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Reactions of p-Substituted Phenols with Nitrous Acid in Aqueous Solution

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ABSTRACT: The reaction of phenols with nitrite (nitrous acid HONO, or its conjugated base, NO_2^-) is of importance in stomach fluids (low pH) and in atmospheric hydrometeors (mild acid and basic pH). The initial reaction associated with the oxidation/nitration of 4-substituted phenols promoted by HONO/ NO_2 depends on the pH of the solution. At low pH, the initial step involves the reaction between HONO and phenol, whereas at basic conditions this involves an electron transfer from the phenoxo anion to nitrogen dioxide (NO_2) producing the nitrite anion. The rate of both processes is determined by the donor capacity of the substituent at the 4-position of the phenol, and the data obtained at pH 2.3 follow a linear Hammett-type correlation with a slope equal to -1.23 . The partition of the gaseous intermediates (NO and NO_2) makes the rate of HONO-mediated oxidation dependent on their gas–liquid distribution. At low pH, the main process is phenol oxidation, even in oxygen-free conditions, and the presence of any 4-substituted phenol decreases the rate of HONO auto-oxidation. © 2013 Wiley Periodicals, Inc. *Int J Chem Kinet* 46: 143–150, 2014

INTRODUCTION

Nitrite is a small molecule that plays important roles in widely different fields such as air pollution [1] and phenol metabolism in the human stomach [2,3]. In spite of the simplicity of its chemical structure, its chemistry and reaction kinetics are very complex due to the large number of interacting compounds produced by nitrite

in aqueous solutions [2–4] with capacity to oxidate and/or nitrate (or nitrosate) a variety of phenols and polyphenols present in polluted air [1,5–7], foods [8], and beverages [3].

In stomach fluids (pH 2.8), nitrite is mainly present in its acidic form, nitrous acid (HONO), due to its pK_a value ($\text{pK}_a = 3.2$) [9]. On the other hand, in atmospheric particles or drops (pH 5–7), nitrite is predominantly present as its conjugated base (NO_2^-), and different reaction pathways for its decomposition and reactions with phenols can be envisaged.

Nitrite is readily decomposed in diluted aqueous solutions. Braida and Ong [10] have shown that decomposition/oxidation of nitrite was faster at lower pH values. At pH 2.85 approximately 40% of nitrite

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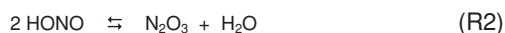
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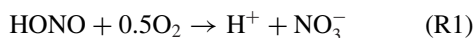
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**Scheme 1**

was removed within 180 min, whereas at pH 11.6 the conversion was less than 5%. The reaction

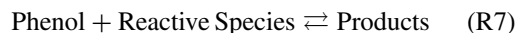


can occur by a complex mechanism such as that depicted in Scheme 1.

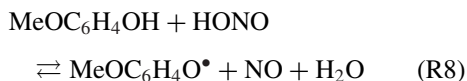
Where the reaction is carried out under constant airflow, removing of gaseous intermediates of low solubility (NO and NO_2), the rate of nitrite consumption increases by a ca. 3.0 factor, thus increasing, by a similar factor, the rate of nitrate formation. This result can be explained by assuming that NO and NO_2 removal avoids the occurrence of several back reactions such as those shown in Scheme 1, thus increasing HONO consumption.

On the other hand, Mudgal et al. [11] have proposed, for the oxidation of nitrite by oxygen in acid solutions, that the mechanism at relatively high concentrations (ca. 5 mM) involves the reaction of a nitrite molecule with a previously produced oxygen/ HONO complex, and/or the reaction of an HONO dimer with oxygen to give nitric acid (HNO_3).

In the presence of a phenol and under mild conditions that disfavor nitrosation, nitration can take place mediated by HONO and/or NO_2 attack. In a study of the reaction between phenol and HONO , Vione et al. [12] have proposed that step (R7) is the rate-determining step:



and that the reaction kinetics suggests that HONO is the main reactive species. Similarly, Beake and co-workers [4] propose that, in the nitration and oxidation of 4-methoxyphenol by HONO in aqueous acid solution, the initial reaction can be represented by



This reaction could be of biological relevance since it involves the production of NO resulting from the interaction of phenols and HONO compounds that are simultaneously present in the stomach cavity [3].

