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Reaction of amino acids with ferrate(VI): Impact of the carboxylic group on the primary amine oxidation kinetics and mechanism

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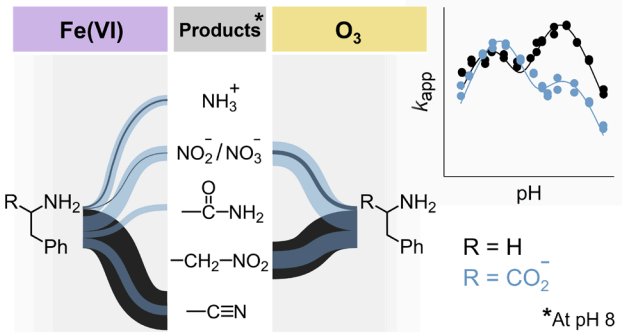


Keywords: Ferrate, rate constants, amino acid, ozone, nitroalkane, nitrile, amide

Synopsis: The elucidated reaction kinetic and mechanism of amino acids with ferrate(VI) contributes to a better understanding of the organic nitrogen fate during water treatment.

Abstract

Ferrate (Fe(VI)) is a novel oxidant that can be used to mitigate disinfection byproduct (DBP) precursors. However, the reaction of Fe(VI) with organic nitrogen, which is a potential precursor of potent nitrogenous DBPs, remains largely unexplored. The present work aimed to identify the kinetics and products for the reaction of Fe(VI) with primary amines, notably amino acids. A new kinetic model involving ionizable intermediates was proposed and can describe the unusual pH effect on the Fe(VI) reactivity toward primary amines and amino acids. The Fe(VI) oxidation of phenylalanine produced a mixture of nitrile, nitrite/nitrate, amide and ammonia, while nitroalkane was an additional product in the case of glycine. The product distribution for amino acids significantly differed from that of uncarboxylated primary amines that mainly generate nitriles. A general reaction pathway for primary amines and amino acids was proposed and notably involved the formation of imines, the degradation of which was affected by the presence of a carboxylic group. In comparison, ozonation led to significantly higher yields of nitroalkanes that could be readily converted to potent halonitroalkanes during chlor(am)ination. Based on this study, Fe(VI) can effectively mitigate primary amine-based, nitrogenous DBP precursors with little formation of toxic halonitroalkanes.

Introduction

Dissolved organic nitrogen (DON) is ubiquitous in natural waters and can form nitrogenous disinfection byproducts (N-DBPs) during chlor(am)ination.[1] Although N-DBPs such as haloacetamides, haloacetonitriles or halonitromethanes are produced at low concentrations in drinking water, they usually account for the majority of the calculated toxicity based on identified DBPs (i.e., toxicity induced by identified and quantified DBPs).[2-4] Therefore, the formation of N-DBPs is of concern, especially considering the general increase in DON in water sources impaired by wastewater effluents, agricultural run-offs, and algal blooms.[5-7] Furthermore, it was recently suggested that the calculated toxicity of identified DBPs represents only a fraction of the measured cytotoxicity, genotoxicity and oxidative stress in drinking water.[3] A significant fraction of toxicity therefore lies in unknown and more complex organic matter structures, prompting fundamental investigations of organic moieties alteration during water treatment. This is particularly true for nitrogenous moieties since N-DBPs are generally associated with higher toxicity. A better understanding of organic moieties transformation during water treatment will help apprehend the formation of identified and unidentified DBPs.

Amino acids, free or combined, and their metabolites account for a significant part of DON, where the total amino acid concentrations typically represent 15–35% of DON,[7, 8] and their role as potential N-DBP precursors has been widely studied.[1, 9-11] Most amino acids contain a primary amine in α position of a carboxylic group. The amine group is highly reactive with chlorine (apparent second-order reaction rate constant: k_{app} = 10^4–10^5 $M^{-1}s^{-1}$ at pH 7),[12] and its transformation may be key to the formation of identified potent N-DBPs.[9] Therefore, the oxidation of primary amines with an alternative oxidant can help mitigate the N-DBP formation.

Ferrate (Fe(VI)) is an iron-based oxidant that has gained interest for micropollutant removal and DBP mitigation.[13-16] In water, Fe(VI) is mostly present as $HFeO_4^-$ or FeO_4^{2-} at near neutral pH (p*K*a = 7.2) and its reaction rate with organic moieties tends to decrease with increasing pH due to the generally lower reactivity of FeO_4^{2-}.[13, 17] In addition, high-valent iron reduction products Fe(IV) and/or Fe(V) were recently found to serve as secondary oxidants in the degradation of several organic moieties.[18-21] These recent studies also highlighted the importance of the choice of buffer. Phosphate has been widely used for its good buffering capacity around neutral pH and its chelating capacity towards Fe(III),[13, 22] but it also inhibits the contribution of Fe(IV)/Fe(V).[18] Removing the contribution of secondary oxidants, which can either be promoted or inhibited by the water matrix,[19, 20, 23] is important to understand the mechanisms and kinetics of the reaction between Fe(VI) and the target compounds. Inhibiting secondary oxidants is a commonly used method when studying ozone (O_3) reactions (i.e., addition of tert-butanol, *t*BuOH, to quench OH radicals).[24] However, it is also important to investigate the contribution of these secondary oxidants to better predict the degradation of target compounds in real waters. This can be done by using non-chelating buffers such as borate.[18]

The reactivity of Fe(VI) with structures such as phenolic, aniline, amine, olefin or organosulfur moieties has notably been studied.[13, 21] However, the oxidation of amino acids by Fe(VI) has received limited attention. The kinetics of amino acid oxidation by Fe(VI) have been studied at pH 12.4,[25] and detailed kinetic and product studies have been conducted on tryptophan and glycine.[26, 27] Tryptophan is a specific case among amino acids, since its side chain, indole, is the primary reaction site. In the case of glycine, the pH dependence of k_{app} cannot be well described by a speciation-based kinetic model.[27] In addition, N_2, N_2O and ammonia have been suggested as the main N-containing products of glycine oxidation.[27] By

