A Twist of the Twist Mechanism, 2-Iodoxybenzoic Acid (IBX)-Mediated Oxidation of Alcohol Revisited: Theory and Experiment

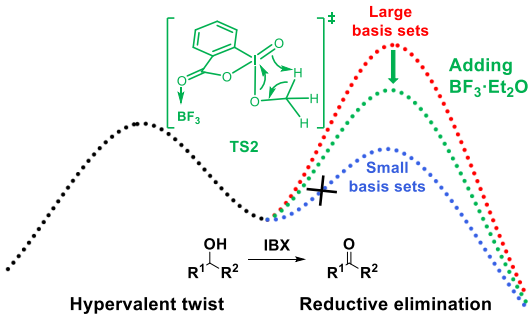
Heming Jiang,[†,‖] Tian-Yu Sun,[†,‡,‖] Xiao Wang,[‡] Yaoming Xie,[‡] Xinhao Zhang,[*,†] Yun-Dong Wu,[*,†,§] and Henry F. Schaefer III[*,‡]

[†]Lab of Computational Chemistry & Drug Design, Key Laboratory of Chemical Genomics, Peking University Shenzhen Graduate School, Shenzhen, 518055 (China)

[‡]Center for Computational Quantum Chemistry, University of Georgia, Athens, GA 30602 (USA)

[§]College of Chemistry and Molecular Engineering, Peking University, Beijing, 100871, China

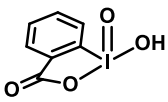
Supporting Information



ABSTRACT: 2-Iodoxybenzoic acid (IBX) is an important species for the oxidation of alcohols to aldehydes or ketones. An often-cited mechanism involving a hypervalent twist as the rate-determining step (RDS) is inconsistent with kinetic isotope effect (KIE) experiments. The computations with larger basis sets reveal that the reductive elimination involving the C-H bond cleavage is the RDS (rate determining step). Further computational/experimental studies suggest that the reactivity can be improved by adjusting the trans influence with Lewis acids.

In recent years, hypervalent iodine molecules have been used widely as functional reagents in organic synthesis, due to their highly polarized and nonclassical three-center-four-electron (3c-4e) hypervalent bond.[1] As a consequence of their environmentally benign character and low toxicity, such compounds are promising as an environmentally sustainable alternative to heavy metal compounds.[2]

Among the most popular hypervalent iodine compounds, 2-iodoxybenzoic acid (IBX)

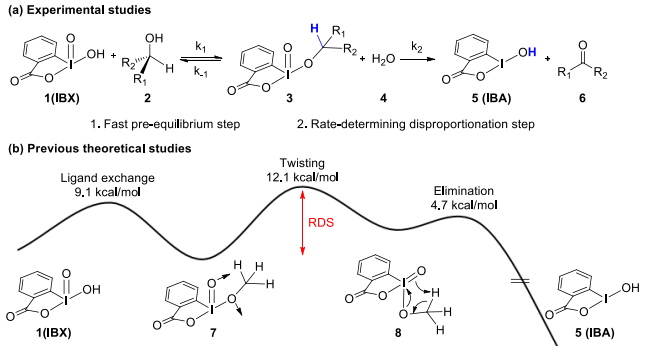


stands out as an important oxidant due to its use of mild reaction conditions and its chemoselectivity.[3,4] IBX was first reported in 1893 by Hartman and Mayer.[3] However, because of strong intermolecular interactions in the crystal lattice, IBX is barely soluble in common organic solvents.[5] For many years, IBX had no synthetic application except as the precursor for the preparation of Dess–Martin periodinane (DMP).[6] In 1994, Frigerio and Santagostino demonstrated that IBX can oxidize alcohols to aldehydes or ketones in dimethyl sulfoxide (DMSO).[7] Subsequently, IBX has been found an increasing number of applications in organic synthesis, such as oxidation through oxygen transfer, other types of dehydrogenation, and total synthesis of natural products.[1(d),8]