Regarding the role of NO_2 in the initial step of the nitration of phenols, it has been shown that NO_2 radicals oxidize deprotonated tyrosine, generating phenoxyl radicals that can further react with another NO_2 radical [13]. Similarly, it has been shown that NO_2 reacts with alkyl-substituted phenols, particularly in nonpolar solvents [14]. It has been proposed that the reaction of NO_2 with phenols can be represented by



This reaction can take place in a single step and/or through the sequence



The reaction of ArO^\bullet radicals with another NO_2 radical can lead to a variety of products that will depend on the employed conditions and the substituent in the aromatic ring [15]. However, Patnaik and Khoury [16] concluded that, in the nitration of phenol, NO_2^- is the active species under a wide range of experimental conditions.

Besides the nitration/oxidation processes described above, the interaction of HONO with phenols at low pH can involve a parallel nitrosation of the aromatic ring [17]. This reaction could be mediated by the attack of the phenol by NO^+ although in this case its rate must be strongly dependent upon the pH of the solution.

Taking into account the relevance of the phenol–nitrite reaction in different systems, in the present work we discuss the relative relevance of different reactive nitrogen species (NO_2 , HONO , NO_2^-) in the nitration of phenol derivatives and how their rates depend on the characteristics of the substituent in a series of p-substituted phenols in aqueous solution.

EXPERIMENTAL

The kinetics of the reaction of para-substituted phenols with HONO and NO_2 in aqueous solution was measured following the phenol, oxygen, and nitrite consumption.

Reagents

Phenol, 2-nitrophenol, 4-nitrophenol, 4-methoxyphenol, 4-cyanophenol, hydroquinone, 4-methylphenol, 4-chlorophenol, 4-methoxy-2-nitrophenol, perchloric acid, and nitrite were purchased from Merck (Germany) and Sigma-Aldrich (China) and used without purification.

Kinetic Studies

Kinetic experiments were carried out in the dark at 23°C in reaction cells with magnetic stirring. Assays were carried out in open cells or septum-closed cells with a minimum dead volume. Some runs were performed with a constant flux of gas (air, nitrogen, or oxygen) through the reacting solution. Extra pure gases were employed in these experiments.

Kinetic runs were started by addition of an aliquot of the phenol derivative (final concentration 1 mM) to a HONO solution at pH 2.3 (final concentration 5 mM). Aliquots of the reaction mixture were taken at each 20 min, and reactants and products were quantified immediately by high-performance liquid chromatography (HPLC) employing a Waters instrument with a diode array detector as previously described [18]. Identification of reactants and products was performed by a comparison of retention times and peak spectra with commercial standards, and quantification was achieved by interpolation in calibration plots. When possible, the course of the reaction was also followed by UV-visible absorption using a Hewlett-Packard 8453 spectrophotometer.

Oxygen consumption along the reaction was quantified using a Hanstech oxygraph with thermostatization and magnetic stirring.

To generate NO₂, 10 mg of metallic copper was incubated at 25°C with concentrated nitric acid (30 mL) and 20 mL of ultra pure water under constant stirring [19]. Nitrogen gas was employed as carrier (at 45 mL min⁻¹). The NO₂/N₂ mixture was bubbled into a spectroscopic cell containing phenol solutions (10 µM) in phosphate buffer 75 mM, pH 7.4, or pH 5.0. In the absence of either copper or nitric acid, no changes were registered in the UV-visible spectrum of phenols. Aliquots (20 µL) were taken and injected into the HPLC system. To determine NO₂, it was reduced to nitrite whose final concentration was estimated by the Griess assay [20]. Briefly, the NO₂/N₂ mixture was bubbled into a solution containing an excess of Trolox (500 µM) in phosphate buffer 75 mM, pH 7.4 to achieve a quantitative NO₂ reduction. After 20 min, aliquots (300 µL) were taken and added to a solution (2.6 mL) containing sulfanilamide (1%) in orthophosphoric acid (5%). The solution was

incubated at 25°C for 10 min and then was added 100 µL of *N*-(1-naphthyl)-ethylenediamine (3%). This solution was incubated at 25°C for 30 min, and its absorption intensity at 545 nm was measured. The nitrite concentration was determined by comparison with a calibration curve employing commercial sodium nitrite (Merck).