88 comparison, the oxidation of aliphatic primary amines by Fe(VI) has recently been shown to
89 form nitrile as a major product and nitrite/nitrate, ammonia, and nitroalkane as minor
90 products.[21] In addition, k_{app} for the methylamine oxidation, which is the uncarboxylated
91 equivalent of glycine, was 18 $M^{-1}s^{-1}$ at pH 9 in phosphate, which is much lower than k_{app} for
92 the glycine oxidation (145 $M^{-1}s^{-1}$ at pH 9) measured by Noorhasan et al.[21, 27] These large
93 differences in reaction products and kinetics between glycine and methylamine raise the
94 question of the impact of the carboxylic substituent on the Fe(VI)/primary amine reaction
95 pathways. Considering the ubiquity of amino acids in natural waters and their potential role
96 in the formation of N-DBPs, a thorough mechanistic investigation of their reaction with
97 Fe(VI) is warranted.
98 This study aims to understand the oxidation of primary amine moieties by Fe(VI). The
99 oxidation kinetics and degradation products of two amino acids were investigated: glycine
100 and phenylalanine. Glycine was chosen because it is the simplest amino acid without a side
101 chain, and a full speciation of its N-containing products has not been provided to date.
102 Phenylalanine, with a phenyl side chain, was selected to determine the impact of the side
103 chain on the Fe(VI) oxidation chemistry of amino acids. Phenylalanine kinetics and products
104 were compared to their corresponding uncarboxylated equivalent, phenethylamine, to
105 establish a general kinetic model and reaction pathways for the oxidation of primary amines
106 with Fe(VI). The practical implications of the amine transformation by Fe(VI) were
107 discussed, especially in comparison with ozonation.
108

109 ## Materials and Methods

110 **Standards and reagents** The purity and suppliers of all chemicals and solvents are
111 given in Table S1 (supplementary information, SI). The 2-nitroethylbenzene standard was

prepared from the ozonation of phenethylamine, which is a method validated in a previous study.[21] Potassium ferrate, which was used in previous studies,[28-30] was purchased from Sigma-Aldrich (K_2FeO_4, PN 723835, 88–98% w/w purity upon purchase,[31] but 60% w/w purity in this study due to the slow reduction of ferrate to ferric oxide). This aged ferrate was previously tested against high purity ferrate and gave similar results for the oxidation of iodide and olefinic compounds.[28, 30, 32] Stock solutions of Fe(VI) (3–4 mM) were freshly prepared by dissolving potassium ferrate in pure water (pH ≈ 9.2), followed by rapid filtration through a 0.2-μm PVDF syringe filter (Whatman) and spectrophotometrically standardized (ε_{510} = 1150 $M^{-1}cm^{-1}$).[33] Stock O_3 solutions were prepared by sparging O_3/O_2 mixtures produced using a LAB-1 ozone generator (Ozone Tech., Daejeon, Korea) in pure water cooled in an ice bath. The O_3 stock concentration (1.0–1.3 mM) was spectrophotometrically standardized (ε_{260} = 3200 $M^{-1}cm^{-1}$).[24]

Kinetic and product experiments. Kinetic studies were performed at room temperature (22±1°C) in the presence of phosphate or borate (10 mM as phosphorus or boron) at pH 5.6–12. At pH > 9, NaOH was added (up to 5 mM) to adjust the phosphate buffer pH, taking into account the increase in pH upon Fe(VI) addition. In all experiments, the ionic strength was not adjusted and varied between 10 and 35 mM. Excess Fe(VI) (10–15 times) was spiked into a 5–10 μM amine/amino acid solution under rapid mixing. At predetermined sampling times, an aliquot was withdrawn to quantify Fe(VI); another was quenched using thiosulfate ([thiosulfate] = 10×$[Fe(VI)]_0$), filtered through a 0.22-μm PVDF syringe filter (Whatman), and kept for amine/amino acid quantification within 10 h. The apparent second-order rate

constants (k_{app}) of amine/amino acid decay were determined as previously described (eq 1):[13, 21]

$$-\ln\left(\frac{[\text{Compound}]_t}{[\text{Compound}]_0}\right) = k_{app}\int_0^t [\text{Fe(VI)}]dt \quad (1)$$

k_{app} measurements of the Fe(VI) decay were also conducted at pH 9 in excess of amine over Fe(VI) (10–25 times, pseudo first-order conditions).

Product formation experiments were conducted in triplicate with 80 µM amino acid and Fe(VI):amino acid ratios of 0.5–15 at pH 7–9. Headspace-free conditions were ensured to limit the loss of volatile products (e.g., nitromethane) until all Fe(VI) was consumed (between 1 h and 2 days). Stoichiometry experiments were conducted at pH 9.4–9.8 in 5 mM phosphate + 1 mM borate (used for a better pH control). At this pH, Fe(VI) self-decay is slow ($k_{app} \leq 10^{-1}$ $M^{-1}s^{-1}$)[31] compared to its reactivity toward amino acids ($k_{app} \geq 2$ $M^{-1}s^{-1}$, see Figure 1b). The formation of products from ozonation was determined in duplicate at pH 7 and 8 in the presence of 50 mM *t*BuOH (an OH radical, $^{\bullet}OH$, quencher) or 0.8 mM H_2O_2 (an $^{\bullet}OH$ promoter).[24] Product yields were determined by a linear correlation between product formation and amino acid consumption (Figures S1–S4).