There have been many experimental and theoretical mechanistic studies of this reaction. In 1996, Frigerio and Santagostino reported the kinetics of oxidation by IBX of alcohols using ^{1}H-NMR spectroscopy.[9] The kinetic evidence supports a two-step mechanism involving a fast pre-equilibrium step leading to intermediate **3**, followed by its rate-determining disproportionation to 2-iodosobenzoic acid (IBA) and carbonyl derivatives (**Scheme 1a**). Corey and co-workers performed a kinetic isotope effect (KIE) experiment for $C_6H_5CH_2CH_2OH$/$C_6H_5CH_2CD_2OH$ oxidation by IBX, and determined a k_H/k_D ratio (kinetic isotope effect, KIE) of 6.3 for this reaction. This result indicates that the rate-determining step (RDS) of the disproportionation of intermediate **3** involves C-H bond cleavage.[10] Moorthy and Nair's experimental measurement of the KIE for CH_3OH/CD_3OD oxidation by IBX derivative, gave a k_H/k_D, of 3.3, also indicating that C-H bond cleavage is the RDS.[11]

In 2005, Su and Goddard carried out density functional theory (DFT) studies using the MPW1K/LACV3P** method on the oxidation of methanol by IBX (**Scheme 1b**).[12] The potential energy surface (PES) revealed that IBX derivative may adopt two configurations **7** and **8**, while the product IBA (**5**) can only exist in a planar form. As a result, elimination of **5** cannot occur directly from intermediate **7**. A hypervalent twist, defined as coordinated motion of an oxo group and an anionic ligand, is

Scheme 1. Previous experimental and theoretical mechanistic studies of alcohol oxidation by IBX.



thus necessary to generate a stable intermediate (**8**), and is followed by reductive elimination involving cleavage of the C-H bond. Goddard's work concluded that the hypervalent twist is the RDS, and this prediction has influenced subsequent research.[11,13-15] However, it is known that the exchange between the apical and the equatorial ligands is an easy process in both λ^3 and λ^5-iodanes.[1] More importantly, the hypervalent twist does not involve C-H bond cleavage, and this seems inconsistent with Corey's KIE experiment. In 2011, Moorthy and Nair proposed hypervalent twist occurs in concert with reductive elimination in a direct single step to account for the discrepancy between the KIE experimental result and the previous DFT results, but they mentioned the possible low accuracy of their molecular dynamics simulations.[11]

A correct mechanistic understanding of the reaction will be important for the enhancement of the reactivity. In response to the above contradiction, we conducted theoretical and experimental studies to address the following three questions:

(1) What is the origin of the discrepancy between computations and experiment when identifying the rate-determining step?

(2) What is the critical factor influencing the energy barrier of the rate-determining step?

(3) How, if possible, might one enhance the oxidative activity of IBX based on the critical factor?

First, several theoretical methods were selected. Four DFT functionals, MPW1K,[16] B3LYP,[17] M06-2X,[18] and ωB97X-D[19] and seven basis sets, LACV3P**, cc-pV*X*Z(-PP)[20] and aug-cc-pV*X*Z(-PP)[21] (*X* = D, T, Q; aug- represents diffuse functions; (-PP) suffix here represents pseudopotential for iodine) were employed. These 28 combinations of DFT functionals and basis sets provide a broad coverage of methods, and some are comparable with those used in the literature.[11-13,22] Solvent effect were taken in account by using the SMD in DMSO.[23] The PESs of methanol oxidation by IBX computed at different levels suggest different rate-determining steps. For example, the MPW1K/ LACV3P** method, which was employed in Goddard's work,[12] predicts that the hypervalent twist (**TS1**) is the rate-determining step, while here the M06-2X/cc-pVQZ(-PP) method predicts that the barrier of the reductive elimination (**TS2**) is higher [**Figure 1(a)**], consistent with Corey's KIE experiment. **Figure 1(b)** summarizes the free energy differences [$G^{\ddagger}$(**TS2**)-$G^{\ddagger}$(**TS1**)] computed at different levels of theory. As the basis set increases,

