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Mechanism of Iodine(III)-Promoted Oxidative Dearomatizing Hydroxylation of Phenols: Evidence for Radical-Chain Pathway

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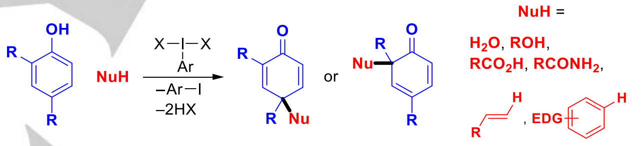
Abstract: The oxidative dearomatization of phenols with the addition of nucleophiles to the aromatic ring induced by hypervalent iodine(III) reagents and catalysts has emerged as a highly useful synthetic approach. However, experimental mechanistic studies of this important process have been extremely scarce. In this report, we describe systematic investigations of the dearomatizing hydroxylation of phenols using an array of experimental techniques. Kinetics, EPR spectroscopy, and reactions with radical probes demonstrate that the transformation proceeds via a radical-chain mechanism, with a phenoxyl radical being the key chain-carrying intermediate. Moreover, UV and NMR spectroscopy, high-resolution mass spectrometry, and cyclic voltammetry show that before reacting with the phenoxyl radical, water molecule becomes activated by the interaction with the iodine(III) center, causing the *Umpolung* of this formally nucleophilic substrate. The radical-chain mechanism allows to rationalize all existing observations regarding the iodine(III)-promoted oxidative dearomatization of phenols.

Introduction

Hypervalent iodine(III)-promoted oxidative dearomatization of phenols, coupled with the addition of nucleophiles to the *ortho* or *para* position of the ring, constitutes a powerful synthetic strategy, enabling access to important molecular scaffolds (Scheme 1).[1] The reaction has been accomplished in both inter- and intramolecular fashion with a variety of nucleophilic species, such as water, alcohols, carboxylates, amides, C–C double bonds, electron-rich aromatic rings, and other.[2] The utility of this process is further reinforced by the fact that its products are versatile synthetic intermediates, which can be directly engaged in a subsequent build-up of the molecular complexity.[3] Particularly noteworthy, the reaction can be made catalytic in the iodine-containing compound by its *in situ* reoxidation, for instance with *m*-chloroperbenzoic acid.[4] This provides an opportunity for the development of practical asymmetric variants of the reaction and, indeed, several such enantioselective catalytic phenol dearomatizations employing chiral iodine-containing compounds have been recently reported.[1c-d,5]



Scheme 1. Oxidative dearomatizing addition of nucleophiles to phenols promoted by iodine(III) reagents.

There are three distinct general mechanisms usually proposed for these phenol dearomatizations with iodine(III) reagents (Scheme 2). The most commonly invoked one assumes the incipient coordination of the phenolic oxygen to the iodine(III) center, forming intermediate **A**. This, due to the strongly electron-withdrawing nature of the hypervalent iodine, primes the attack of the nucleophile on the ring (pathway 1; **TS1**), resulting in simultaneous dearomatization and reduction of iodine. Such a mechanism has been supported by the recent computational study by Houk and Xue on the asymmetric spirolactonization, wherein it has been shown to proceed via a feasible energy barrier (~21 kcal·mol^{-1}) and to reproduce the experimentally observed enantioselectivity.[6] In the second mechanistic pathway, often referred to as dissociative, intermediate **A** undergoes a unimolecular fragmentation, reducing iodine and yielding phenoxenium ion **B** (pathway 2; **TS2**). The latter subsequently reacts with the nucleophile to afford the dearomatized product. The dissociative pathway has been advocated for in a computational work by Harned on the hydroxylation of *p*-cresol using phenyliodine(III) diacetate (PIDA), however the calculated energy barrier was rather high (>28 kcal·mol^{-1}).[7] This was later followed up by a Hammett study, the only existing experimental investigation on the hypervalent iodine-promoted dearomatization

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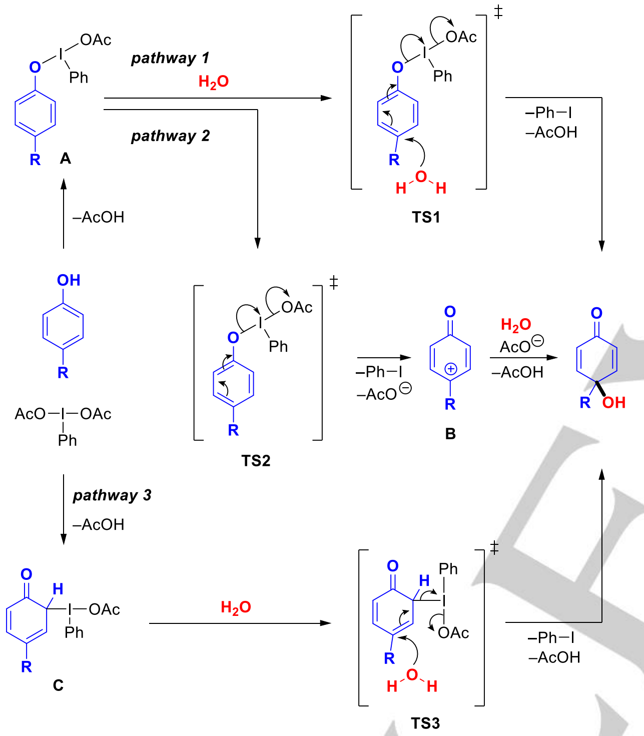
of phenols, which has been also interpreted in favor of the dissociative mechanism.[8] Namely, the reaction has been found to proceed preferentially with phenols containing electron-donating substituents, able to stabilize the positive charge, rather than with these containing electron-withdrawing groups. The final mechanistic alternative involves the initial electrophilic addition of the iodine(III) reagent to the phenolic ring (pathway 3). Resulting intermediate **C** is then attacked by the nucleophile, substituting the iodine-based leaving group in an S_N2' fashion (**TS3**). According to the calculations by Ariafard, this pathway is the most energetically favorable option in the PIDA-promoted addition of methanol to *p*-cresol, requiring to cross a viable ~24 kcal·mol^{-1} barrier.[9] The incorporation of an iodine atom into the phenol ring, observed in some reactions with PIDA, also indirectly lends support to this mechanistic possibility.[10]



Scheme 2. General mechanistic pathways proposed for the oxidative dearomatizing addition of nucleophiles to phenols, exemplified by a PIDA-promoted hydroxylation.