Kinetic fitting and partial charge calculation. Nonlinear least-square regressions were applied for the kinetic data fitting using SigmaPlot, version 14.0 (Systat Software, Inc.). Details of the kinetic model development are given in Text S2 (SI). The partial atom charges were estimated via Chem3D 12.0 (ChemOffice, Cambridge Soft.) using the extended Hückel calculation method after minimizing the energy using the MM2 force field method.[34]

Analytical methods. Fe(VI) was spectrophotometrically monitored at 415 nm after a reaction with 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS).[35] All phenyl-

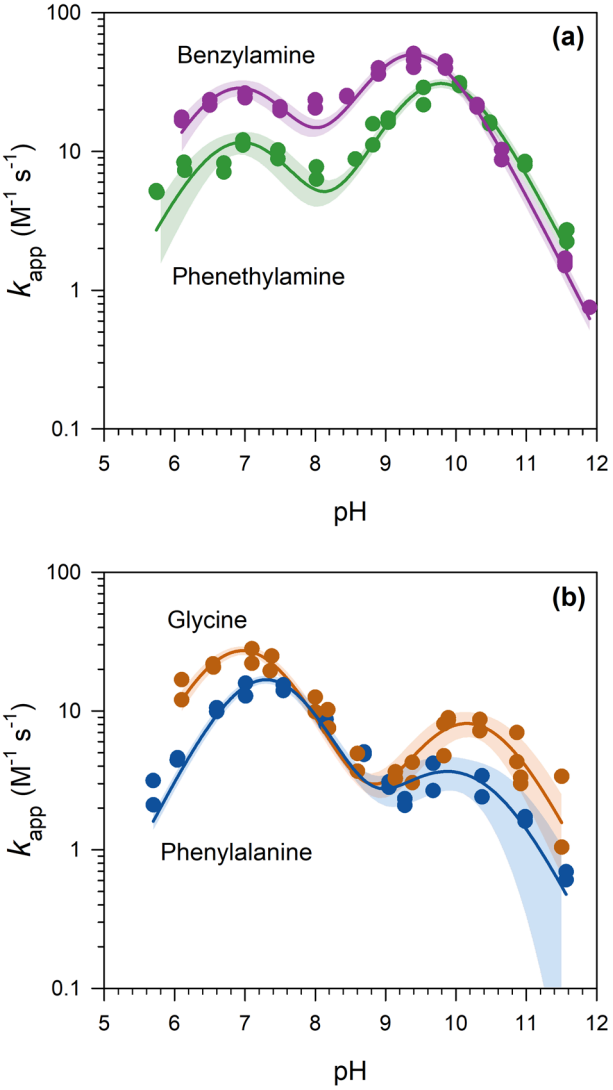
155 containing compounds were monitored by HPLC-UV (Ultimate 3000, Dionex).[21] Glycine,
156 inorganic nitrogen (ammonia, nitrite, nitrate, cyanate) and small organic acids (formate,
157 acetate, oxalate, oxamate) were monitored by ion chromatography (940 Professional IC
158 Vario, Metrohm).[21] Formaldehyde was measured by HPLC-UV after derivatization with 2,4-
159 dinitrophenylhydrazine.[36]
160

161 ## Results and Discussion

162 **Reaction stoichiometry and kinetics.** The apparent reaction stoichiometry of glycine
163 and phenylalanine oxidation by Fe(VI) (Δ[Fe(VI)]/Δ[amino acid]) was investigated in
164 phosphate at pH 9.5 and found to be 2–2.5 for glycine and 2.5–3 for phenylalanine (Figure
165 S5). The phenylalanine stoichiometry was consistent with the stoichiometry previously
166 determined for uncarboxylated primary amines under identical conditions.[21]
167 Good linearity was observed between amine/amino acid decay and Fe(VI) exposure
168 across the pH range of 5.6–12 (examples are shown in Figure S6), and between Fe(VI) decay
169 and time when using an excess amine/amino acid at pH 9 (previously shown for methylamine
170 and phenethylamine,[21] see Figure S7 for amino acids). These results suggest that the reaction
171 follows second-order kinetics (first-order with respect to each reactant). Figure 1 shows k_{app}
172 of two primary amines (benzylamine and phenethylamine) (Figure 1a) and two amino acids
173 (glycine and phenylalanine) (Figure 1b) determined in phosphate as a function of pH. Two
174 bell shapes were observed across the studied pH range. The first one occurred at pH 6–8 and
175 was more pronounced for amino acids. In this pH range, k_{app} was similar for primary amines
176 (up to 5–26 $M^{-1}s^{-1}$) and amino acids (up to 5–27 $M^{-1}s^{-1}$). The second bell shape was observed

177 at pH 9–11 and more pronounced for primary amines. In this pH range, k_{app} was significantly

178 higher for primary amines (up to 17–54 M^{-1} s^{-1}) than for amino acids (up to 2.5–9 $M^{-1}s^{-1}$).



179

180 FIG.1

181 **Figure 1.** pH dependence of the apparent second-order rate constants (k_{app}) for the oxidation

182 of (a) primary amines and (b) amino acids by Fe(VI) in phosphate. The symbols represent

183 experimental data, the lines represent the fitting, and areas represent the 95% confidence

184 interval of the fitting (see Table S9).

185

The k_{app} were also determined in excess of amino acids at pH 9. k_{app} of 7.9±0.7 M^{-1} s^{-1} and 10±1.4 M^{-1} s^{-1} were obtained for glycine and phenylalanine, respectively (Figure S8). These k_{app} were about 2.6 and 3.3 times higher than k_{app} determined in excess of Fe(VI), which is consistent with the reaction stoichiometry (Figure S5). The same consistency between k_{app} and stoichiometry was previously found for phenethylamine and methylamine.[21]

The kinetics of glycine significantly differed from the literature.[27] In a previous study, k_{app} were determined by monitoring Fe(VI) decay using stopped-flow spectrophotometry in the presence of excess glycine (10–150 mM) and high phosphate concentration (0.2 M). At pH 9, Noorhasan et al. reported a k_{app} of 145±9 M^{-1} s^{-1},[27] well above 7.9±0.7 M^{-1} s^{-1} reported here (Figure S8). The impact of buffer concentration was tested on phenethylamine and revealed an enhancement of the rate constants by both phosphate and borate buffers, which was not due to an increase in ionic strength (see Text S1). Unless this effect is much stronger for glycine (which couldn't be verified due to analytical limitations), the increase in reactivity observed due to the buffer (1.5 times higher when increasing the phosphate concentration from 10 to 100 mM at pH 9) is not sufficient to explain the higher glycine k_{app} observed by Noorhasan et al. (18 times higher). Along with the phosphate concentration, the use of a large excess of glycine (10–150 mM) may have contributed to the discrepancies between the two studies. Regardless, rate constants determined in diluted solutions and with lower buffer concentrations may be more representative of the real water matrix condition.