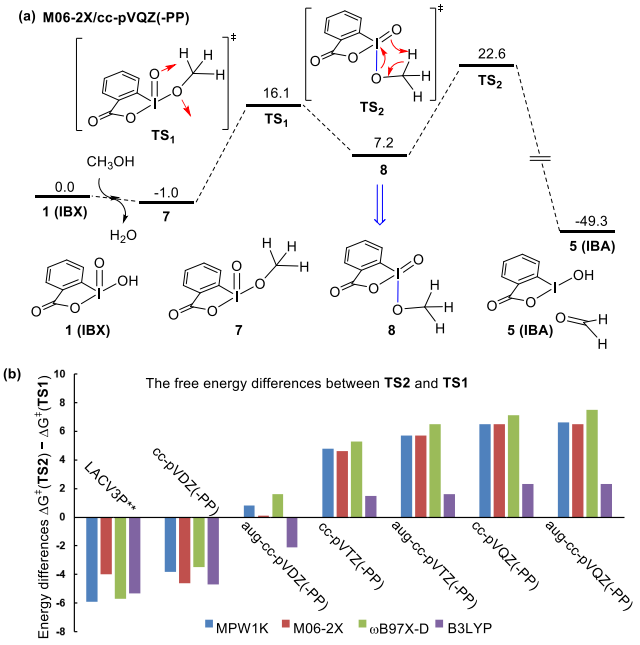


Figure 1. (a) The potential energy surface (PES) of methanol oxidation by IBX; the fast ligand exchange step is ignored. (b) The free energy differences (in kcal/mol) between **TS2** and **TS1** estimated by different methods.

the values of [$G^{\ddagger}$(**TS2**)-$G^{\ddagger}$(**TS1**)] change from negative to positive. When the basis set reaches the TZ quality this value almost converges, and the theoretical result is consistent with experiment. To further verify the reliability of the methods, we compared the optimized geometries with an available crystal structure.[11] **Table S2** lists a total of 14 critical geometrical parameters associated with the iodine atom. Judging by these parameters, 12 geometrical parameters from the M06-2X/cc-pVQZ(-PP) method are in better agreement with experiment than those from the MPW1K/LACV3P** method used by Goddard.[12] More importantly, all I-O bond lengths are described more reliably by M06-2X/cc-pVQZ(-PP). This is essential for estimating the relevant energetics, especially the barrier for the reductive elimination. Since the quadruple-ζ basis sets give the best results (**Table S3**), we chose cc-pVQZ(-PP) for the subsequent computations.[24]

The dependence on the basis set size may be attributed to the importance of *f* functions. Because *f* orbitals of the iodine atom are not considered with LACV3P** and cc-pVDZ(-PP), the interaction between I and O in I-OCH_3 bond may have been underestimated. Consequently, the barrier for breaking the I-O bond in **TS2** was also underestimated, which may explain why previous computations led to results which are inconsistent with Corey's KIE experiments. When larger basis sets are employed, the prediction of the binding energy of I-OCH_3 bond is more

reliable, and **TS2** becomes the RDS with the triple-ζ and quadruple-ζ basis sets. On the other hand, **TS1** does not involve the breaking of an iodine-oxygen bond and is less affected by the basis sets (**Figure S2**).

In terms of functionals, **Figure 1b** shows that B3LYP predicts different relative energies (by 4~5 kcal/mol with large basis sets) from MPW1K, M06-2X and ωB97X-D. The latter three functionals predict the same preference with these basis sets, and give results very close to each other, within 2 kcal/mol. The functional, M06-2X gives the best structural results (**Table S3**), and consequently M06-2X was chosen as the functional for the following computations.[25]

In **Figure 1a**, the PES of methanol oxidation by IBX is given by the M06-2X/cc-pVQZ(-PP) method, and similar potential energy surfaces are also given by some other methods. Since the ligand exchange is a fast pre-equilibrium step, the transition state of the step from IBX to intermediate **1** was ignored.[9]

