Journal of Pharmaceutical Sciences 106 (2017) 1347-1354

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Iron(III)-Mediated Oxidative Degradation on the Benzylic Carbon of Drug Molecules in the Absence of Initiating Peroxides

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ARTICLE INFO

Article history:
Received 23 November 2016
Revised 19 January 2017
Accepted 24 January 2017
Available online 1 February 2017

Keywords:
drug degradation
oxidation
aromatic cation radical
iron
iron(III)

ABSTRACT

Metal ions play an important role in oxidative drug degradation. One of the most ubiquitous metal ion impurities in excipients and buffers is Fe(III). In the field of oxidative drug degradation chemistry, the role of Fe(III) has been primarily discussed in terms of its effect in reaction with trace hydroperoxide impurities. However, the role of Fe(III) acting as a direct oxidant of drug molecules, which could operate in the absence of any hydroperoxide impurities, is less common. This work focuses on Fe(III)-induced oxidation of some aromatic drug molecules/drug fragments containing benzylic C-H bonds in the absence of initiating peroxides. Alcohol and ketone degradates are formed at the benzylic carbon atom. The formation of a π-stabilized cation radical is postulated as the key intermediate for the downstream oxidation. Implications are briefly discussed.

Introduction

Pharmaceutical scientists are always concerned with the degradation of the active pharmaceutical ingredients in the formulated drug products. The degradation could be caused by light, heat, moisture, acid, base, oxygen-centered radicals, etc.[1,2] It is also known that some degradation processes could involve metal ions,[1-4] and metal ion–catalyzed/mediated chemical transformations are well known in organic chemistry.[5] One of the most ubiquitous metal ions present in buffers and excipients is iron(III).[3] In the drug degradation literature however, to the best of our knowledge, the role of iron(III/II) has been primarily discussed in terms of its effect in the reactions with trace hydroperoxide impurities.[2] Detailed reports of Fe(III) acting as a direct oxidant of drug molecules are not common. There are only a few reports where Fe(III) or Fe(II) acts as direct oxidant in the small-molecule drug degradation process, although no mechanistic insight has been provided.[6-10] The use of Fe^{3+} salts has been recommended[2] as part of oxidative susceptibility screening procedures for new drug substances entering development. In this context, Fe^{3+} is positioned as a probe to oxidize electron-rich compounds (such as pyrroles). Reactivity of compounds in the Fe^{3+}-screening test might indicate the propensity of these molecules to participate in "single electron transfer" reactions to dioxygen. However, such Fe^{3+} reactivity during oxidative susceptibility testing is generally considered uncommon[2,4] and the Fe^{3+} reaction itself was not considered to be the "risk" in an actual tablet formulation.

In a recent drug development effort in our laboratories, the drug substance contained a biaryl methane moiety and was formulated as a tablet. It was found that oxidative degradation products (the alcohol and ketone on the benzylic carbon, Scheme 1) were formed in the tablet under accelerated stress conditions and in the package in the absence of light. These degradation products could not be formed in solution, under the usual oxidative forced stress conditions (dilute H_2O_2 in water/methanol, and peroxy radical–based stress using azobisisobutyronitrile in water/methanol). Further investigation revealed that these oxidative degradation products could only be obtained in significant yield from the reaction of the drug substance with $FeCl_3$ in 0.1 N HCl (Scheme 1). Furthermore, another biaryl methane drug substance in development showed no such reactivity and did not form these oxidative degradation products in the tablet under accelerated stability conditions.

The chemical literature suggests that Fe^{3+} is capable of oxidizing C-H bonds of benzylic carbon atoms via aromatic radical cations which may explain (*vide infra*) the formation of the observed oxidative degradation products in oxygen-saturated solutions. These findings prompted us to study the generality of the Fe(III)-mediated oxidative degradation of drug molecules and drug

This article contains supplementary material available from the authors by request or via the Internet at http://dx.doi.org/10.1016/j.xphs.2017.01.025.

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http://dx.doi.org/10.1016/j.xphs.2017.01.025
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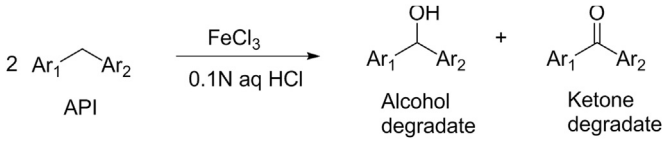


Scheme 1. Oxidative degradation of drug substance by Fe(III).

fragments containing benzylic hydrogen(s). The compounds studied are shown in Figure 1. This work begins to elucidate the underlying mechanism responsible for the oxidation and sheds light on what structural elements are important for this mechanism to be operative. The impact on forced stress testing procedures and drug product development is briefly discussed.