Modeling the pH dependence of k_{app}. In contrast to many organic compounds,[23, 37, 38] the pH-k_{app} dependence of primary amines with or without a carboxylic group did not follow a simple species-specific model (using $HFeO_4^-/FeO_4^{2-}$ (p*K*a = 7.2)[17] and ammonium/amine (p*K*a = 9.24–9.84)) (see Figure S10 and Text S2.1). Instead, the bell shapes suggest the existence of other proton-involved mechanisms, such as the reversible formation of an

intermediate for which (de)protonation is required before further degradation.[39, 40] A model using two ionizable intermediates (one for the neutral amine and one for the protonated amine) was found to accurately describe the pH-k_{app} dependence for primary amines and amino acids (shown by the lines in Figure 1). The final model contained two constants for the reaction between $HFeO_4^-$ and the amine (neutral and protonated), and two constants of the equilibrium between the intermediate degradation to the reactants and its degradation to further products (details are given in Texts S2.2 and S2.3, and the final model parameters are shown in Table S9). These constants suggest that $HFeO_4^-$ is the only Fe(VI) species reactive towards the amine, and that the formed intermediates require deprotonation to undergo further degradation. The lack of reactivity of FeO_4^{2-} is consistent with the typical Fe(VI) reactivity with organic moieties.[41]

Despite the kinetic evidence that supports the formation of ionizable intermediates, they were not identified, and their nature can only be hypothesized. The formation of metal/substrate complexes that can undergo reversible deprotonation has been proposed for Fe(VI) and permanganate,[37, 40] but the formation of complexes from the reaction between primary amines and Fe(VI) and their role in the observed kinetics still remain to be experimentally demonstrated.

Effect of high-valent iron intermediates on k_{app}. The kinetics determined in phosphate buffer shown in Figure 1 only represent the Fe(VI) contribution.[18, 21] To investigate the involvement of secondary oxidants Fe(IV)/Fe(V), phosphate can be substituted with borate. The k_{app} determined in borate buffer corresponds to the contribution of Fe(VI) and Fe(IV)/Fe(V).[18, 19] By comparing the ratio between k_{app} determined in phosphate and borate buffers, the relative contribution of Fe(VI) and Fe(IV)/Fe(V) can be estimated (see details in Text S3).[20, 21] At pH 8, the contribution of Fe(IV)/Fe(V) was found to increase over time

from approximately 30% to 60% for both amino acids (Figure S13). By comparison, similar Fe(IV)/Fe(V) contribution in simple primary amine oxidation has been suggested (30–40% at pH 8).[21] These contributions are much lower than the Fe(IV/Fe(V) contribution reported for sulfamethoxazole and bisphenol S (> 70% at pH 8) and slightly higher than those reported for phenol and bisphenol F (20–30% at pH 8).[20] These differences might notably be due to a competition between Fe(IV)/Fe(V) self-decay and their reactivity with the substrate.

Reaction products and yields. The products of the oxidation of phenylalanine and glycine by Fe(VI) were monitored at pH 7–9 in phosphate buffer and pH 8 in borate buffer. The experimental data for all products are shown in Figures S1 and S2, and the corresponding chemical structures are shown in Table S2. The nitrogen-containing product distribution is shown in Figure 2. The formation of a mixture of phenylacetonitrile, phenylacetamide, nitrite/nitrate and ammonia was observed for phenylalanine, with no dominant product across the studied pH range. In phosphate buffer, when pH increased from 7 to 9, the yields of phenylacetonitrile and nitrite/nitrate decreased from 31% to 10% and from 39% to 7%, respectively (Figure 2a). Conversely, the yields of phenylacetamide and ammonia increased from 2% to 25% and from 19% to 39%, respectively. The phenyl-containing carbonyl speciation shifted from phenylacetic acid and phenylacetaldehyde (3% at pH 7 to 31% at pH 9) to benzaldehyde and benzoic acid (44% at pH 7 to 7% at pH 9) with increasing pH (Figure S1, d & e). Minor yields of phenylpyruvate were also detected (1–7%, Figure S1f).

Similar products were formed from glycine compared to phenylalanine, such as cyanate, nitrite/nitrate, ammonia, formaldehyde, and formate (Figure 2b and Figure S2). Although oxamate was not observed for glycine (Figure S2b), its uncarboxylated equivalent, formamide, might account for a significant fraction of the missing nitrogen. Formamide could not be quantified in this study due to analytical limitations. This hypothesis is based on the

formation of phenylacetamide, which is the equivalent product of formamide from phenylalanine (Figure 2a). A notable difference between phenylalanine and glycine was found for the nitrogen oxidation product. A significant formation of nitromethane was observed from glycine (up to 25%, Figure 2b), whereas the formation of 2-nitroethylbenzene was negligible from phenylalanine (<1%, Figure 2a).