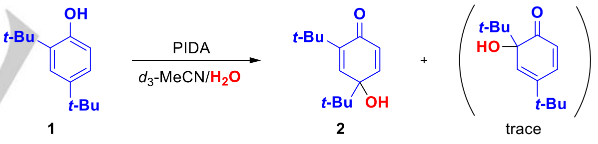
Interestingly, none of the mechanisms presented in Scheme 2 can fully account for all the observed characteristics of the reaction. Namely, the two associative pathways 1 and 3 do not provide explanation why the addition of a nucleophile displays a clear preference to occur at the position of the phenolic ring containing a substituent, while the other *ortho* or *para* sites are unsubstituted, thus more sterically available. They offer also wrong predictions from the electronic viewpoint, as the nucleophile addition via both **TS1** and **TS3** should be favored next to an electron-withdrawing group, while the Hammett plot shows a precisely opposite trend.[8] On the other hand, the major flaw of the dissociative pathway 2 is that it cannot rationalize the enantioselectivity of the reactions carried out in the presence of chiral iodine(III) reagents or catalysts. This is because the iodine species is not directly involved in the stereodetermining bond forming step between phenoxenium ion **B** and the nucleophile.

The present mechanistic ambiguity and the contradictory conclusions stemming from the computational studies hinder a rational design of more efficient and selective catalysts for this important reaction. In this context, we decided to undertake systematic investigations of the mechanism of the hypervalent iodine(III)-promoted oxidative dearomatization of phenols. The obtained results provide fresh and significant insights. Foremost, they strongly suggest that the reaction in fact follows a radical-chain pathway, involving a nucleophilic phenoxyl radical as the key intermediate.[11] Oppositely, the formally nucleophilic substrate (NuH in Scheme 1) actually undergoes an *Umpolung* by a coordination to the iodine(III) center and reacts as an electrophile in an single-electron transfer (SET) process. The putative radical-chain mechanism emerging from our investigations allows to encompass all the experimental observations, including the regioselectivity, the Hammett relationship, and the ability to accomplish asymmetric transformations.

Results and Discussion

Kinetics

We started our investigations by examining the kinetics of a model oxidative dearomatizing hydroxylation of 2,4-di-*tert*-butylphenol **1** promoted by PIDA in MeCN/H_2O mixture (Scheme 3). The reaction uniformly yields the 4-hydroxylation product **2** in high selectivity (>98%), with a trace formation of the 2-hydroxylated side-product.



Scheme 3. A model oxidative dearomatizing hydroxylation of 2,4-di-*tert*-butylphenol **1** promoted by PIDA in acetonitrile.

First, the progress of the reaction was monitored over time at two different H_2O contents in the reaction mixture, namely 5% and 10% (v/v). The formation of the product is clearly faster in the latter case (Figure 1a). The analysis of the decay of the starting material **1** shows that the reaction displays an overall pseudo-first order in the concentrations of the substrates, as the linear dependences of LN([**1**]/[**1**]$_0$) vs. time were observed (Figure 1b). Interestingly, when the reaction was carried out under identical conditions, but using phenyliodine(III) bis(trifluoroacetate) (PIFA), instead of PIDA, the formation of product was virtually instantaneous (full conversion in the first NMR spectra; see below for a plausible explanation of this phenomenon).

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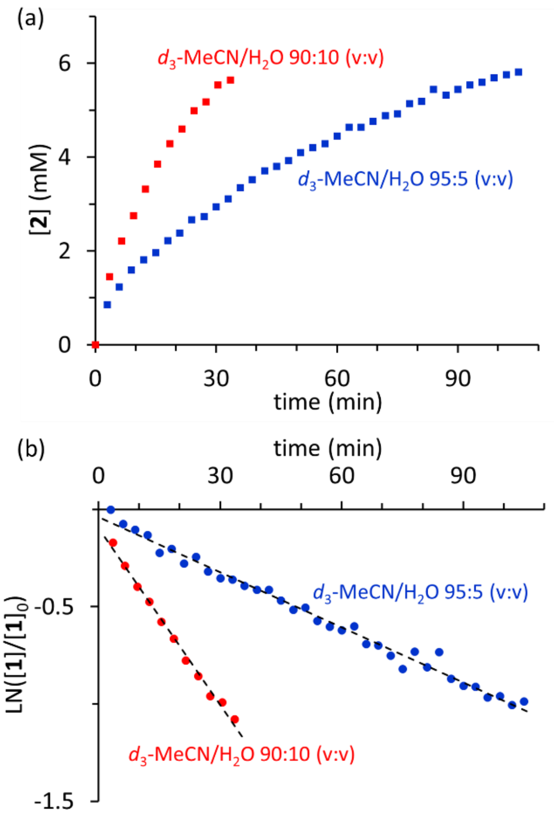

Figure 1. (a) Time-course of the reaction shown in Scheme 3 carried out in d_3-MeCN/H_2O 95:5 and 90:10 (v:v) mixtures; $[\mathbf{1}]_0$=10 mM, $[PIDA]_0$=10 mM, 0 °C; concentrations were determined by ^1H NMR spectroscopy relative to internal standard. (b) Plots of LN($[\mathbf{1}]/[\mathbf{1}]_0$) vs. time.