Materials

All chemicals were used as received. Ferric chloride hexahydrate was obtained from Acros Organics (Geels, Belgium). Trifluoroacetic acid, hydrochloric acid (1.0 N), ethylenediamine tetraacetic acid (EDTA) disodium salt dihydrate and HPLC-grade solvents were obtained from Fisher Scientific (Fair Lawn, NJ). Dextro-methorphan HBr H_2O, 4-benzylaniline, 4-methoxybenzophenone, 4,4'-dimethoxybenzhydrol, 4-4'-dimethoxybenzophenone, 4-methylbenzophenone, benzophenone, and diphenylmethanol were obtained from Sigma-Aldrich (St. Louis, MO). Brodimoprim and epinasine hydrochloride were obtained from Brookview Scientific (Carmel, IN) and Combi Blocks (San Diego, CA), respectively. 1-Benzyl-4-methoxybenzene, 1-benzyl-4-methylbenzene, and diphenylmethane were obtained from Oakwood Chemicals (Columbia, SC). Bis(4-methoxyphenyl)methane was obtained from Beta Pharma Scientific (Branford, CT). 4-Methoxybenzhydrol and 4-methylbenzhydrol were obtained from Tokyo Chemical Industry (Tokyo, Japan). 2-(3-Chlorobenzyl)-5-methoxypyridine, 4-bromo-1-chloro-2-(4-methoxybenzyl)benzene, 3,3-diphenylpropan-1-amine and 4,4-diphenylpiperidin-1-ium chloride were obtained from our building block collection.

Experiment and Analysis

The oxidative degradation experiments were carried out in 20-mL scintillation vial by adding 5 mL of 0.5 mg/mL $FeCl_3$ solution in 0.1 N aqueous HCl to 5 mL substrate solution (0.1 mg/mL) in 0.1 N aqueous HCl at room temperature. When the substrate was not soluble in aqueous HCl, the substrate solution was prepared in 75/25 (v/v) 0.1 N aqueous HCl/acetonitrile (MeCN). Solutions of compounds **1**, **2**, **3**, **9**, **10**, **11**, and **12** (Fig. 1) were prepared in 0.1 N aqueous HCl. Solutions of compounds **4**, **5**, **6**, **7**, and **8** (Fig. 1) were prepared in 75/25 (v/v) 0.1 N aqueous HCl/MeCN. After stirring the reaction mixtures for desired time, an aliquot was clarified by 0.45-μm filtration and analyzed by HPLC and Liquid chromatography-mass spectrometry (LC/MS). Degradation yield was estimated as UV peak area percent relative to the parent substrate at a specific wavelength (215 nm).

Reversed-phase chromatography was carried out on an Acquity UPLC (Waters Corporation, Milford, MA) equipped with a binary pump, heated column compartment, diode array detector, and autosampler. The chromatographic conditions included a BEH C18 Acquity/Waters UPLC column of dimensions 50 mm × 1.0 mm and 1.7-μm particle size held at 30°C; flow rate was maintained at 0.3 mL/min; injection volume was 3 μL; tray temperature was 25°C; mobile phase A consisted of 0.05% trifluoroacetic acid in 95/5 (v/v) water/MeCN; mobile phase B consisted of 0.05% trifluoroacetic acid in MeCN. The column was equilibrated for 1 h before running experiments. The mobile phase gradients and detector wavelengths used for each compound are listed in the Supplementary Material.

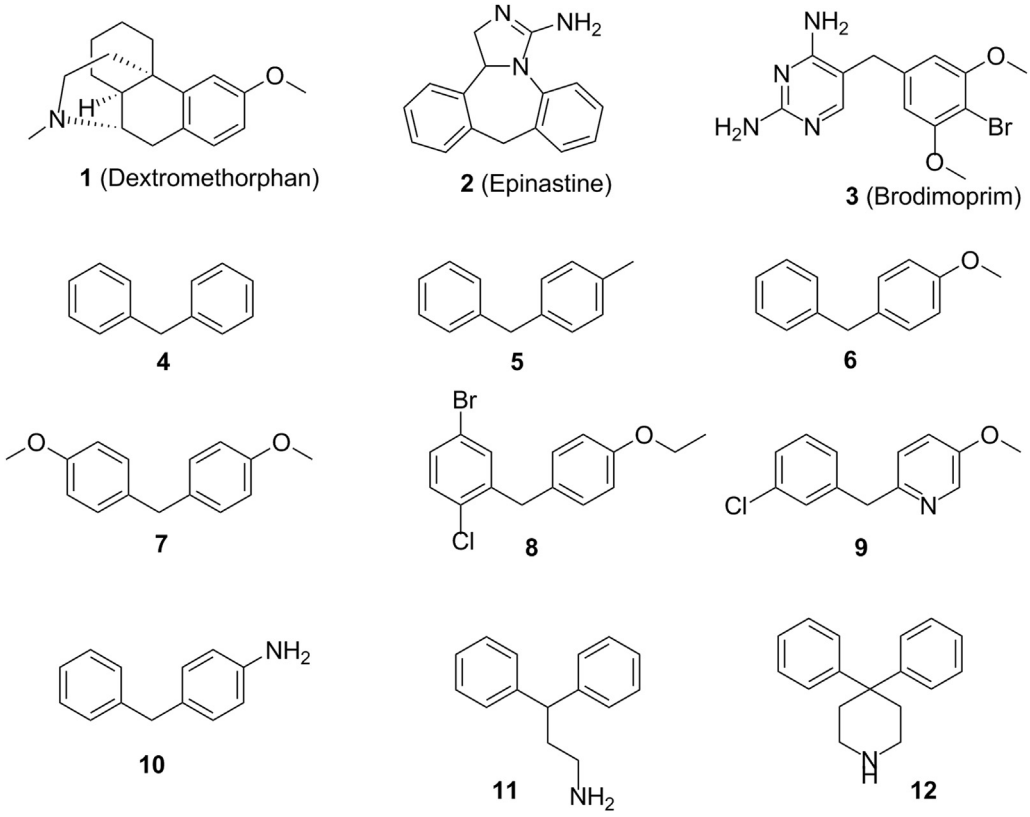


Figure 1. Model drugs and "drug fragments" studied.