Density cumulant functional theory (DCT)[26] was also used to compare the energy difference between **TS2** and **TS1**. Benchmark studies of DCT show that the accuracy of orbital-optimized DCT (ODC-12) was close to the "Gold Standard" coupled cluster theory with singles, doubles, and perturbative triples [CCSD(T)] for various types of systems with a favorable O(N6) computational scaling ("N" represents the system size).[27] Recently, ODC-12 implemented in PSI4 program[28] has been shown to provide reliable results for transition metal complexes, which share many common properties with hypervalent iodine reagents.[29] Therefore, we used ODC-12 with the Roos relativistic ANO-RCC basis for iodine[30] and cc-pVDZ for the other atoms[20] to conduct the computations (see SI for computational details). The results show that the energy of **TS2** is 8.5 kcal/mol higher than that of **TS1**. This supports our DFT prediction that reductive elimination, rather than the hypervalent twist in the disproportionation of intermediate **7**, is the RDS.

Further examination of solvent and steric effects was conducted. The computations in different solvents with the implicit solvent model (**Figure S6**) and the PES of the ortho-methyl substituted IBX (Me-IBX) (**Figure S5**) showed that barriers are barely affected and the elimination remains the RDS.

After confirming that the reductive elimination is the RDS, we attempted to enhance the reactivity of IBX by reducing the **TS2** barrier. As shown in **Figure 1a**, intermediate **8** is 8.2 kcal/mol higher in energy than intermediate **7**. We suggest that if the intermediate **8** can be stabilized, according to the Hammond postulate,[31] it will be possible also to lower the barrier of **TS2**. Inspired by Zhdankin's and Suresh's work, we envisioned that a trans influence affects the stability of the hypervalent iodine reagent.[22(a),32,33] In intermediate **8** (**Scheme 1b**), it is reasonable to modify the -CO-O- linker to reduce the trans influence. The trans influence of the linker in IBX derivatives can be estimated from the I-OH bond length. The shorter the I-OH bond length, the weaker might be the trans influence of the linker.

As shown in **Figure 2**, ten other IBX derivatives were compared. The trans influence of their linkers is distributed in the range of 1.94-2.08 Å and was plotted against the energy barriers of **TS2**. Our results show that there is a strong correlation between the barriers of **TS2** and the trans influence. The IBX derivatives with -SO_2-O- (**9**) and -CF_2-O- (**10**) linker have the lowest energy barrier of **TS2**, and they are lower by 2.2 kcal/mol than that of IBX. The **TS2** barriers of derivatives **11**, **12** and **13** are also lower than that of IBX. So the above five derivatives are likely to be substitutes of IBX with higher oxidative activity. 2-Iodoxybenzenesulfonic acid (IBS), the IBX derivative with an -SO_2-O- linker, was synthesized by Ishihara in 2008.[13,34] Ishihara's experiments showed that the rate of alcohol oxidation by IBS is much faster than with IBX. This is consistent with our computations. IBS is currently the most reactive oxidant among IBX derivatives, but is unstable when acting as an oxidant, limiting its application.[33-35] Considering the challenge of synthesizing various IBX derivatives, we are curious if the trans influence of -CO-O- could be weakened by coordination with the small molecules.

Inspired by Togni's work,[36] we further explored with Lewis acid additives. The theoretical prediction shows that among the four oxygen atoms in IBX, the coordination between the carbonyl oxygen and BF_3 is the most favorable (**Figure S9**), and in

