Simple Procedure for 2-Iodoxybenzoic Acid Synthesis by Oxidation of 2-Iodobenzoic Acid at a Boron-doped Diamond Anode

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**Abstract:** For the first time, the electrochemical synthesis is described of 2‑iodoxybenzoic acid (IBX), a benign, well‑established, popular and highly selective oxidising agent. The objective of the work was to investigate the possibility of generating IBX electrochemically in aqueous solutions using boron doped diamond anodes. In 0.2 M H2SO4 aqueous solution, 2‑iodobenzoic acid (IBA) was found to be oxidised at potentials > 1.6 V vs. SCE, initially to 2‑iodosobenzoic acid (IsBA), which was oxidised to IBX at potentials > 1.8 V vs. SCE. Reductions of IBX to IsBA and IsBA to IBA occurred at similar potentials of ca. -0.7 V vs. SCE. The voltammetry results were confirmed by performing a series of batch electrolyses at different electrode potentials. Thus, depending on the electrode potential chosen, IBA can be oxidised anodically either to IsBA or IBX with 100% overall selectivity. The only side‑reaction was O2 generation, but charge yields did not decrease below 55% even at conversions >95%.



Hypervalent iodine compounds constitute a class of metal‑free and structurally diverse chemical entities with unique applications in oxidation chemistry [1]. Trivalent and pentavalent iodine reagents (λ3‑iodanes and λ5‑iodanes according to IUPAC notation) are most commonly employed, with 2‑iodoxybenzoic acid (IBX, for structure see Scheme 1) as the best-known example. First prepared in 1893 by the oxidation of 2‑iodosobenzoic acid (IsBA, for structure see Scheme 1) with KMnO4 in alkaline solution [2], the discovery of IBX’s solubility in dimethyl sulfoxide (DMSO) ensured its popularity as a highly selective oxidant for alcohols [3]. Since then, vast numbers of IBX applications in organic synthesis have been reported[4]. Later, IBX was commonly prepared by the oxidation of 2‑iodobenzoic acid (IBA, for structure see Scheme 1) by using potassium bromate and sulfuric acid [5]. However, this method involves handling toxic and explosive KBrO3, not to mention Br2 vapours evolving during the synthesis. Moreover, remaining traces of KBrO3 seem to make IBX particularly shock-sensitive [6]. To circumvent this problem, a more user friendly method of IBX preparation was developed, by replacing the bromate oxidant with Oxone® (2KHSO5·KHSO4·K2SO4) [7]. It is clear that oxidation states of iodine in the mentioned molecules increase in order IBA < IsBA < IBX.

So far, the utilization of IBX or IsBX has been limited to the laboratory scale, due to the safety issues associated with handling large amounts of potentially shock-sensitive reagent. We envisaged that this may be overcome by generating IBX electrochemically, thereby avoiding the need to use stoichiometric amounts of another oxidant (bromate, Oxone®) and eliminating the production of waste products. Studies of anodic oxidations of aromatic iodine compounds leading to oxidation of the iodine atoms themselves are quite rare in the literature. Usually, oxidative dimerization of iodobenzene or formation of diphenyliodonium cation is mentioned, when benzene is present in the non-aqueous environment[8]. The oxidation of iodobenzene and related *ortho* and *para* compounds was studied in the 1920s [9]; the nature of oxidation products depended largely on the electrolyte composition and anode material. Using a platinum anode in glacial acetic acid, iodobenzene was converted successfully mainly to iodosobenzene acetate and partially (max. 20% yield) also to iodoxybenzene acetate, though part of the organic compounds were always lost, most likely due to disruption of the aromatic ring. Under similar conditions, *o‑* and *p-*iodotoluene oxidation led to oxidation of the methyl or to de-iodinated products. Oxidation of *o‑* and *p-*iodobenzoic acids was more successful, leding to formation of mainly iodoso compounds and limited amounts of the respective iodoxy compounds. Again, substantial losses of organic compounds were detected. In another old report, the possibility of reversible transformation of iodosobenzene and iodoxybenzene was confirmed, leading to the construction of iodoso‑iodoxybenzene pH electrodes [10], though the compounds were prepared by chemical oxidation. More recently, I,I-difluorides have been produced by anodic oxidation of *p-*nitro and *p-*methoxyiodobenzenes in Et3N∙3HF [11]. Nishiyama and Amano [12] used iodosobenzene trifluoroacetate produced by anodic oxidation of iodobenzene on glassy carbon electrodes as a mediator for oxidation of various organic compounds.