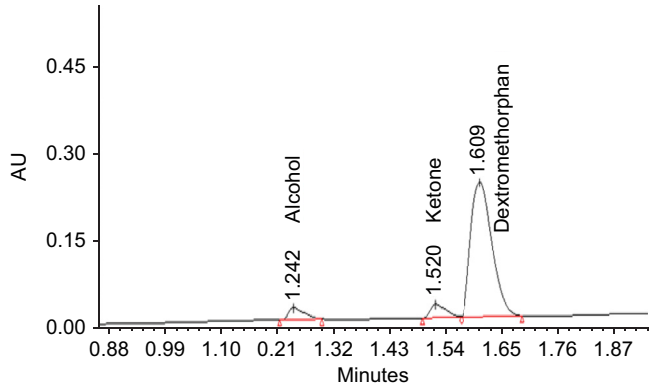


Figure 2. Chromatogram obtained after the reaction of dextromethorphan **1** and $FeCl_3$ is run for 48 h.

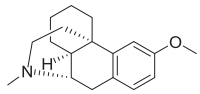
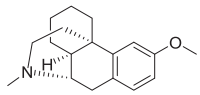
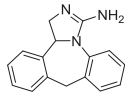
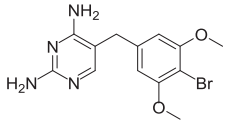
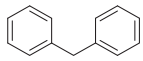
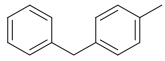
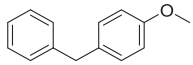
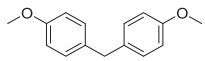
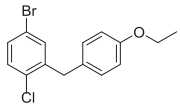
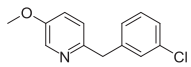
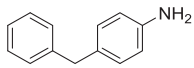
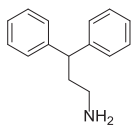
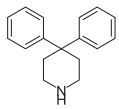
For the LC/MS analysis, an Agilent 1100 series HPLC (Agilent Technologies, Santa Clara, CA) equipped with a quaternary pump, diode array detector, and autosampler was used to separate the components of the reaction mixture before MS analysis. The chromatographic conditions used for each compound are listed in the Supplementary Material. An LCQ Fleet Thermo Scientific (Thermo Electron North America LLC, West Palm Beach, FL) mass spectrometer was used coupled to the HPLC. The mass spectrometer was equipped with an electrospray ion source. The capillary temperature was set at 250°C, and the spray voltage was 4.5 kV.

When commercially available, the retention time and UV spectra of compounds with the same structures as of the expected structures of the degradation products obtained from the reaction of Fe^{3+} with the substrate were acquired. The following comparisons were made to show that the structures of the degradation products obtained are same as of the commercially available authentic samples: benzophenone and diphenylmethanol with degradation products from **4**, 4-methylbenzophenone and 4-methylbenzhydrol with degradation products from **5**, 4-methoxybenzophenone and 4-methoxybenzhydrol with degradation products from **6**, 4,4'-dimethoxybenzophenone and 4,4'-dimethoxybenzhydrol with degradation products from **7**.

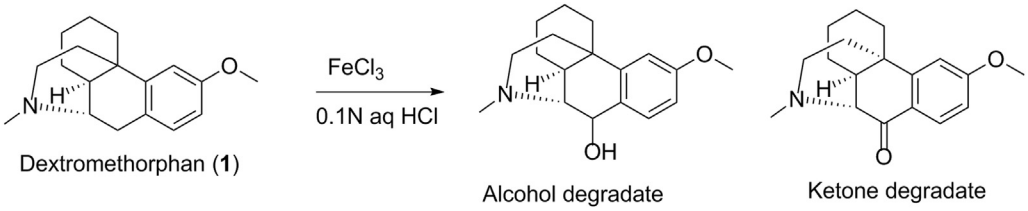
EDTA Titration Experiments

The effect of EDTA on the formation of the degradation products was illustrated by varying the molar ratio of EDTA/$FeCl_3$ (0 to 1.3) in the reaction mixture. The experimental setup is as follows. Stock solutions of **1** (0.37 mM) and $FeCl_3$ (1.23 mM) were prepared in 0.1N aqueous HCl. A stock solution of $Na_2EDTA.2H_2O$ (EDTA, 15.68 mM) was prepared in water; 5 mL of the stock solution of **1**, required volume of EDTA stock solution, 3 mL of $FeCl_3$ stock solution, and enough 0.1N aqueous HCl to make the final total volume of 10 mL

Table 1
Iron(III)-Mediated Oxidative Degradation of Drugs and Drug Fragments

Compound	Structure	Solvent[a]	%Alcohol[b]	%Ketone[b]
1		A	6.0	6.2
1		B	9	24.8
2		A	0	0
3		A	0	0
4		B	0.9	10.6
5		B	2.4	16.7
6		B	7.5	7.2
7		B	5.9	13.8
8		B	8.0	15.0
9		B	0	0
10		A	0	0
11		A	0	0
12		A	0	0

[a] Solvent A: 0.1N aqueous HCl; Solvent B: 0.1N aqueous HCl-MeCN (75:25 v/v).
[b] After 48 h of reaction.