To ascribe the orders to the concentrations of specific reagents, we performed an initial rate study for the reaction shown in Scheme 3. The analysis of the obtained data results in an experimental rate law (1), wherein the reaction is zeroth order in the concentration of phenol **1** (Figure 2a), first order in the concentration of PIDA (Figure 2b), and second order in the concentration of H_2O (Figure 2c). This is in line with the overall pseudo-first order, determined for the reactions monitored over a longer period (Figure 1; H_2O is present in a great excess, rendering its concentration constant with conversion, hence its influence on the rate does not appear in those experiments).

$$rate = k[\mathrm{PIDA}][\mathrm{H_2O}]^2 \qquad (1)$$

Assuming the above form of the rate law, the thermodynamic parameters of the process were determined by the means of Eyring plot (Figure 3). Notably, the reaction displays a strongly negative entropy of activation (–42.4 cal·mol^{-1}·K^{-1}), implying an associative character of the rate-determining events. This is in a good agreement with rate law (1) that is overall third-order, including two waters, whose involvement should be indeed associated with a large loss of entropy. The free-energy barrier is calculated to 21.9±0.7 and 23.0±0.9 kcal·mol^{-1} at 0 and 25 °C, respectively.

Finally, we established that the reactions carried out using H_2O and D_2O show no measurable difference in the rates (Figure S1).

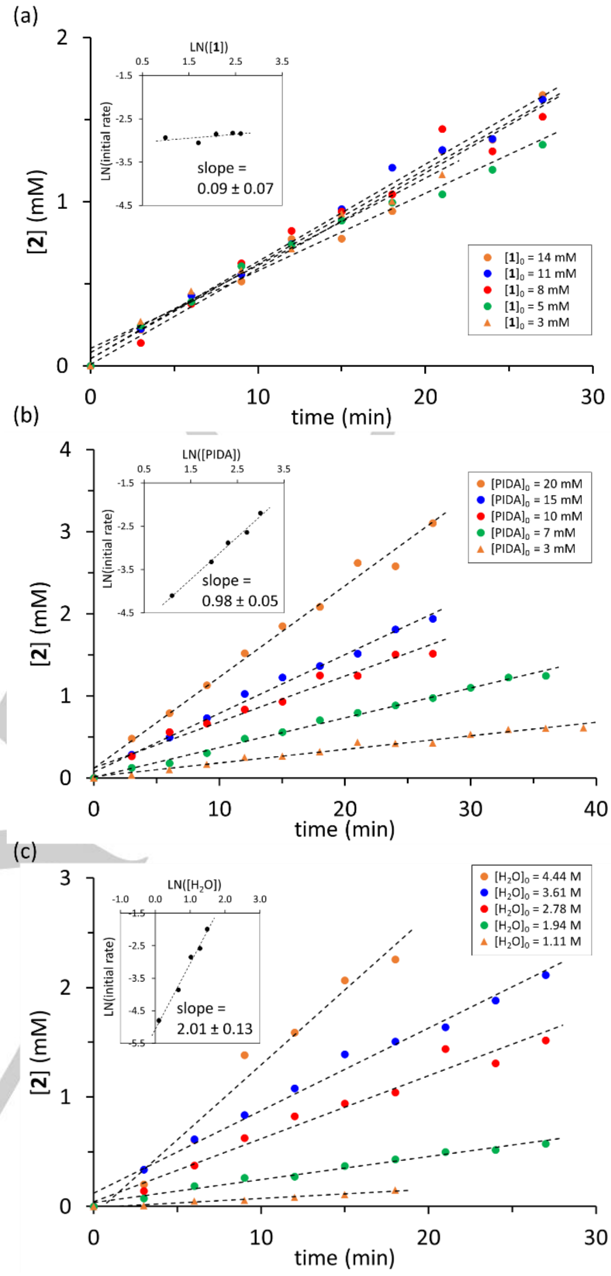

Figure 2. Initial rate measurements for the reaction shown in Scheme 3 with varied concentration of (a) **1**, (b) PIDA, and (c) H_2O. The insets show corresponding LN-LN plots; if not otherwise stated: $[\mathbf{1}]_0$=10 mM, $[PIDA]_0$=10 mM, $[H_2O]_0$=2.78 M, 0 °C, d_3-MeCN; product concentration was determined by ^1H NMR spectroscopy relative to internal standard.

The results of above kinetic experiments are not easily matched with the mechanisms depicted in Scheme 2. Foremost, in all three of them phenol substrate participates prior to the respective rate-determining steps (**TS1**-**TS3**), in a direct contrast with the observed absence of phenol concentration in the rate law. Additionally, the observed intriguing second order dependence of the rate on the concentration of H_2O cannot be satisfactorily explained on the basis of those mechanisms. In particular, the substantial rate enhancement with the increase of water content speaks strongly against the dissociative mechanism (Scheme 2, pathway 2), in which H_2O is engaged only after the rate-determining dissociation of intermediate **A**. This is further

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reinforced by the large negative entropy of activation, unlikely for a dissociative process. The measured experimental free energy barrier (22-23 kcal·mol^{-1}) is also considerably lower than that determined computationally for pathway 2 (>28 kcal·mol^{-1}),[7] but in agreement to those computed for pathways 1 and 3 (21-24 kcal·mol^{-1}).[6,9] However, the computational studies on the associative mechanisms have shown that in both the transition states of type **TS1** and **TS3** (Scheme 2, pathways 1 and 3) for the barriers to be feasible, the attack of nucleophile must proceed with a simultaneous deprotonation by an acetate anion (not shown in the scheme).[6,9] This is, however, inconsistent with the lack of a solvent kinetic isotope effect upon the exchange of H_2O for D_2O. Overall, the data allows with high confidence to discard the pathways shown in Scheme 2 as the correct reaction mechanisms.