RESULTS

In this study, the following questions regarding phenol oxidation/nitration promoted by nitrite were addressed:

- i. How does the presence of a phenol modify the rate of nitrite decomposition?
- ii. What is the dependence of the reaction rate with the oxygen concentration and the reaction cell dead volume and with gas bubbling during the reaction?
- iii. How does the rate of phenol nitration depend on the phenol substituent at the 4-position?
- iv. What are the main reaction products and their formation mechanism, and what is the stoichiometry of phenol, oxygen, and nitrite consumption?
- v. How does the rate of the process depend on the pH of the solution?
- vi. What is the nitrogen reactive species that reacts with the phenol in the initial step?

The main results obtained are summarized in Tables I and II.

- i. How does the presence of a phenol modify the rate of HONO decomposition?

The presence of phenol decreases the rate of nitrite consumption, and the magnitude of the protection depend on the substrate (Table I), which is a factor of ca. 10 for 4-nitrophenol. It must be concluded that, in the absence of continuous bubbling, the phenols “protect” nitrite molecules. A plausible explanation of these results is given in the next section.

- ii. What is the dependence of the reaction rate with the oxygen concentration and what is the effect of the dead volume and gas bubbling during the reaction?

In closed reaction cells, the rate of 4-methoxyphenol (MeOPh) consumption increases with the oxygen percentage in the gas phase. On the other hand, the rate of nitrite consumption is not accelerated by oxygen. In fact, nitrite consumption is faster in nitrogen-purged solutions than under air or pure oxygen.

Table I Initial Rate of Phenol and HONO Consumption During Phenol-Nitrite Reactions in Open Cells

Substituted Phenol	Hammett σ Parameter	Rate of Phenol Consumption ($\times 10^4$ M h $^{-1}$)	Rate of Nitrite Consumption ($\times 10^4$ M h $^{-1}$)
1,4-Dihydroxybenzene	-0.34	36.5 ± 7.5	11.0 ± 1.5
4-Methoxyphenol	-0.27	7.5 ± 0.3	3.9 ± 0.2
4-Methylphenol	-0.17	3.6 ± 0.9	5.1 ± 0.05
Phenol	0	4.5 ± 0.4	2.3 ± 0.1
4-Chlorophenol	0.23	1.2 ± 0.06	6.6 ± 3.1
4-Cyanophenol	0.66	1.5 ± 0.2	5.9 ± 1.1
4-Nitrophenol	0.78	0.50 ± 0.05	1.2 ± 0.1
4-Hydroxybenzoic acid	0.45	0.80 ± 0.20	—
None	—	—	11.0 ± 1.7

The Hammett σ parameter of the p-substituent at pH 2.8 is also presented.

Table II Initial Reaction Rates for the Reaction of 4-Methoxyphenol (1 mM) with Nitrite (5 mM) at pH 2.3 under Different Conditions

Condition	MeOPh Consumption rate ($\times 10^4$ M h $^{-1} \times 10^4$)	Nitrite Consumption Rate ($\times 10^4$ M h $^{-1} \times 10^4$)
Exposed to air	7.5 ± 0.3 (0.5 ± 0.2) ^a	3.9 ± 0.2 (0.2 ± 0.1) ^a
Closed under air	4.7 ± 0.003	2.2 ± 0.3
Prepurged with O ₂	18.0 ± 0.6	2.0 ± 0.3
Prepurged with N ₂	3.7 ± 0.03	4.2 ± 0.1
Air bubbling	20 ± 2	31.4 ± 7
N ₂ bubbling	8.1 ± 0.7 ^b	29 ± 5 ^c

^aValues between parenthesis correspond to measurements carried out at pH 5.7.

^bConstant at ca. 50% conversion.

^cConstant at ca. 30% conversion.

Nitrogen purging of the solution prior to a reaction increases the initial rate of nitrite consumption, but it reduces the rate of MeOPh consumption without avoiding it. This implies that the process has at least two pathways, one oxygen dependent and another oxygen independent.

Generation of volatile products and intermediates (NO and NO₂) implies that the rate of the reaction can be modified by their gas/solution partition and, in particular, by continuous bubbling of the reaction vessel [10]. The results shown in Table II support this proposal. The data given in this table show that continuous bubbling with air dramatically increases the rate of nitrite and MeOPh consumption, indicating that fluxing of reactive NO_x compounds minimizes back reactions, increasing the rate of the process. Nitrogen bubbling also increases the initial rate of nitrite decomposition, becoming constant at ca. 30% conversion. The initial rate of MeOPh also increases, but the phenol concentration also becomes constant at ca. 50% conversion.