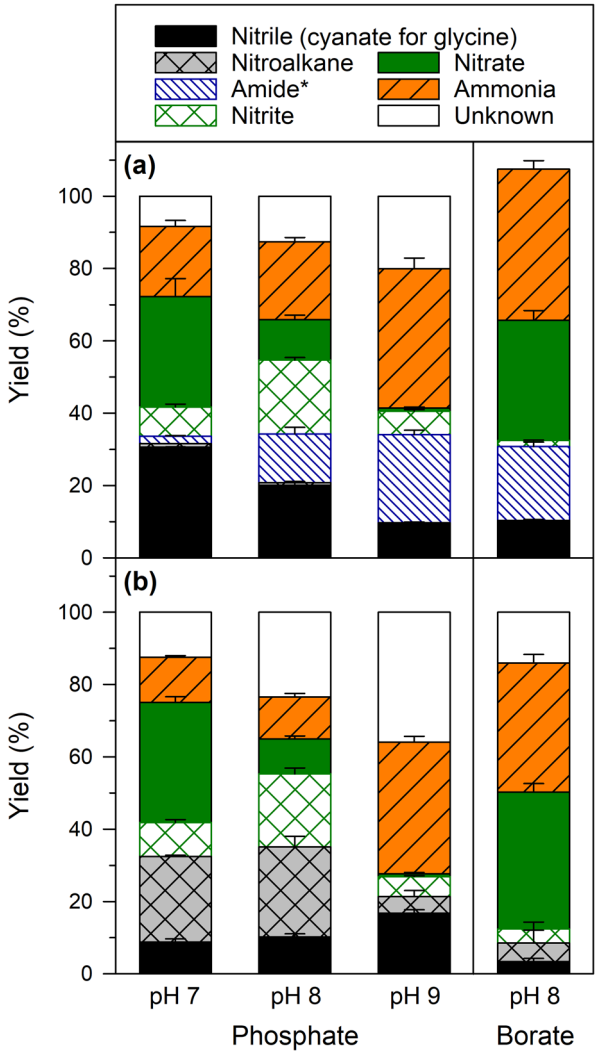


Figure 2. Molar yields of nitrogen-containing products from the oxidation of (a) phenylalanine and (b) glycine by Fe(VI). The yield determinations and the full names of the products are shown in Figures S1 and S2. *The formamide formation from glycine could not be measured.

Experimental conditions: $[\text{Amino acid}]_0$ = 80 μM, $[\text{Fe(VI)}]_0$ = 20–480 μM, pH 7–9 (10 mM phosphate or borate).

Previously, the oxidation of glycine by Fe(VI) at pH 9 was reported to lead to 25–40% ammonia, 75–85% acetate, and 20–40% CO_2.[27] In addition, N_2 and N_2O were suggested as co-products of acetate. The observed ammonia formation in the present study is consistent with Noorhasan et al. (36% at pH 9, Figure 2b). However, acetate was not detected, while formaldehyde (18% at pH 9) and formate (26% at pH 9) were present (Figure S2, d & e). Cyanate was also formed (17% at pH 9, Figure 2b), while it was previously not detected. The previously proposed formation of N_2 and N_2O cannot be dismissed considering the significant fraction of nitrogen missing at pH 9 (35%, Figure 2b), but it is less likely because N_2 and N_2O were proposed as co-products of acetate, which was not formed here. Instead, formamide is proposed as a more likely product based on the formation of phenylacetamide from phenylalanine (Figure 2a), although experimental proof is still needed.

The products obtained from phenylalanine and glycine greatly differed from the products previously obtained for phenethylamine and methylamine, respectively.[21] At pH ≥ 8, the oxidation of uncarboxylated primary amines in phosphate buffer mostly produced nitrile (or cyanate for methylamine) (≥ 90%) with minor yields of nitrite/nitrate and ammonia.

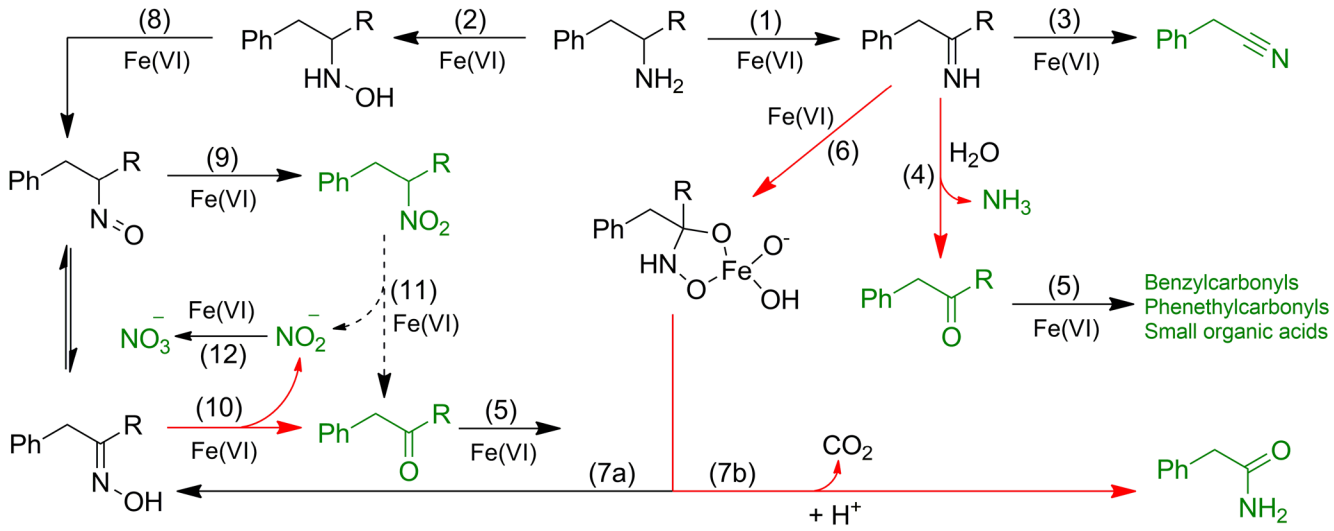
In borate buffer, the product speciation of phenylalanine and glycine shifted to lower nitrile (or cyanate) yields (from 11–20% to 3–10%) and higher ammonia yields (from 13–22% to 34–42%) (Figure 2). This was also observed for uncarboxylated primary amines.[21] In addition, phenylacetamide and nitrite/nitrate yields slightly increased in borate buffer for phenylalanine (+ 3–7%, Figure 2a). For glycine, the nitrite/nitrate yield increase in

290 borate buffer was more pronounced (+12%), while the nitromethane formation was greatly
291 inhibited (from 25% to 5%) (Figure 2b).

292 **Pathways and mechanisms of phenylalanine and phenethylamine oxidation by**
293 **Fe(VI).** Based on the products identified from the oxidation of phenylalanine and
294 phenethylamine, a general pathway is presented in Scheme 1. The products in green were
295 quantified in this work or in a previous study.[21] Red arrows represent pathways that are
296 favored by the presence of a carboxylic group on the alpha carbon (Cα) of the amine, which
297 is discussed in this section.