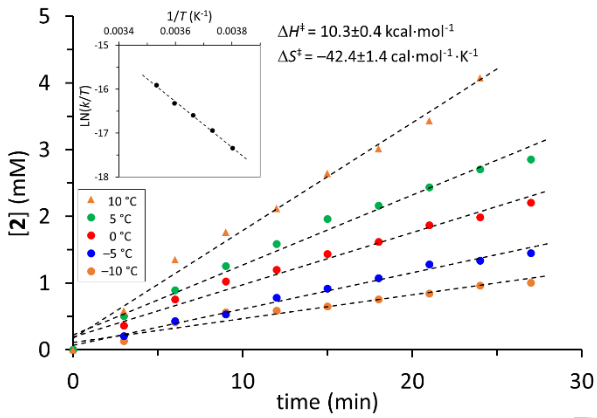


Figure 3. Temperature-dependence of the initial rate for the reaction shown in Scheme 3. The inset shows corresponding Eyring plot, assuming rate law (1); $[\mathbf{1}]_0$=10 mM, $[\text{PIDA}]_0$=10 mM, $[H_2O]_0$=2.78 M, d_3-MeCN; product concentration was determined by ^{1}H NMR spectroscopy relative to internal standard.

The only mechanistic possibility that we could conceive, able to encompass the observed kinetic characteristics of the reaction is a radical-chain process. Specifically, the engagement of phenol in a kinetically irrelevant step of the chain would allow to attain the observed zeroth kinetic order. This is perfectly feasible, assuming that phenoxyl radical, derived from the phenol, has the highest relative stability of all the chain-carrying radicals, so that the step which consumes it determines the overall propagation rate. Conversely, fast steps involving the other chain-carrying radicals, including the one engaging the phenol and regenerating the phenoxyl radical, would not contribute to the overall rate. To achieve the second order in the concentration of H_2O and at the same time conform to the lack of solvent kinetic isotope effect, two H_2O molecules would need to be involved in fast pre-equilibria within the rate-determining sequence, whose final irreversible step, however, should not include the breaking of an O–H bond. This is also viable within the radical-chain mechanism, which is proposed and discussed below.

In the following sections we present investigations aiming at substantiating the involvement of radicals in the investigated reaction and elucidating further details of the mechanism.

EPR spectroscopy

The possible involvement of free radicals in the mechanism of dearomatization of phenols with hypervalent iodine oxidants should not in fact be surprising. On one side, the propensity of phenols to undergo a facile single-electron oxidation coupled with a proton transfer, is well-known and stems from the favorable formation of resonance-stabilized phenoxyl radicals.[12] It constitutes the basis for the antioxidant activity of phenols employed both by Nature and in technological applications.[13] Phenoxyl radicals are also intermediates in numerous reactions of biological and synthetic importance.[14] On the other side, the free radical chemistry of iodine(III) species is also rich, in particular, they can serve both as the initial source of radicals and sustain the propagation of a free radical chain.[15] This is due to the relative ease of formation of an iodanyl(II) radical by the cleavage of the weak hypervalent bond, either via homolysis or a SET from a reducing agent. Finally, radical pathways have been explicitly proven for closely related I(III)-promoted processes engaging aryl ethers.[16]