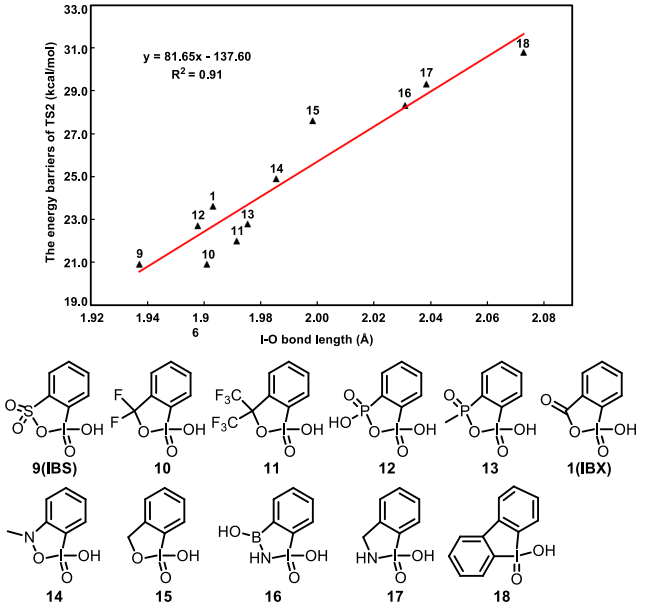


Figure 2. Correlation between the energy barriers of **TS2** and the trans influence.

this case, the **TS2** barrier is reduced by about 2.2 kcal/mol according to computations (see inlet of **Figure S13**). Experiments have been conducted in the present study to test this prediction. Three commonly used Lewis acids BF_3, $ZnCl_3$ and $AlCl_3$ could be considered. However, it was revealed that, of the three Lewis acids, only the BF_3-IBX complexes were found in mass spectrometric (MS) studies (**Figures S11, S12**). Therefore, only BF_3 was selected for the following reactivity measurements. We used ^{1}H-NMR spectroscopy to conduct kinetics experiments to verify our computations. DMSO is a solvent with strong coordinating ability and can also coordinate with BF_3 (**Figure S10**). To ensure a certain concentration of BF_3 coordinating with the –CO-O- linker in IBX, large amounts of Et_2O•BF_3 were added to the reaction system. As shown in **Figure S13**, Et_2O•BF_3 indeed accelerates the reaction. With 160 equivalents of Et_2O•BF_3, we estimate a rate increase of about 5-6 folds, in reasonably good agreement with the theoretical preditions.

The poor solubility caused by strong I-O intermolecular interactions in the crystal lattice greatly limits the application of IBX to organic synthesis.[1] We speculate the coordination between the carbonyl oxygen of IBX and BF_3 may weaken I-O intermolecular interactions and promote IBX dissolvability in common

organic solvents. Further experiments reveal that IBX can dissolve in acetonitrile (ACN) with the additive of $Et_2O•BF_3$. The reactivity was explored with benzyl alcohol and the isolated yield can reach 95% within 3 minutes at room temperature (**Figure 3**). While it is difficult to synthesis IBX derivatives with a weak trans influence linker,[34,35] the use of $Et_2O•BF_3$ is a simple and efficient strategy with which to improve the IBX solubility and reactivity in the common organic solvent ACN (**Figure S14**).

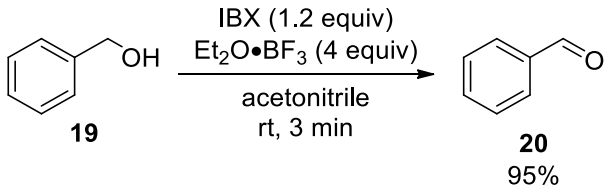


Figure 3. Experiment: the oxidization reaction of benzyl alcohol by IBX and $Et_2O•BF_3$.

In summary, our computations show that rather than the hypervalent twist, reductive elimination is the RDS for alcohol oxidation by IBX. This conclusion is consistent with Corey's results from KIE experiments. Subsequent investigations show that the linker's trans influence in IBX derivatives can affect the barrier associated with the reduction elimination. The Lewis acid BF_3 is predicted to coordinate preferably with the linker carbonyl oxygen, and therefore, reduces the barrier associated with **TS2**. Kinetics experiments using ^{1}H-NMR spectroscopy confirm our prediction, and we find this reaction can take place in common organic solvent of ACN in room temperature. Attempts to expand the substrate scope are in progress in this laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Computational and experimental details and figures (Word)

AUTHOR INFORMATION

Corresponding Author

* E-mail: zhangxh@pkusz.edu.cn
* E-mail: wuyd@pkusz.edu.cn
* E-mail: ccq@uga.edu

Author Contributions

‖These authors contributed equally.

Notes

The authors declare no competing financial interest.

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