298 *Initial step.* The possible pathways for the initial step are summarized in Scheme S1 and
299 developed here. An electron abstraction from the lone pair of the nitrogen was proposed for
300 the oxidation of aniline and tramadol (tertiary amine) by Fe(VI).[42, 43] The resulting aminium
301 radical cation can deprotonate to a N-centered radical or form a carbon-centered radical via
302 either a 1,2-H-atom shift or decarboxylation (for amino acids, decarboxylation of aminium
303 radical cation is shown in Scheme 2).[44, 45] The same N-centered or C-centered radicals might
304 be formed from hydrogen abstraction at N or Cα, which has been suggested for the reaction
305 of amines with •OH and organic radicals.[45, 46] N-centered radicals may notably undergo
306 oxygen transfer with Fe(VI)/Fe(V), leading to N-hydroxylation (pathway 2 in Scheme 1),[47-49]
307 while C-centered radicals are known to rapidly react with O_2 to form peroxyl radicals and
308 further degrade to an imine (pathway 1 in Scheme 1) and a superoxide.[50] Experimental
309 evidence of C-centered radical formation from phenylalanine and phenethylamine was
310 attempted by monitoring superoxide released from the peroxyl radical degradation with
311 tetranitromethane.[51] The results suggest that some superoxide was formed, at estimated yields
312 of 30–47% of the consumed phenylalanine and phenethylamine at pH 7 (see details in Text
313 S4). A significant fraction of the imine (1) is therefore formed via C-centered radicals but

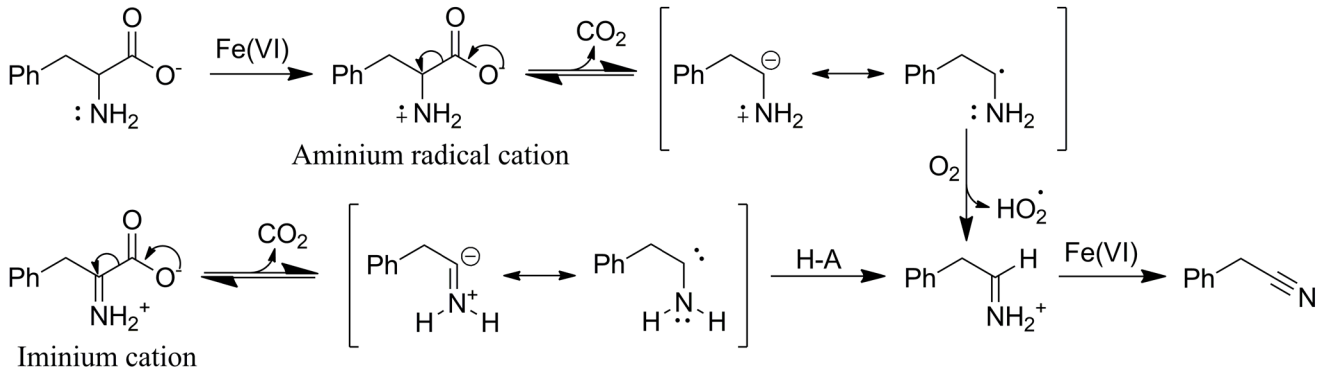
other pathways cannot be excluded. Such pathways may involve Fe(VI)-amine complexes that undergo consecutive hydrogen abstractions without releasing radical intermediates, as proposed for alcohol oxidation.[52] Similarly, oxygen transfer (2) may occur without the release of radical, as for the N-hydroxylation of aniline.[53]



Scheme 1. Proposed degradation pathways and mechanisms of phenylalanine (R = CO_2^-) and phenethylamine (R = H) by Fe(VI). The green structures represent quantified compounds, and the red arrows represent pathways favored by the carboxylate substitution. The dotted arrow indicates a slow reaction.

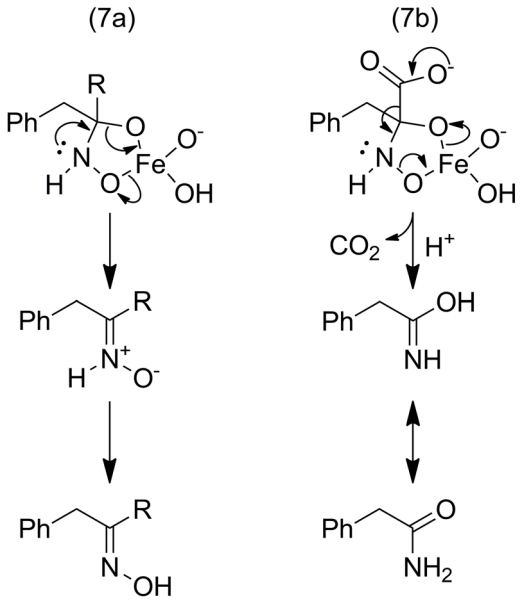
Imine pathway. In the case of uncarboxylated primary amines, the main reaction pathway for imine is its oxidation to nitrile (3).[21] Although the mechanism remains unclear, the selective oxidation of primary amines to nitriles has been widely studied in organic synthesis,[54] and hydrogen abstraction from the C of the imine by the oxygen of a strongly polarized oxoammonium salt has notably been proposed.[55] Similar hydrogen abstraction by the oxygen of Fe(VI) may occur in pathway (3). The Fe(VI):phenethylamine stoichiometry of 2.5:1 at pH 9.4-9.8 combined with the high nitrile yield at this pH (>90%) suggests that the

oxidation of imine to nitrile requires less than 2 Fe(VI) (at least 1 Fe(VI) is required for the oxidation of amine to imine).[21] In the case of amino acids (except glycine), decarboxylation is necessary to obtain a nitrile. It is suggested here that decarboxylation can occur via either the formation of an aminium radical cation (e.g., formed after an initial electron abstraction from the neutral amine) or the iminium cation (imine pK_a values are usually near neutral pH) (Scheme 2).[56-59] In both cases, a decarboxylated imine is released, which is mostly oxidized to nitrile.[21]



Scheme 2. Proposed decarboxylation pathways.

The imine can also undergo hydrolysis and decompose to a carbonyl and ammonia via well-known mechanisms (4).[60-62] Further oxidation of carbonyls is then possible (5) (e.g., oxidation of aldehyde to carboxylic acid, oxidation of phenylpyruvate to benzaldehyde or phenylacetic acid, data not shown). The cycloaddition of Fe(VI) onto the imine is also proposed (6), similar to the adduct previously suggested for the reaction of imines with permanganate.[63, 64] The decomposition of this cycloaddition adduct can be initiated by delocalization of the nitrogen lone pair onto the Cα-N bond (7a, Scheme 3), which leads to an aldoxime. In the presence of a carboxylic group, the decomposition can also be initiated by decarboxylation and release an amide (7b, Scheme 3).