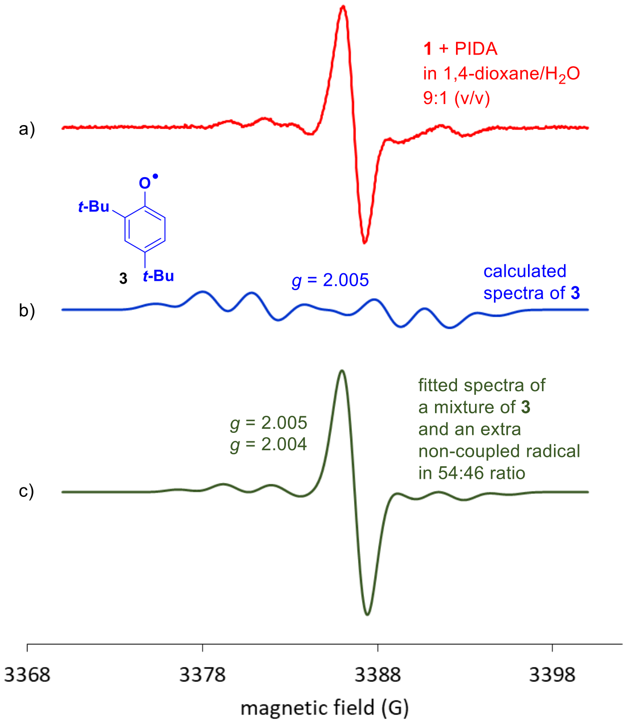


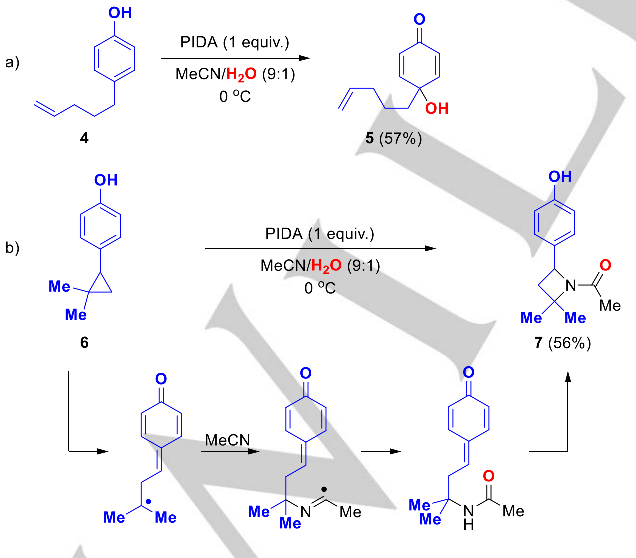
Figure 4. (a) EPR spectrum of phenol **1** and PIDA in 1,4-dioxane/H_2O 9:1 (v/v); $[\mathbf{1}]_0$=100 mM, $[\text{PIDA}]_0$=100 mM, 25 °C. (b) DFT-calculated spectrum of phenoxyl radical **3**. (c) A simulated spectrum of a mixture of **3** and an additional non-coupled radical based on fitting to the experimental data (see the SI for details).

To probe the presence of free radicals, we measured an electron paramagnetic resonance (EPR) spectrum of the reaction mixture for the model dearomatization depicted in Scheme 3. Due to a strong dielectric absorption of microwave radiation by $MeCN/H_2O$ mixtures, acetonitrile was replaced with less polar 1,4-dioxane (the reaction also proceeds well in the latter solvent, albeit at a lower rate; see Table S9 for details). The registered EPR spectrum confirms that free radicals are indeed generated under these conditions (Figure 4a).[17] The analysis of the obtained signal discloses that it arises from a mixture of two radical species present in ~1:1 ratio (Figure 4c). One of them is the phenoxyl radical **3** (*g* factor 2.005), derived from phenol **1**, as identified by the density functional theory modelling (Figure 4b). The other is an unknown radical (*g* factor 2.004), which does not exhibit any strong hyperfine coupling to hydrogens. Putatively, it may be some iodanyl(II) species, similar to that generated in the recently reported electrochemical oxidation of iodoarenes (see below for a discussion on the possible identity of this intermediate).[18,19]

The formation of phenoxyl radical **3** under the reaction conditions does not yet prove that it is involved in the mechanism of the reaction and the creation of product. However, its intermediacy would provide good rationalization for the observed selectivity of the addition at the substituted *ortho*- or *para*-position of the phenolic ring, as the delocalized unpaired electron is stabilized more efficiently next to a substituent via hyperconjugation or resonance.

Reactions with radical probes

To test for the actual intermediacy of phenoxyl radical in the investigated process, we have synthesized two phenols containing in-built radical clocks.[20] Upon subjecting to the standard dearomatization conditions, phenol **4** having a pendant olefin, afforded exclusively a direct hydroxylation product **5**, without any signs of cyclization (Scheme 4A). Such outcome may be due to the high stability of the phenoxyl radical, rendering the cyclization slow or altogether energetically disfavored.[21] Conversely, the PIDA-promoted hydroxylation of phenol **6**, bearing a much faster 2,2-dimethylcyclopropane radical clock,[22] lead to the formation of compound **7** as the dominant product, with no direct hydroxylation of the phenolic ring observed (Scheme 4B). Product **7** likely origins from the sequence starting by the ring opening of the cyclopropylcarbinyl radical and a subsequent reaction of the resulting ternary radical with MeCN. After an oxidative incorporation of oxygen, intermediate amide[23] undergoes a facile intramolecular Michael addition, restoring the aromaticity and forming the azetidine ring. Irrespective of the unusual course of the reaction with phenol **6**, the characteristic opening of the cyclopropyl ring lends strong support to the involvement of phenoxyl radical in this process.



Scheme 4. PIDA-promoted dearomatizing hydroxylations of phenols containing radical clocks. The yields were determined in crude reactions mixtures by ^{1}H NMR spectroscopy relative to internal standard.

The iodine(III)-promoted oxidative dearomatizing additions of nucleophiles to phenols are generally quite robust and they do not usually require the exclusion of air. In particular, the reaction depicted in Scheme 3 works equally well under an inert atmosphere and when exposed to oxygen (Table S9). This should not be considered as opposing a radical mechanism, however, because although some processes involving radicals are sensitive to oxygen, other are not. The latter group often proceeds via long radical chains, which once initiated can continue unperturbed.[24] We evaluated whether the reaction can be interrupted by a more potent radical trap than O_2, namely 2,2,5,5-tetramethylpiperidin-1-oxyl (TEMPO). It was found that substoichiometric amounts of TEMPO do not impact the rate of the reaction, and as much as 4 equiv. are required to slow down the dearomatization by ~2-fold (Figure 5). While the inhibitory effect of TEMPO is only moderate, probably due to the large steric hindrance of phenoxyl radical **3**,[25] it strongly points to the radical mechanism of the transformation.