Boron doped diamond (BDD) electrodes have attracted much attention over the last three decades due to their unique properties, in this context specifically their high overpotentials for O2 and H2 evolution in aqueous solutions, enabling their use for reactions over a wide potential range of ca. ‑1.5 to +2.05 V vs. SCE (where[13]. Mechanisms of electrode reactions depend on applied electrode potentials: at > 2.3 V vs. SCE, oxidations occur via •OH radicals generated electrochemically (Eq. 1, 2) [14], while at lower potentials, reactions proceed via electron transfer.

(Eq. 1)

(Eq. 2)

The aim of the work for which results are reported below was to examine the possibility of electrochemical oxidation of IBA and IsBA to IBX at BDD electrodes in aqueous solutions. BDD was chosen as the electrode to minimise rates of the undesired O2 evolution reaction at high anodic potentials.

Figure 1 shows cyclic voltammograms of a BDD electrode in a solution of 5×10-4 mol dm-3 IBA + 0.2 mol dm-3 H2SO4. On the positive-going potential sweep from a start potential of 0.0 V (SCE), two oxidation current peaks occurred at potentials of 1.58 V (SCE) and 1.95 V (SCE). On the subsequent negative-going potential sweep, a reduction current peak **pδ** (Ep = ‑0.82 V) occurred, linked to the oxidation current peak **pα** (Ep = 1.58 V); the smaller reduction peak **pγ** (Ep = -0.68 V) was linked to the oxidation current peak **pβ** (Ep = 1.95 V). At potentials > 2.0 V and < ‑1.0 V the O2 and H2 evolution reactions, respectively, occurred at significant rates, even on BDD electrode.



**Figure 1.** Cyclic voltammograms of stationary BDD | 4.9 10-4 mol dm-3 2-iodobenzoic acid in 0.2 mol dm-3 H2SO4. Starting at 0 V, (positive-going) electrode potential was scanned at 100 mV s-1. Room temperature. Upper vertex potential is stated in the figure inset. Data were corrected for uncompensated resistance of the electrolyte solution.

The nature of the peaks in Figure 1 was elucidated by comparing the voltammograms for IBA with the corresponding voltammograms for IsBA and IBX. Voltammograms for IsBA are presented in Figure 2. If the negative potential limit in Figure 2 was less negative than required for reduction of IsBA, peak ***pα*** did not occur in the voltammogram, but at sufficiently low potentials, corresponding to peak ***pδ*** at which IsBA reduction occurred, then peak ***pα*** was evident on the subsequent positive-going potential sweep. Hence, peak ***pα*** was due to the oxidation of IBA to IsBA, while peak ***pδ*** was due to IsBA reduction to IBA.

Remaining peaks were identified with help of cyclic voltammograms of BDD | IBX solution in Figure 3. Reduction of the IBX on the electrode resulted in peaks ***pγ*** and ***pδ*** due to IBX reduction to IsBA and subsequent reduction of IsBA to IBA. If the lower potential limit was sufficiently negative for IBA to be generated, then the subsequent positive-going potential sweep resulted in peak ***pα***. Unfortunately, peak ***pβ*** was not evident due to presence of IBX stabilisers (benzoic acid, salicylic acid), as discussed in experimental section. Benzoic acid undergoes oxidation at BDD at potentials > 1.9 V (SCE) [14c], so its oxidation current was convoluted with IsBA re-oxidation to IBX, making peak ***pβ*** difficult to detect. Similarly, reduction peaks ***pγ*** and ***pδ*** were convoluted, precluding evaluation of peak ***pγ*** due to reduction of IBX to IsBA. The peaks ***pα*** and ***pβ*** correspond to oxidation of IBA to IsBA and IsBA to IBX, respectively. On the subsequent negative-going potential scan, the IBX was reduced firstly to IsBA (peak ***pγ***) and consequently IsBA undergoes reduction to IBA (peak ***pδ***). The reactions taking place can be summarised in Scheme 1 shown below.



**Figure 2.** Cyclic voltammograms of stationary BDD | 4.8x10‑4 mol dm‑3 2‑iodosobenzoic acid in 0.2 mol dm-3 H2SO4. Starting from 0 V, (negative-going) electrode potential was scanned at 100 mV s-1. Room temperature. Lower vertex potential is stated in the figure inset. Data were corrected for uncompensated resistance of the electrolyte solution.



**Figure 3.** Cyclic voltammograms of stationary BDD | 2.5×10‑4 mol dm‑3 2‑iodoxybenzoic acid in 0.2 mol dm-3 H2SO4. Scan starts at 0 V in negative direction, electrode potential swept with rate of 100 mV s-1. Room temperature. Lower vertex potential stated in the figure inset. Data corrected for uncompensated resistance of the electrolyte solution.