Scheme 2. Fe(III)-mediated oxidative degradation of dextromethorphan **1**.

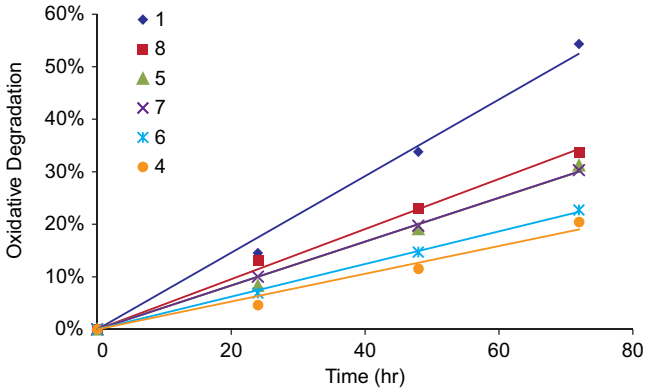


Figure 3. Fe(III)-mediated total degradation in 0.1N aqueous HCl/MeCN (75/25 v/v) at ambient temperature.

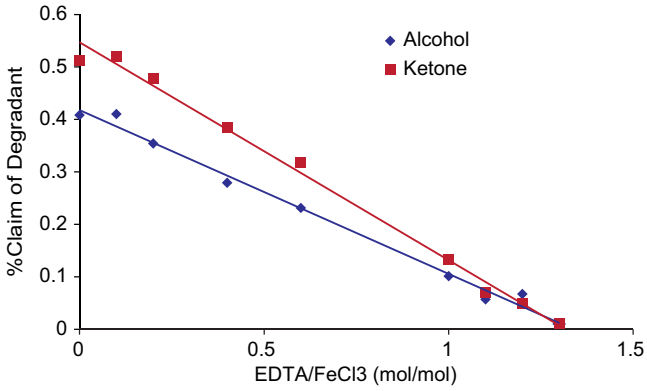


Figure 5. Effect of EDTA on the formation of alcohol and ketone degradation products from dextromethorphan **1** in 0.1N aqueous HCl (24-h time points).

were taken in a 20-mL scintillation vial. The vials were capped and the reaction mixtures were stirred at room temperature for 24 h after which aliquots from each experiment were analyzed by HPLC.

Experiments With Varying Fe^{3+} Concentration

The effect of the concentration of Fe^{3+} on the degradation of **1** was studied as follows. Six stock solutions of $FeCl_3$ (0.31 mM, 0.62 mM, 1.23 mM, 2.46 mM, 4.92 mM, and 9.24 mM) and a stock solution of **1** (0.37 mM) were prepared in 0.1N aqueous HCl. In separate scintillation vials containing 6 mL of stock solution **1**, 6 mL of each of the $FeCl_3$ stock solutions were added. The resulting mixtures were stirred for 48 h and then analyzed by HPLC.

Results

A typical experiment, run with dextromethorphan **1** in 0.1N aqueous HCl, shows the formation of 2 degradation products (Fig. 2). LC/MS of the peaks at 1.24 min and 1.52 min correspond to the alcohol and ketone degradation products, respectively (shown in Scheme 2). The overall outcome of the experiments is listed in Table 1. Note, in Table 1, two solvent systems A and B were used; B was used when increased solubility was needed to get the drug (fragments) into solution. Table 1 lists separately the %alcohol and % ketone degradates formed, and no other significant degradates were observed.

Figure 3 plots the total oxidative degradates of the reactive compounds (1, 4-8) over 72 h. The reaction rates of all 6 compounds

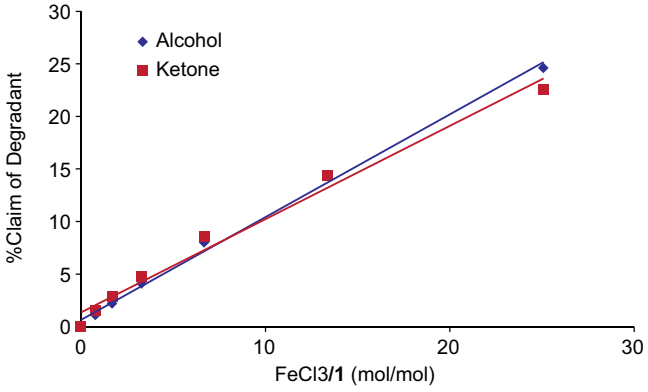


Figure 4. Effect of $FeCl_3$ on the formation rate of alcohol and ketone degradation products from dextromethorphan (**1**).

are all within about a factor of 2. The plotted lines shown are linear and are simply to aid the eye. There may be some slight nonlinearity over the 72 h shown for several of the compounds. The effect of varying the concentrations of Fe^{3+} on the oxidative degradation is examined using **1** (dextromethorphan) as the model compound is shown in Figure 4 (48 h reaction time). The amount of degradation products (alcohol and ketone) increased linearly with increase in the molar ratio of $FeCl_3$/**1** (0 to 25).