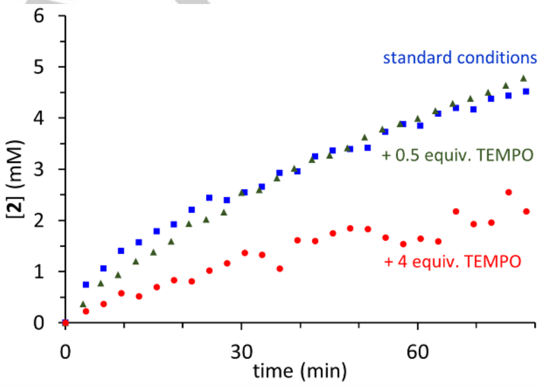


Figure 5. Time-course of the reaction shown in Scheme 3 carried out at in the absence and presence of TEMPO; [**1**]$_0$=10 mM, [PIDA]$_0$=10 mM, d_3-MeCN/H_2O 9:1 (v/v), 0 °C; product concentration was determined by ^{1}H NMR spectroscopy relative to internal standard; the fluctuations of the red data points are due to interference from TEMPO.

UV spectroscopy, NMR, and HRMS studies on the interaction of PIDA and H_2O in MeCN

Having established that phenoxyl radical is implicated in the mechanism of the investigated reaction, we pursued to gain additional insight into how the bond between the ring and the nucleophile is formed. Unlike phenoxenium ion (**B** in Scheme 2), phenoxyl radical will not directly react with H_2O providing the final product, as such step is deemed energetically disfavored due to the generation of a hydrogen atom (H·). Therefore, we conjecture that H_2O needs to undergo a prior activation, presumably by PIDA, as implied by rate law (1). The necessity for the nucleophile to interact with the hypervalent iodine species to become capable of reacting with phenoxyl radical would explain the asymmetric induction rendered by chiral hypervalent iodine reagents.

The interaction of iodine(III) compounds with nucleophilic species, such as H_2O and MeOH, has been a subject of some investigations.[26] It has been for instance determined that in an aqueous solution, PhI(OTs)OH (Koser's reagent) is completely transformed into an equilibrium mixture of fully dissociated $[PhI(OH_2)OH]^+$ and $[Ph(HO)I–O–I(OH_2)Ph]^+$ ions.[27] A high-resolution mass spectrometry (HRMS) study of the solution of

PIDA in MeCN/H_2O mixture has also qualitatively demonstrated the existence of analogous species.[28] We set out to more thoroughly investigate the behavior of PIDA when exposed to H_2O under the conditions relevant to the oxidative dearomatizing hydroxylation of phenols.

First, we looked for an indication of any interaction between PIDA and H_2O using UV spectroscopy. The UV spectrum of the solution of PIDA in MeCN indeed undergoes an evident alteration in the presence of H_2O (Figure 6).

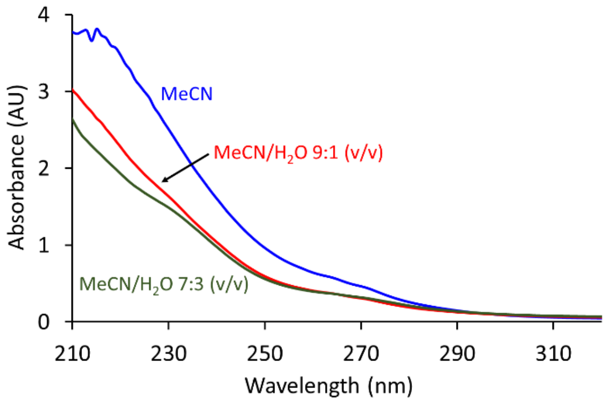


Figure 6. UV spectrum of PIDA in pure MeCN and MeCN/H_2O mixtures; [PIDA]=0.2 mM.

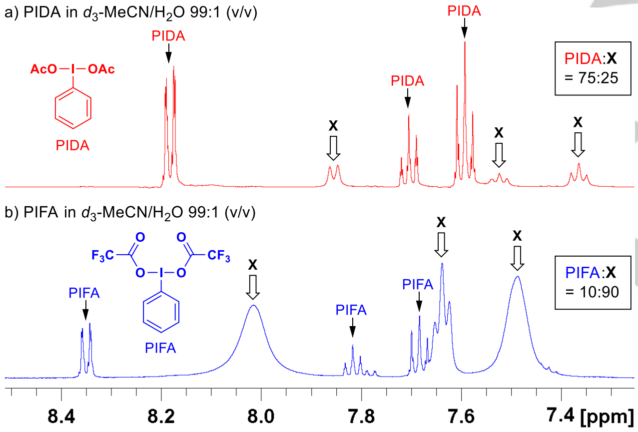


Figure 7. 500 MHz ^{1}H NMR spectra of (a) PIDA and (b) PIFA in d_3-MeCN/H_2O 99:1 (v/v) mixture; [PIDA/PIFA]=50 mM. New signals appearing in the presence of H_2O are indicated with **X**.

To establish what the origins of the observed changes in the UV absorption pattern of PIDA are, we turned to nuclear magnetic resonance (NMR) spectroscopy. The ^{1}H NMR spectra of PIDA in d_3-MeCN contains a set of 3 aromatic protons peaks at 8.18, 7.71, and 7.59 ppm. Upon the addition of H_2O, a new set of somewhat broad signals of aromatic protons emerges (Figure 7a, indicated with **X**). The novel NMR peaks are more shielded compared to those of PIDA, but they are still considerably downfield, indicating the presence of an I(III) substituent in the ring. In the case of PIFA, a similar phenomenon was also observed, however, the new NMR signals are much broader and the quantity of the corresponding species is considerably higher, as much as 90% in d_3-MeCN/H_2O 99:1 (v/v) mixture (Figure 7b). This correlates with the very high rate of phenol dearomatization promoted by PIFA (see above).

