I(III) catalytic systems,⁷ reducing the generation of byproducts and the overall number of steps. However, peroxides, in particular *m*CPBA (*meta*-chloro perbenzoic acid), are still needed as stoichiometric terminal oxidants and the direct oxidation of the substrate is difficult to suppress. Consequently, the development of aerobic processes that can generate HI reagents *in situ* without oxidizing the substrate is a highly desirable contribution in the transition to a greener chemistry.

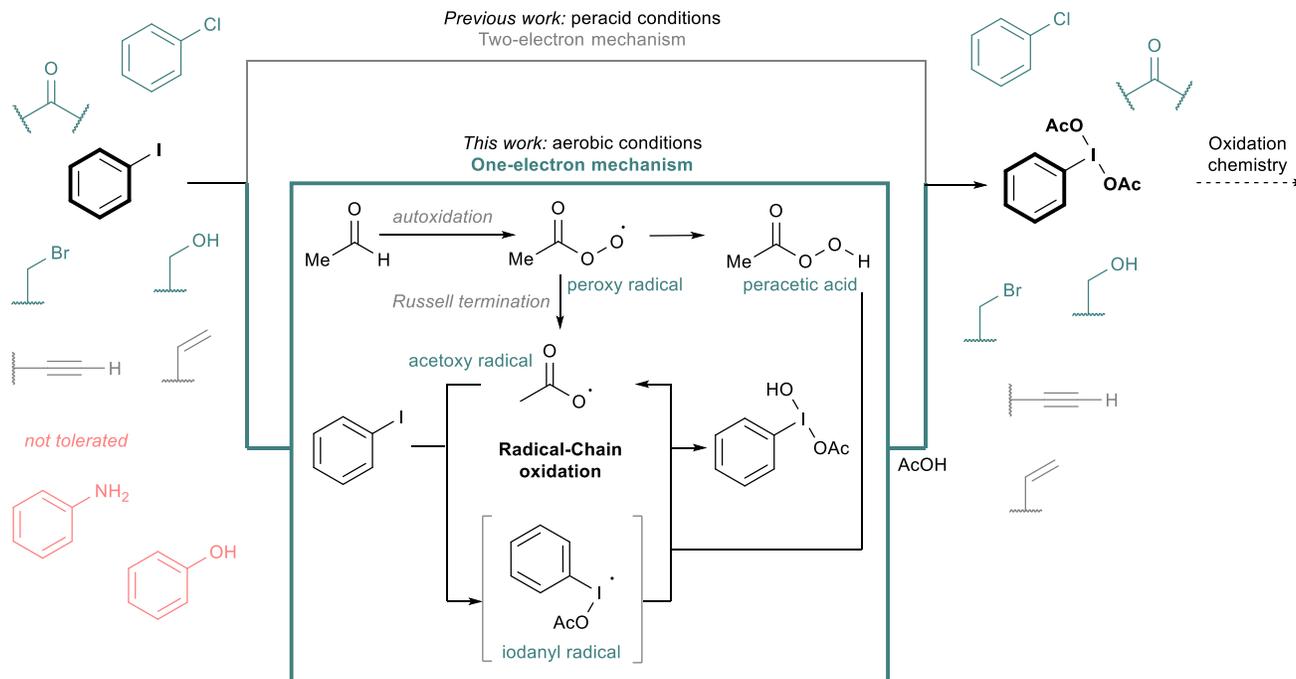
The group of Powers recently developed a powerful methodology based on O₂-promoted aldehyde autoxidation for the conversion of iodobenzene to a variety of I(III) reagents.⁸ The method could also be used for oxidative functionalizations using a catalytic amount of iodobenzene. This was an important progress, as the stoichiometric use of pre-formed peroxides was not needed anymore. On the first look, this result was synthetically highly useful, but did not appear to be mechanistically intriguing. In fact, peracids are one of the main autoxidation products of aldehydes, and they are themselves the most successful two-electron oxidants to convert I(I) to I(III). Preliminary mechanistic investigations highlighted the presence of a radical chain process, as expected for an autoxidation reaction.⁸ Most researchers would have been satisfied by this superficial understanding of the reaction, which appeared only as a clever way to generate peroxides *in situ*. The present work in CHEM consists of experimental and theoretical investigations, which completely shatter this simplistic view of the reaction.⁹ Powers and co-workers indeed demonstrated that the competent oxidant is not the peracid, but an acetoxy radical formed during the autoxidation process, resulting in an unprecedented stepwise one-electron oxidation of I(I) to I(III) (Scheme 1).