- iii Effect of the substituent on the reaction of p-substituted phenols with HONO.

The consumption of several p-substituted phenols induced by nitrite addition is shown in Fig. 1. These data show that the rate of the process increases when the capacity of the substituent to donate charge increases. The initial rate of the process is given in Table I and plotted against the Hammett σ parameter in Fig. 2. This figure shows a clear correlation with a slope (ρ parameter) of -1.23. This implies that the species that attacks the phenol in the rate-limiting step is highly electrophilic. Conversely, it is interesting to note that there is not a clear trend in the rate of nitrite consumption with the characteristics of the added phenol.

- iv Main reaction products and stoichiometry of phenol, oxygen, and nitrite consumption.

Product distribution and the stoichiometry of the reactants consumption (oxygen, phenol, or nitrite) depends on the phenol, the pH, the presence of oxygen, fluxing of the reaction mixture, and addition of NO₂ or nitrite as coreactants. The main features of the reaction will be described without attempting a comprehensive interpretation of the results.

4-Methoxyphenol. This compound is perhaps the most studied. A remarkable fact is that *p*-benzoquinone

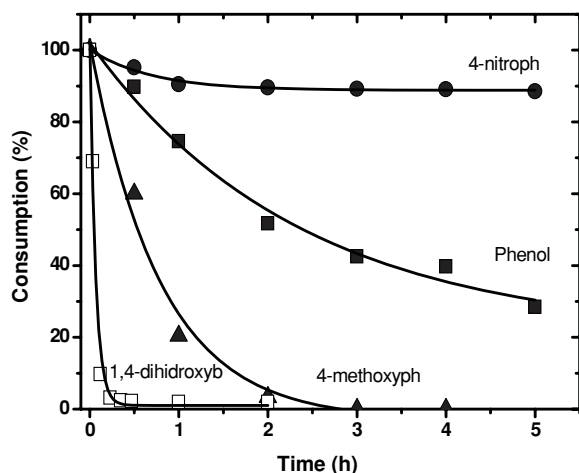


Figure 1 Consumption of phenols mediated by HONO. Phenol solutions (1 mM at pH 2.3) were incubated with nitrite at 5 mM concentration. Consumption of phenols was assessed by the HPLC technique. Symbols: (●) 4-nitrophenol, (■) phenol, (▲) 4-methoxyphenol, and (□) 1,4-dihydroxybenzene.

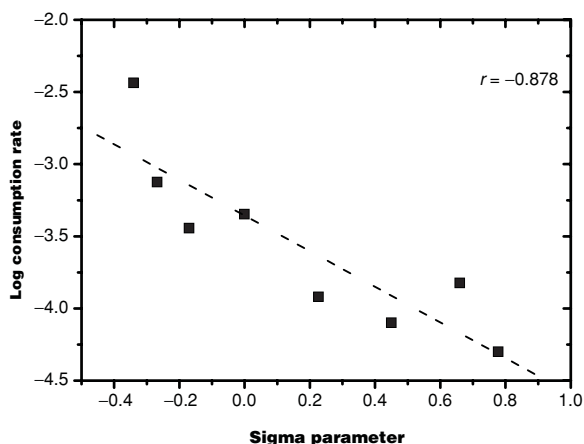


Figure 2 Dependence of the initial phenol consumption rate with a Hammett sigma parameter $a = -3.35$; $b = -1.234$; $r = -0.878$, and $p < 0.00414$.

(27%) (cyclohexa-2,5-diene-1,4-dione) is the main product of its reaction with nitrite, in spite of the initial blockage of the 4-position [4]. Another identified product is 4-methoxy-2-nitrophenol (41%) that could arise from the interaction of NO_2 with the 4-methoxyphenoxyl radical.

1,4-Dihydroxybenzene (hydroquinone). Regarding this compound, HONO acts as an oxidant producing benzoquinone as the main product (50%). This compound is generated during the interaction of the semiquinone radical with NO_2 and/or oxygen. This process could be relevant to catechol (1,2-dihydroxybenzene) structures

such as those frequently present in foods and beverages [3,21].