In the HRMS spectrum of the solution of PIDA in MeCN/H_2O 9:1 (v:v) mixture, the major species are $[PhIOH]^+$ (220.9456) and $[Ph(HO)I–O–IPh]^+$ (440.8846), in line with the previous report.[28] The only peak from acetate-containing species detected is a small $[Ph(AcO)I–O–IPh]^+$ (482.8945) signal. In the corresponding solution of PIFA, just the former two ions are detected.

Collectively, above results show that under typical conditions employed in the oxidative dearomatizing hydroxylation of phenols, a considerable fraction of the hypervalent iodine reagent is converted into species containing HO–I^{III} and I^{III}–O–I^{III} moieties. These constitute the activated forms of H_2O, possessing an oxidative ability and exhibiting electrophilic character. As such, they should be prone for a single electron transfer coupling reaction with the nucleophilic phenoxyl radical, forming the alcohol product and generating an iodanyl(II) radical.

Electrochemical properties of I(III)-H_2O adducts

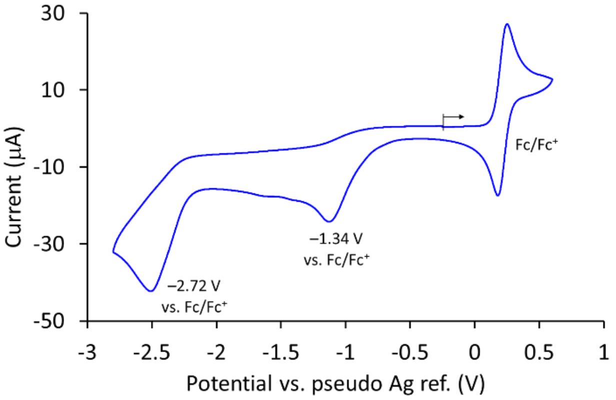
As the final part of our investigations, using cyclic voltammetry, we studied the oxidizing ability of the I(III)-H_2O adducts, whose formation was described in the previous section.

First, as a reference, the reduction of PIDA was recorded voltammetrically at a glassy carbon electrode in MeCN, in the presence of ferrocene (Fc) as an internal redox standard (Figure 8a). The registered voltammogram displays two irreversible reduction waves. The first one occurs at the peak potential of –1.34 V relative to Fc/Fc$^+$, in a full agreement with the previously reported value.[16b]

We then performed a similar measurement for the solution of PIDA in MeCN/H_2O 9:1 (v:v) mixture, wherein the species of interest are being present. In this case, the direct application of Fc/Fc$^+$ internal redox standard turned out to be impossible, because in this solvent mixture the iodine(III) oxidants reacted with ferrocene, as noticeable by the change of the solution color. This is a very similar behavior to that reported previously by Compton and co-workers, in the case of PIDA solution in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).[16b] Following the procedure applied in the above work, the voltammetry was thus recorded against a silver/silver hexafluorophosphate reference electrode, without ferrocene. In a separate measurement, the redox potential of ferrocene was determined to be 0.05 vs. Ag/Ag$^+$ (Figure S4), allowing for referencing the data obtained in both solvents. The recorded voltammogram contains three irreversible reduction waves (Figure 8b). The first one is broad and it occurs at the peak potential of –0.65 V relative to Fc/Fc$^+$. The other two waves most likely originate from the sequential reduction of PIDA, as they display peak potentials analogous to those in Figure 8a.[29]

The electrochemical characteristics of the solution of PIDA in MeCN/H_2O mixture demonstrates that it contains species that are considerably stronger oxidants than PIDA itself (by more than 0.6 V). The superior oxidizing ability of the I(III)-H2O adducts compared to PIDA provides rationalization for the selective transfer of the OH group to the phenoxyl radical, furnishing the hydroxylation product, while its acetoxylated analog is not formed under the conditions shown in Scheme 3.[30]

(a) PIDA + ferrocene in MeCN



(b) PIDA in MeCN/H_2O 9:1 (v/v)

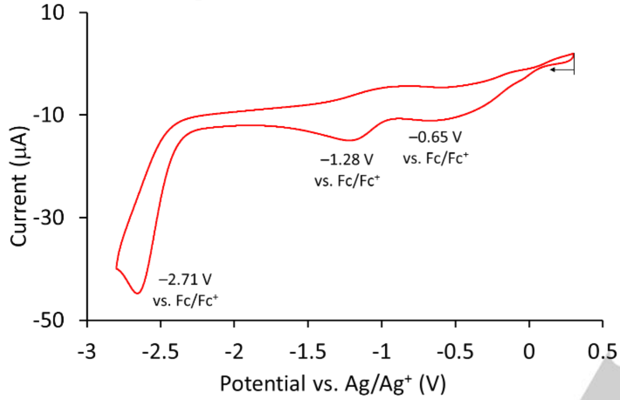


Figure 8. Voltammograms of (a) PIDA and ferrocene in MeCN and (b) PIDA in MeCN/H_2O 9:1 (v:v) mixture; [PIDA]=1 mM, [ferrocene]=1 mM, [*n*-Bu_4NPF_6]=0.1 M, scan rate=0.1 V·s^{-1}, glassy carbon electrode (radius = 1.5 mm). In (a) ferrocene was used as an internal redox reference potential. In (b) a Ag/$AgPF_6$ reference electrode ($E_{ferrocene}$ = 0.05 V vs. Ag/Ag^+, measured separately in MeCN/H_2O 9:1 (v:v)) was used due to reaction between ferrocene and PIDA. Voltammetric starting potential and initial scan direction are indicated with black arrows.