Figure 5 explores the effect on the reaction rate of $FeCl_3$ with dextromethorphan upon addition of the strong Fe(III) chelator, EDTA. Clearly the degradation reaction is almost completely inhibited as the molar ratio of EDTA to $FeCl_3$ approaches 1.

Figure 6 groups the reactive and unreactive compounds for visual comparison of structural motifs.

Discussion

Mechanism for Direct Oxidation by Fe^{3+}

The current solution phase investigation of direct $FeCl_3$ oxidation of benzylic carbon was driven by the observation from Scheme 1 operating in a solid state tablet formulation (details not described in this work) to generate alcohol and ketone degradates. Moreover, these degradation products could only be formed by the $FeCl_3$ oxidative susceptibility testing, but not peroxy radical–based forced stress tests. In the pharmaceutical literature,[3,11-13] the role of Fe^{3+} in oxidative drug degradation is typically ascribed to its ability to catalyze the oxidation of hydroperoxides to peroxy and alkoxy radicals (Eqs. 1 and 2) which ultimately oxidize the drug substance. In our case, we have no source of ROOH (one of the most reactive molecules studied in this work, dextromethorphan **1**, and the reaction of dextromethorphan with $FeCl_3$ were tested[14,15] negative for the presence of hydroperoxide).

$$Fe^{3+} + ROOH \rightarrow ROO^{\cdot} + Fe^{2+} + H^{+} \quad (1)$$

$$ROOH + Fe^{2+} \rightarrow RO^{\cdot} + Fe^{3+} + OH^{-} \quad (2)$$

Although we were not able to find any example of direct oxidation of drug compounds by Fe^{3+} where the mechanistic aspect of the oxidation is described, it is known that transition metal ions are capable of oxidizing electron-rich aromatic rings to form aromatic radical cations.[5,16,17] When an aromatic radical cation is attached to a "benzylic" side chain, the overlap of the σ-orbital of the benzylic hydrogen with the SOMO (singly occupied molecular orbital) from the aromatic cation radical weakens the σ-bond significantly, facilitating the cleavage of the C-H bond.[17] The

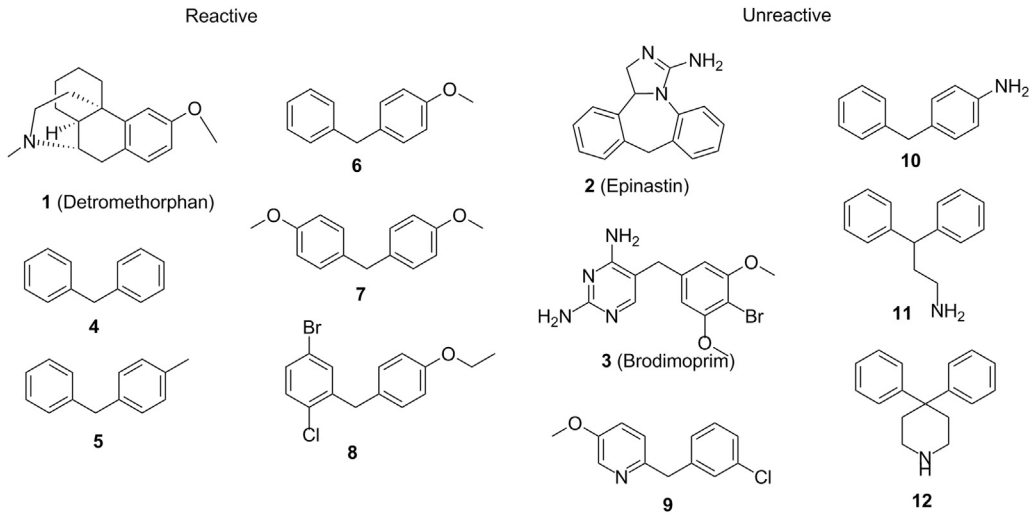


Figure 6. Reactive and unreactive molecules in the Fe(III)-mediated oxidative degradation reactions.