In the next step, preparative batch electrolyses (oxidation of IBA) at constant potentials between 1.83 and 2.08 V (SCE) were performed in order to confirm generation of IsBA and IBX from IBA on the BDD electrode. The electrode potential values were selected based on the voltammograms showed in Figures 1 and 2. Most importantly, analysis (by LC-ESI-MS/MS) of the reactions mixtures after all electrolyses performed proved that the only organic compounds found in the system were IBA, IsBA and IBX and sum of their molar amounts remained equal to the amount of IBA introduced to the system. In other words, selectivity of the conversion of IBA to either IsBA or IBX using BDD anode was 100%. In agreement with expectations, IBA at an electrode potential of 1.83 V (SCE) was converted exclusively to IsBA. The reaction rate was nearly totally mass transport limited, since at the applied potential and prevailing hydrodynamic conditions, the intrinsic rate of oxidation of IBA to IsBA was much faster than the IBA transport rate towards the electrode. The charge yield of the reaction at the end of the electrolysis (IBA conversion > 95% in 3.1 hours) was nearly 70 %., see Table 1 and Supporting information. This result is in the agreement with voltammograms presented in Figure 1 showing that the ‘onset of IsBA oxidation’ was near 1.8 V (SCE). Thus, subsequent oxidation of IsBA to IBX at 1.83 V (SCE) was very slow.

However, when the electrode potential was increased to 1.93 V (SCE), the rate of IsBA oxidation to IBX was increased and a small proportion of IsBA reaching the electrode was converted directly to IBX. Thus, two stages of the electrolysis could be distinguished. In the first, the main oxidation product was IsBA, which in the subsequent second stage was converted slowly to IBX. Hence, the oxidation rate was determined both by the mass transport rate and oxidation kinetics. This led to necessity of longer reaction time (5 hours to achieve 82% IBA conversion) and consequently decrease of charge yield to about 52 %, the remaining current being used for O2 evolution. This is typical for two consecutive reactions where the intermediate product formation rate is higher that the rate of its consumption, which is confimed by the selectivity values presented in Table 1. Further increase of the electrode potential to 2.03 and 2.08 V (SCE) led to an increase in the rate of IsBA oxidation, so that IBX was the sole product of the oxidation. This time, the of overall charge yield remained around 53% due to shorter to electrolysis time (> 85% IBA conversion achieved in 3.2 hours). The results are summarized in Table 1. For more details about the electrolysis see the Supporting information).

The results showed the excellent selectivity of the reactions shown in Scheme 1 relative to the competing O2 evolution reaction. This was even more evident at the low concentrations (≈ 5x10-4 mol dm-3) of the organic compounds studied, the solubility of which was so limited in aqueous environments; an issue that remains to be solved by future research. Solubilities of IBA, IsBA in water at room temperature were determined to be ~8.5 and ~4.5×10-4 mol dm-3,respectively. Several options are possible including electrolysis of two-phase dispersions, using appropriate water soluble IBX derivatives or optimization of the electrolyte solution composition.

It can be concluded that, as described above, electrochemical production of IBX in solution from its precursors on BDD electrode is a simple and straightforward procedure with high application potential in organic synthesis. We believe that this is next step towards application of IBX and related benign metal-free oxidation agents in organic compounds synthesis/production. Two main approaches can be foreseen. Firstly, IBX (or its derivative) prepared in solution in catalytic concentrations/amounts could be used as a mediator for indirect electrochemical oxidation. Secondly, concentrated solution/dispersion of oxidation agent could be produced electrolytically and the solution used for the desired chemical treatment. Finally, the oxidant could be used in pure form after separation from the electrolyte solution, but with the hazard of handling of potentially dangerous solids.



**Scheme 1.** Oxidation reaction of **A:** IBA to IsBA, and **B:** IsBA to IBX.

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| **Table 1.** Summary of the batch electrolysis results performed. BDD electrode, constant potential *E* (SCE), room temperature, electrolyte stirring. X – integral conversion of IBA, S – integral selectivity for given substance, ΦP – charge yield for product P. Definition of the parameters are given in the Supporting information. | | | | | |
| E  / V | XIBA | SIsBA  / % | SIBX  / % | ΦIsBA  / % | ΦIBX  / % |
| 1.83 | 96 | 100 | 0 | 68 | 0 |
| 1.93 | (72),82[a] | (80),~50[a] | (20),~50[a] | (37),~17[a] | (14),~35[a] |
| 2.03 | 86 | 0 | 100 | 0 | 54 |
| 2.08 | 87 | 0 | 100 | 0 | 53 |
| [a] Value in parenthesis relates to the state in *time = t*end / *3* | | | | | |
|  |  | | | | |

Experimental Section

Experimental details are given in the Supporting information.

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**Keywords:** IBX • 2-iodoxybenzoic acid • 2-iosodobenzoic acid • anodic oxidation • electrosynthesis

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