Scheme 3. Possible degradation pathways of the proposed Cα-N cycloaddition intermediate that results from the addition of Fe(VI) onto the imine (pathway 6, Scheme 1).

A comparison between the phenethylamine[17] and phenylalanine product distributions suggests that the presence of a carboxylic group favors reaction pathways (4) and (6) (< 10% ammonia yield for phenethylamine vs. 21–63% ammonia/phenylacetamide yield for phenylalanine) compared to reaction pathway (3) (imine yields of 61–90% for phenethylamine vs. 10–31% for phenylalanine). This observation is supported by several reaction mechanisms. First, decarboxylation is a necessary step to obtain a nitrile. Therefore, this pathway may be inhibited for phenylalanine. The increasing nitrile yields with decreasing pH for phenylalanine may notably be explained by the increasing fraction of iminium cation and its acid-assisted decarboxylation (Scheme 2). Conversely, the increasing yields of amide and ammmonia with increasing pH are consistent with the competition between pathways (3), (4) and (6). Second, the presence of a carboxylic group increases the electrophilicity of the imine carbon, which can favor the competitive nucleophilic attack (imine hydrolysis) and consequently inhibit the nitrile

367 formation. Partial charge calculations for the neutral imine and deprotonated carboxylate using
368 the extended Hückel semi-empirical method shows a higher positive partial charge on the imine
369 carbon when it was substituted by a carboxylate (δ = +0.584e for phenylalanine) compared to
370 the absence of a substituent (δ = +0.270e for phenethylamine). In addition, the absence of amide
371 formation from phenethylamine is consistent with pathway (7b) (Scheme 3), which requires
372 the presence of a carboxylate. The other degradation pathway for the Cα-N cycloaddition
373 intermediate is aldoxime formation (7a), which is indistinguishable from the N-hydroxylation
374 pathway (2) in terms of products.

375 *N-hydroxylation pathway.* When N-hydroxylation occurs (2), the produced
376 hydroxylamine is rapidly oxidized to a nitroso compound (8),[65, 66] which can tautomerize to
377 an aldoxime (Scheme 1).[67] The former is oxidized to nitroalkane (9), while the latter is
378 oxidized to nitrite (10), which is further oxidized to nitrate (12) (Scheme 1).[21, 65, 66, 68]
379 Nitroalkane can also be oxidized to nitrite (11), but this reaction was previously found to be
380 quite slow at pH 7 and may not be a significant reaction pathway for nitrite/nitrate
381 formation.[21] N-Hydroxylation has been shown to be a relevant pathway in the Fe(VI)
382 oxidation of phenethylamine but only at pH 7 (33% in phosphate).[21] For phenylalanine, N-
383 hydroxylation is also enhanced at lower pH but with overall higher yields (6-43% at pH 9–7
384 in phosphate, Figure 2a). However, the main difference lies in the product speciation after N-
385 hydroxylation. For phenethylamine, the N-hydroxylation products were 58% nitroalkane and
386 42% nitrite/nitrate, while only nitrite/nitrate was formed from phenylalanine (Figure 2a).[21]
387 This shift from nitroalkane to nitrite/nitrate between amine and amino acids has been
388 observed for ozonation,[69] although nitroalkanes can still be produced (see the section
389 "comparison with ozone and $^{\bullet}$OH"). Lim et al. suggested that this shift might come from the
390 decarboxylation of the nitroso compound (shown in Scheme S2), which forms a

391 decarboxylated aldoxime that is efficiently oxidized to nitrite/nitrate by both O_3 and Fe(VI)
392 (10) (Scheme 1).[21] Another possibility is the stabilization of the aldoxime by hydrogen
393 bonding between the carboxylate and N-OH, which further shifts the tautomeric equilibrium
394 toward aldoxime and hence the nitrite/nitrate formation (Scheme S2).[67]

395 Unlike phenylalanine, the oxidation of glycine by Fe(VI) showed that nitromethane
396 could be produced (Figure 2b). Supplementary experiments conducted at pH 7 on
397 methylamine, which is the uncarboxylated equivalent of glycine, showed a significantly
398 higher proportion of nitroalkane (40%) compared to phenethylamine (19%) (Figure S16).
399 This difference may be due to the lack of substitution on Cα of the amine for methylamine
400 (primary C) compared to phenethylamine (secondary C). Similarly, Cα of the amine with a
401 higher degree of substitution in phenylalanine (tertiary C) may inhibit the nitroalkane
402 formation compared to glycine (secondary C), although mechanistic considerations are
403 uncertain. The nitroalkane formation from other amino acids must be investigated to
404 conclude whether nitromethane formation from glycine is a specific case.

405 *Effect of high-valent iron intermediates on reaction pathways.* While the reactivity of
406 Fe(IV)/Fe(V) is inhibited in the presence of phosphate buffer, it may be involved in the
407 oxidation of amino acids in real waters. The contribution of Fe(IV)/Fe(V) can be estimated at
408 pH 8 by comparing the product speciation in phosphate and borate buffer (Figure 2). The
409 main effect of borate buffer was the product shift from nitrile to ammonia (Figure 2), which
410 has also been reported for uncarboxylated primary amines.[21] This shift suggests that
411 Fe(IV)/Fe(V) affects the primary amine oxidation products with or without a carboxylic
412 group by favoring imine hydrolysis (4) over imine oxidation to nitrile (3). In addition, N-
413 hydroxylation (2) and/or Cα-N cycloaddition (6) may be favored by Fe(IV)/Fe(V), although
414 the increase was marginal (< 10% increase for phenylacetamide and nitrite/nitrate formation

from phenylalanine, Figure 2a). Finally, the clear shift from nitrite (and nitromethane for glycine) to nitrate in borate buffer suggests a fast oxidation of nitrite and nitromethane by Fe(IV)/Fe(V) relative to the oxidation of amino acids (Figure 1).