The first indication for a new oxidation mechanism came when the authors compared their results with the direct oxidation of PhI to PhI(OAc)₂ with peracetic acid. As expected, this oxidation works well and is thermodynamically favorable. However, Hammett studies demonstrated that it is kinetically highly unlikely under the present conditions and peracetic acid is therefore not the active oxidant in the new reaction system. Other closed-shell oxidants formed during the reaction were then examined, but none of them was competent. The authors therefore came to the conclusion that an open-shell (radical) intermediate was probably involved in the oxidation. The first step in the autoxidation process is hydrogen-atom-abstraction (HAA) of acetaldehyde, followed by recombination with oxygen to form a peroxy radical. The peroxy radical can then either react with the aldehyde via HAA to form peracetic acid, or undergo dimerization to form an unstable tetroxide intermediate, which fragments to form an acetoxy radical (Russell termination). Electron paramagnetic resonance (EPR) measurements and headspace gas analysis confirmed the presence of an acetoxy radical intermediate during the acetaldehyde-promoted aerobic oxidation of iodobenzene. The involvement of an acetoxy radical allowed also to rationalize the results of the Hammett studies and its key role was further supported by kinetic competition experiments between cyclohexane and iodobenzene, as well as kinetic isotope effects studies.

Once the acetoxy radical had been identified as the most probable oxidant, computational studies were employed to elucidate the mechanism of the oxidation step. All two-electron pathways were again examined, but they were not competitive. In contrast, the reaction of the acetoxy radical with iodobenzene to generate the key intermediate, an I(II) iodanyl radical, is only slightly endergonic with a low energy barrier (8.9 Kcal/mol). The second single electron oxidation from I(II) to I(III) then occurs via addition to peracetic acid, which regenerates the acetoxy radical, acting as the chain carrier. This step is rate limiting with a barrier of 23.7 Kcal/mol. The authors could show that the obtained hydroxy/acetoxy iodine(III) compound is converted to iodobenzene diacetate in presence of acetic acid. An alternative productive termination step consists of the coupling of the acetoxy and iodanyl radicals.

With these thorough studies, Powers and co-workers have discovered a new mechanism for the oxidation of I(I) to I(III). However, it was not clear yet if this difference of mechanism would have an impact on synthetic applications. What is the functional group tolerance? Are sensitive substrates not compatible with classic peracid methods better tolerated under these conditions? Does this provide a solution to the challenge of *in situ* oxidant synthesis versus substrate oxidation? To answer these questions, the authors have carried out a robustness study to compare their method with the standard peracid oxidation. The hypervalent iodine reagent PhI(OAc)₂ was synthesized in presence of various functionalized compounds and both the yield of iodobenzene diacetate and the amount of recovered compound were examined. Regardless of their differences in mechanism, the functional group tolerance for both oxidation methods was similar. Electron-rich aromatic compounds and unsaturated carbon-carbon bonds are problematic for both methodologies, whereas other functional groups such as halogens, alcohols and ketones are better tolerated in both cases. Even if the new method is not superior, results comparable with the best state-of-the-art approaches are obtained under milder conditions and it is thus likely that this methodology will be adopted by the scientific community.

Overall, this study has revealed a new mechanism for the generation of I(III) *in situ* by oxidation of I(I) with oxygen and acetaldehyde. With the reaction mechanism better understood, further improvements of the process can be envisaged. The importance of single electron chemistry in hypervalent iodine compounds synthesis has been demonstrated and becomes now a viable alternative to the well-established two-electron oxidation with peracids. Despite this exciting success, the search for the "magic oxidant" able to oxidize organic iodines selectively in presence of any other compounds is still ongoing, as it would definitively be a major advance in the development of green oxidation methods.



Scheme 1. Speculative mechanism for the aldehyde-promoted aerobic oxidation of iodobenzene based on an unprecedented one-electron pathway.

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