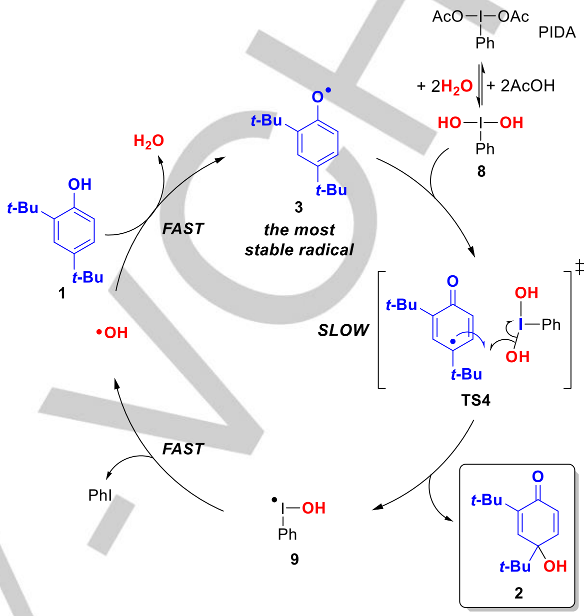
Overall mechanism

The results of the experiments presented in the previous sections suggest that the iodine(III)-promoted oxidative dearomatizing hydroxylation of phenols follows a radical-chain mechanism, summarized in Scheme 5.

Phenoxyl radical **3** is the key chain-carrying intermediate, which due to its high stability will be the dominant radical species present in the reaction mixture. A single-electron oxidation of **3** by an I(III)-H_2O adduct (the strongest oxidant present in the reaction mixture), coupled with the OH-transfer, yields product **2** and generates a iodanyl(II) radical. Owing to the stability of **3**, this step is slow and, thus, it determines the overall rate of the reaction. Based on rate law (1), we propose that the actual oxidant is phenyliodine(III) dihydroxide **8**, however, it may possibly be another related I^{III}–O species. Importantly, in putative **TS4**, the O–H bond is not being broken, hence there will be no KIE upon exchanging H to D, in line with the experimental findings.[31]

Iodanyl(II) radical (**9** or a related species) is moderately stable and it is most likely the second radical detected by the EPR (Figure 4). Its fragmentation leads to PhI and a hydroxyl radical, which is quenched by the phenol, regenerating **3**. The overall transformation of **9** to **3** is fast, thus, the concentration of phenol **1** does not enter the rate law.[32]

Here it is important to remark that Scheme 5 presents only the propagation steps of the radical chain. With the current data, we are not able to establish the specific course of initiation and termination steps, i.e. how the radicals are created and how they fade. These aspects of the mechanism are yet to be elucidated.



Scheme 5. Putative radical-chain mechanism for the dearomatizing hydroxylation of 2,4-di-*tert*-butylphenol **1** promoted by PIDA.

Nonetheless, the mechanistic picture depicted in Scheme 5 is able to accommodate all the reported characteristics of the iodine(III)-promoted dearomatization of phenols. First, it explains the regioselectivity of the reaction – the addition will take place preferentially next to a substituent providing the highest stabilization of the delocalized unpaired electron in the phenoxyl radical, overrunning the steric factors. Secondly, the *Umpolung* of the nucleophile, by the association with the I(III) center, renders electron-rich phenols more reactive, rationalizing the negative slope of the Hammett plot.[8] Finally, the requirement for the nucleophile to be activated by the I(III) reagent during the reaction with the phenoxyl radical allows for the enantioselective formation of the product, in the case when a chiral hypervalent iodine reagent or catalyst is applied.

We would like to stress that above findings regarding the radical-chain mechanism are only directly applicable to the specific case of the hypervalent iodine-mediated dearomatizing hydroxylation of phenols. To assess their relevance to the other related dearomatizing phenol functionalizations, additional investigations are required.

Conclusion

In summary, the mechanism of iodine(III)-promoted oxidative dearomatizing hydroxylation of phenols was investigated by an array of experimental techniques. Obtained results disprove the previously proposed pathways and they strongly point to the radical-chain mechanism. Specifically, it was determined that the phenol substrate is converted into the corresponding phenoxyl radical, which constitutes the key chain-carrying intermediate. In turn, the nucleophilic coupling partner needs to become activated by the coordination to the I(III) center in order to react with the phenoxyl radical, to generate the product together with a iodanyl(II) radical that further propagates the chain. The radical-chain mechanism, as the only one, is able to rationalize all the features of the reaction. This conclusion is also in a good agreement with the known propensity of both phenols and hypervalent iodine(III) regents to undergo single-electron redox processes. Computational studies aimed at elucidating further details of the radical pathway are currently underway.

We are convinced that the established mechanism is valid for the iodine(III)-promoted oxidative dearomatizing hydroxylation and, with a high degree of confidence, alkoxylation of phenols. As far as the other dearomatizations of phenols, such as the spirolactionization, are concerned, we believe that further experimental studies are needed to draw definite conclusions. Nevertheless, the presented results provide important new insights and a framework for understanding and improving the iodine(III)-mediated reactions involving phenols. They carry also major implications for the design of novel processes employing hypervalent iodine reagents and catalysts, including asymmetric ones.

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Keywords: phenol dearomatization • hypervalent iodine • mechanistic investigations • radical-chain pathway

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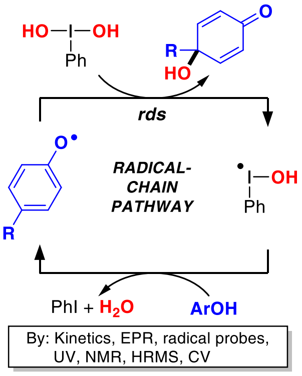

A radical way: All-around experimental investigations demonstrate that the hypervalent iodine-promoted dearomatizing hydroxylation of phenols proceeds via a radical-chain pathway.

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