Comparison with ozone and •OH. The oxidation of serine and glycine by ozone and •OH has been reported to form mainly nitrate and ammonia, respectively, at pH 8–8.5.[70, 71] However, McCurry et al. reported the formation of up to 26% nitromethane after ozonation at pH 7, which formed trichloronitromethane (chloropicrin) upon chlorination.[72] Subsequent studies showed low nitrate yields at low O_3 doses or short contact times and high nitrate yields at high O_3 doses or long contact times, which indicates the presence of an intermediate that can be oxidized to nitrate.[73, 74] Nitroalkane may be an intermediate formed during amino acid ozonation that has been overlooked due to an absence of monitoring or experimental conditions involving large excesses of O_3.

Therefore, partial ozonation of phenylalanine and glycine was performed in the presence of *t*BuOH to investigate the formation of products from the reaction of amino acids with O_3 (detailed data and yield determination are shown in Figures S3 and S4). The ozonation of phenylalanine and glycine at pH 7 led to 10% and 38% nitroalkane, respectively; the remainder was mostly recovered as nitrate (Figure 3). Increasing pH to 8 was found to enhance nitroalkane formation to 29 and 54% for phenylalanine and glycine, respectively. As previously reported,[70, 74] when the •OH formation was promoted (i.e., O_3/H_2O_2), the product speciation shifted to ammonia for glycine (Figure S17). Almost no N-containing products were recovered from phenylalanine (< 20%) due to the very high reactivity of the benzyl side chain with •OH, forming tyrosine which is rapidly further oxidized.[75, 76] Overall, the product speciation obtained from phenylalanine and glycine ozonation confirms that the formation of nitroalkane is possible and at higher yields compared to Fe(VI), especially at a more basic

pH. At pH 8, when using Fe(VI) and O_3, phenylalanine produced <1% and 29% nitroalkane, respectively, while glycine produced 25% and 54% nitroalkane, respectively (Figures 2 and 3).

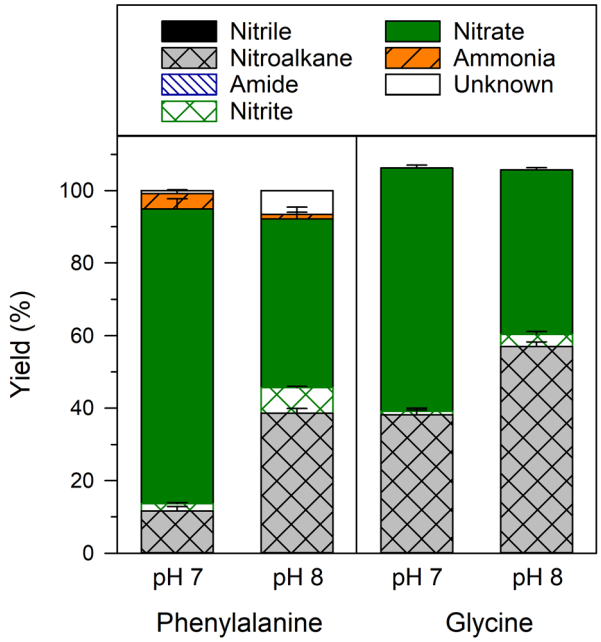


Figure 3. Molar yields of nitrogen-containing products from the oxidation of phenylalanine and glycine by O_3. The yield determinations are shown in Figures S3 and S4 and the full names of the organic structures. *The formamide formation from glycine was not measured. Experimental conditions: $[\text{Amino acid}]_0$ = 80 µM, $[O_3]_0$ = 80–480 µM, 50 mM *t*BuOH, pH 7–8 (5 mM phosphate), duplicated experiments.

Practical implications. Phenylalanine oxidation by Fe(VI) led to a complex mixture of nitrite/nitrate, ammonia, nitrile and amide. A similar product speciation was observed for glycine oxidation with the addition of nitroalkane. The oxidation of other amino acids such as alanine, valine or (iso)leucine is expected to form similar products, while amino acids with reactive side chains such as tryptophan, cysteine or tyrosine should form different products.[13,

[26] In real waters, the majority of amino acids are combined in peptides. The lack of reactivity observed for N-acetylphenylalanine (Figure S18) suggests that peptide bonds are unreactive toward Fe(VI). Therefore, the N-terminal and reactive side chains are expected to be the main reactive sites, and the N-terminal is expected to be the main site of transformation of the organic N in amino acids.

When Fe(VI) is used in water treatment, nitriles, amides, nitrite, nitrate, ammonia and potentially nitroalkanes can be formed from amino acids. Nitriles are expected to remain stable during eventual postchlorination and do not induce significant cytotoxicity or oxidative stress in *in vitro* bioassays.[21] Amides also resist chlorination, but their biological effect (e.g., cellular toxicity) is currently unknown. Specific side chains such as a carboxylic group (i.e., aspartic acid) can promote halogenation on Cα of nitrile and potentially of the amide, which forms concerning N-DBPs.[9] Therefore, the reactivity of chlorine with nitriles and amides from specific amino acids requires further investigation. In contrast, nitroalkanes are known to be reactive toward chlorine and form potent halonitroalkanes.[77, 78] In addition, the formation of nitrite can be of concern, since it can enhance the formation of halonitromethanes during chlorination.[79, 80]

Based on the observed products from the oxidation of phenylalanine and glycine, using Fe(VI) instead of O_3 is likely to reduce the health risks associated with the formation of nitroalkanes when subsequent chlorination is applied, especially at pH slightly above neutral. Further investigation is nevertheless necessary on the impact of amino acid structures or Fe(VI)/O_3 treatment conditions on nitroalkane yields. The effect of Fe(IV)/Fe(V) on nitrite and nitroalkane yields should also be evaluated in various real waters, since Fe(IV)/Fe(V) can efficiently oxidize nitrite and nitroalkane to harmless nitrate or be quenched by water matrix components such as dissolved organic matter.[19, 21]

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Appendix A. Supplementary data

4 texts, 9 tables, 18 figures and 2 schemes are available for further information addressing materials, experimental procedures and additional data. This material is available free of charge via the Internet at

Notes

The authors declare no competing financial interest.

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