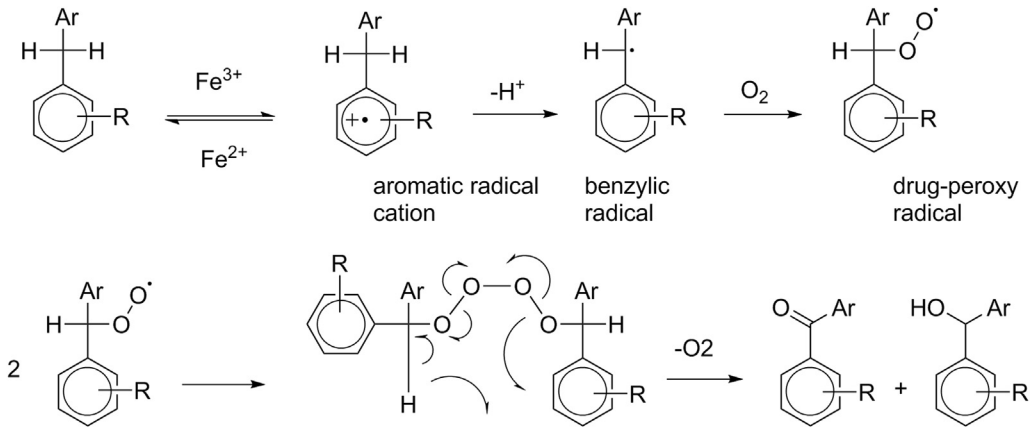
electron from the cleaved H atom is donated to the aromatic ring whereas the proton is lost. This yields the benzylic radical (Scheme 3, top row, third structure). In oxygen-saturated solution, this benzylic radical can then react with oxygen to form the corresponding peroxy radical (last step, Scheme 3, upper row) which then via Russell mechanism[18] yields alcohol and ketone degradation products. It should be noted that a subset (the active pharmaceutical ingredient (Scheme 1), dextromethorphan **1** and 1-benzyl-4-methoxybenzene **6**) of the molecules studied in this work, when subjected to peroxy radical–based forced stress condition[19,20] using azobisisobutyronitrile in MeOH/water over 2 days at 40°C, does not yield the alcohol and ketone degradation products. These data support the hypothesis of drug-peroxy radical disproportionation which is required for the Russell mechanism to operate (Scheme 3, lower row).

The Role of the Concentration of Fe^{3+} and the Effect of EDTA on the Oxidative Degradation

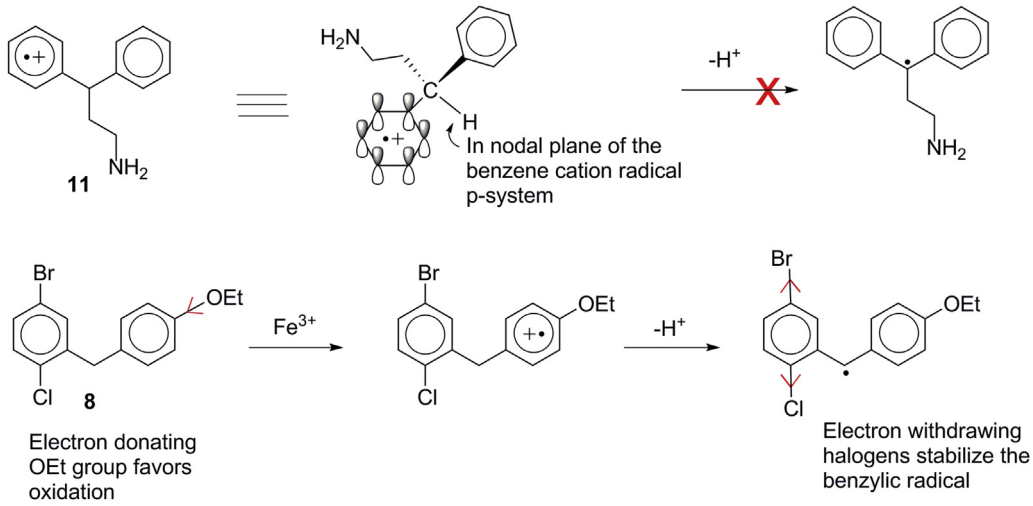
The above mechanism and rationale account for the formation of oxidative degradation products (alcohol and ketone) from the drug substances containing benzylic C-H, in the presence of Fe^{3+} alone. The data in Figure 4 are consistent with Scheme 3, in that the rate of degradation of **1** would be expected to be directly proportional to the Fe^{3+} concentration (Scheme 3). As a further proof of Fe^{3+} causality, Figure 5 highlights that a strong chelator of Fe^{3+}, such as EDTA, can shut down the reaction. EDTA when ligated to Fe^{3+} stabilizes the ferric (Fe^{3+}) oxidation state over the ferrous (Fe^{2+}) which is manifested in its redox potential.[21,22] The redox potential of Fe^{III}-EDTA/Fe^{II}-EDTA ($E^0 = 0.12$ V) is much lower than that of Fe^{III}/Fe^{II} ($E^0 = 0.77$ V). This shift in redox potential for the Fe^{III}-EDTA/Fe^{II}-EDTA couple makes the Fe^{III}-EDTA complex much less oxidizing than the solvated Fe^{III} (i.e., $FeCl_3$ in aqueous or H_2O-MeCN solution) which in turn inhibits the oxidation of the aromatic ring to form the aromatic radical cation. When the molar ratio of EDTA/$FeCl_3$ nears 1, the degradation reaction is almost completely inhibited which is consistent with the fact that the high stability of Fe^{III}-EDTA complex (log K = 25.1) makes the removal of solvated Fe^{3+} from solution as Fe^{III}-EDTA complex very efficient even when the Fe^{3+}/EDTA ratio is close to unity at low pH.[23,24]

Stereoelectronic Effects on the Rate of Oxidative Degradation

Table 1 lists the oxidative degradation profiles for all molecules tested and Figure 6 groups the reactive and unreactive molecules. It is evident from the set of unreactive molecules that incorporation of nitrogen atom(s) even in 1 ring of the biaryl systems makes the molecules (**3**, **9**) unreactive. This is probably due to the protonation of



Scheme 3. Proposed mechanism for the formation of oxidative degradation products (alcohol and ketone) via aromatic radical cation intermediate.



Scheme 4. The preferred conformation of the aromatic cation radical derived from **11** places the benzylic C-H σ-bond in the nodal plane of the [pi symbol]-system of the cation radical which minimizes the overlap of the SOMO of the cation radical and the σ-bond of the benzylic CH.

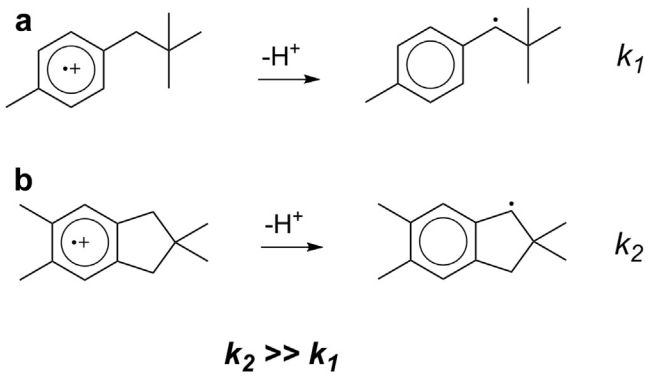
these aromatic rings at low pH which changes the electronic properties of the molecules making them inert toward the Fe^{3+}-mediated oxidation. Similar trend has been observed when one of the aromatic rings bears an amino substituent (**2**, **10**). Compound **12** with a quaternary benzylic carbon does not show any oxidative degradation as expected from the lack of benzylic hydrogen. But, interestingly, compound **11** shows no degradation although it contains a benzylic hydrogen. This observation could be explained in terms of the orientation of the benzylic hydrogen with respect to the π-system of the aromatic cation radical as demonstrated by Onopchenko et al.[25] using *p*-cymene cation radical generated by the oxidation with Co^{3+}. As shown in Scheme 4 (top row), the preferred conformation of the aromatic cation radical derived from **11** places the benzylic C-H σ-bond in the nodal plane of the π-system of the cation radical which minimizes the overlap of the SOMO of the cation radical and the σ-bond of the benzylic C-H. This lack of orbital overlap prevents the loss of proton leading to the benzylic radical and hence renders the molecule unreactive toward oxidation.

The data in Figure 3 show that all the reactive compounds found here only differ in rate by about a factor of 2. Within this factor of 2, the rate of oxidation varies as follows: **1** > **8** > **5** = **7** > **6** > **4**. The oxidative susceptibility trend **8** > **5** = **7** > **6** > **4** may be rationalized qualitatively in terms of the electronic effects of the substituents on the aromatic rings. Going from **4** to **7**, electron density on the aromatic rings increases because of the electron-donating effect of the methoxy group, and the higher electron density makes the ring more susceptible toward oxidation. The methyl substituent (which is an electron-donating group) on **5** makes it equally reactive to the methoxy-substituted **7**. Compound **8** which bears a methoxy substituent on one of the phenyl rings, and chloro and bromo substituents on the second ring, shows higher rate of degradation than **4**, **5**, **6**, and **7**. In this case, as shown in Scheme 4 (bottom row), the aromatic cation radical likely forms on the ethoxy-bearing phenyl ring owing to its higher electron density. The resulting benzylic radical can then be stabilized by the presence of the electron-poor (due to the presence of electron-withdrawing bromo and chloro substituents) second ring. Combination of these 2 electronic effects may be responsible for the higher degradation rate of **8**.

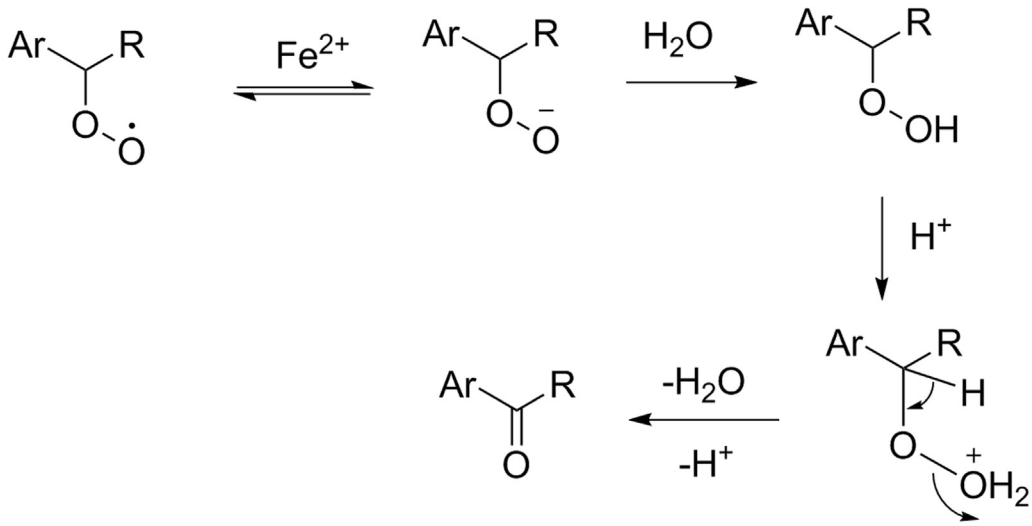
Dextromethorphan (**1**), on the other hand, shows the highest rate of degradation in Figure 6. Baciocchi et al.[26] in an elegant article demonstrated the stereoelectronic effects on the deprotonation of alkylaromatic cation radicals generated by anodic oxidation. As outlined in Scheme 5, the authors showed that the rate of deprotonation from the cation radical **B** is much higher than that from **A**. Because of the conformational constraint imposed on **B**, the σ-orbital of the benzylic C-H and the SOMO of the aromatic cation radical are favorably (coplanar) oriented for maximum overlap leading to facile loss of proton. Similar stereoelectronic effects are most likely operating on the highly constrained structure of dextromethorphan (**1**), facilitating the formation of the benzylic radical.

Solvent Effects in the 0.1 N HCl $FeCl_3$ Reaction: Presence of Acetonitrile

Molecules with low aqueous solubility were tested in 0.1N aqueous HCl/MeCN (75:25 v/v, solvent B in Table 1). Under these conditions, all reactive compounds except **6** give a higher yield of ketone degradation product than alcohol (Table 1). The only reactive molecule in Table 1 with enough solubility to be tested in 0.1N aqueous HCl (no acetonitrile) is dextromethorphan (**1**). Table 1 shows that with 25% acetonitrile present, the ratio of ketone/alcohol was 2.8, whereas without acetonitrile, the ketone and alcohol degradates form in equal amounts from **1**, as expected from Scheme 3. These data suggest that the presence of MeCN as cosolvent may be responsible for the higher yield of ketone in compounds **4-8** (Table 1). Although a detailed understanding of this effect is not central to the current work, we report here some thoughts and experiments around understanding this observation.



Scheme 5. Stereoelectronic effects on the rate of deprotonation of aromatic cation radicals.



Scheme 6. Proposed mechanism for the conversion of the peroxy radical to ketone in MeCN-aqueous HCl medium.

First, we ruled out the involvement of alkoxy radicals. It has been shown previously[19] that the presence of MeOH (1% or more) in the reaction medium quenches the alkoxy radical reactivity. When we performed the degradation reaction of dextromethorphan (**1**) in the presence of MeOH (5:20:75 MeOH:MeCN:0.1N aq HCl), the product distribution ratio between alcohol and ketone did not change with respect to the reaction run in the absence of MeOH (i.e., in 25:75 MeCN:0.1N aq HCl). This observation rules out the involvement of any alkoxy radical in the mechanistic pathway favoring the formation of ketone over alcohol, in the presence of MeCN. We also examined the possibility of the (excess) $FeCl_3$ reacting with the alcohol degradates (formed as in Scheme 3) to form the associated ketone degradates. The alcohol degradate of compound **4**, diphenyl methanol, was tested under similar conditions as Table 1 and found to be unreactive compared to the high ketone yields seen in Table 1. Alcohol groups at the benzylic position appear to stop reactivity as shown in Scheme 3.

The only plausible rationale for higher ketone yields we can speculate involves the Fe^{2+} species which are formed in Scheme 3. It is known[27] that Fe^{2+} can reduce peroxy radicals to peroxy anions (Eq. 3) which will readily protonate (particularly at the low pH in Scheme 3) to form hydroperoxides (Eq. 4).

$$ROO^{\cdot} + Fe^{2+} \rightleftharpoons ROO^{-} + Fe^{3+} \quad (3)$$

$$ROO^{-} + H_2O \rightarrow ROOH + OH^{-} \quad (4)$$

Thus, Fe^{2+} may reduce the peroxy radical formed from the aromatic cation radical (Scheme 3) to the corresponding hydroperoxide. The hydroperoxide formed at low pH can then eliminate water[28] to yield the ketone degradate as shown in Scheme 6. In this way, peroxy radicals produced in the upper portion of Scheme 3 have 2 routes available: the Russell termination[18] in the lower portion of Scheme 3 or the reaction with Fe^{2+} shown in Scheme 6. We propose that the net effect of acetonitrile in the reaction medium leads to a larger role of Scheme 6 and thus to elevated levels of ketone degradates.

Conclusions

In this body of work, we show that Fe^{3+} alone can lead to the oxidation of benzylic carbon of drug molecules. The likely mechanistic pathway involves initial formation of aromatic cation radicals, but the unpaired electron is transferred to the benzylic carbon atom where oxygen addition is favored. Alcohol and ketone degradates result. This oxidation can happen in the solid state in a tablet dosage form, as well as in the $FeCl_3$ forced stress oxidative susceptibility screening procedures typically employed and studied here. Stereoelectronic effects and heteroatom type and placement near the benzylic carbon atom significantly impact reactivity. Much more work is needed to map out a better understanding of heteroatom location and protonation effects on Fe^{3+} reaction rates with these types of drug molecules containing benzylic hydrogen. In these solution studies, a solvent effect on the distribution of oxidative degradation products is observed where, in general, the ketone degradation product is favored over alcohol in aqueous/MeCN reaction medium.

Acknowledgments

We thank Leah Buhler for providing background data, Brittany Pierce for help in the laboratory, and Marcela Nefliu for insightful discussion.

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