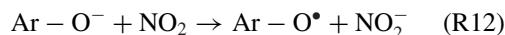
Phenol. The lack of substitution at the 4-position reduces the efficiency of benzophenone formation (to less than 5%) and the main products 4-nitrosophenol, 2-nitrophenol, and 4-nitrophenol arise through the combination of a phenoxyl radical with NO or NO_2 .

v Effect of pH on the reaction rate.

Most of the reaction rates were measured at room temperature and pH 2.3, conditions under which nearly 80% of nitrite is protonated (HONO). Increasing the pH to 5.7 notably reduces the rate of the process. At this pH, most (ca. 99%) of nitrite is deprotonated (NO_2^-). Since there is no change in the protonation of phenol in this pH range, it can be concluded that the reaction is initiated by the interaction between HONO and the phenol [2–4,12]. The reduced rate caused by increasing the pH can then be related to a decrease in the fraction of protonated HONO.

vi Nitrogen reactive species that reacts with the phenol in the initial step.

To assess whether the reaction of 4-methoxyphenol involves NO_2 and/or HONO in the rate-determining step, we compared the results obtained in two limiting situations of very low and high NO_2 concentrations. For this purpose, a 4-methoxyphenol solution was continuously fluxed with a nitrogen/ NO_2 gas mixture. On the other hand, phenol/HONO mixtures were continuously bubbled with air to keep low the steady-state NO_2 concentrations. In spite of this, the rate of the process increases notably (Table II). Furthermore, the rate of the process is maximum at low pH where the presence of HONO predominates. On the other hand, different results were obtained under a NO_2 -enriched flux. The data given in Fig. 3 show that, under these conditions, the rate increases when the pH of the solution increases. This is compatible with a rate-limiting step involving deprotonated phenols. Furthermore, the electrophilicity of NO_2 can explain the faster reaction of the methoxy derivative (see Fig. 3). This result is fully in agreement with the reported effect of p-substituents on the rate of reaction (R12) [22]:



DISCUSSION

Several factors make it difficult to interpret the obtained results regarding the reaction between nitrite and phenols. The main factors are the following:

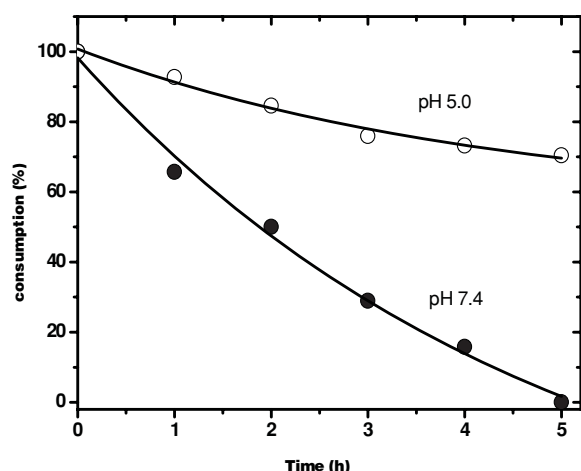


Figure 3 HPLC-based consumption of 4-methoxyphenol mediated by NO_2 . 4-Methoxyphenol solutions (10 μM), at pH 7.4 (●) and 5.0 (○) were fluxed with NO_2 as described in the Experimental section.

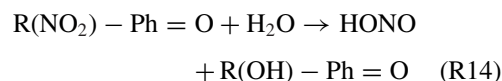
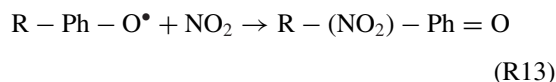
- i. The species that interchange in the systems are NO , NO_2 , N_2O_3 , N_2O_4 , HONO , NO^+ , NO_2^- , and HNO_3 [2,23].
- ii. The gas-liquid partitioning of several of these species between the reacting solution and the dead space volume [3].
- iii. The possible interaction between several of these species and the target molecule (substituted phenols) [2].
- iv. The reversibility of several of the steps involved in the process [4].
- v. The large number of secondary reactions of phenol-derived intermediates and products that depend on the phenol studied. In particular, it can be expected and is frequently observed a peculiar behavior of ortho-diphenols, due to the predominance of *o*-quinones arising from the disproportionation of semiquinone radicals with NO_2 or O_2 . This is in agreement with the results obtained employing *p*-hydroxyphenol.
- vi. The large number of oxidized, nitrated, and/or nitrosated final products that depend on the experimental conditions are employed.
- vii. The pH dependence of the process associated with the protonation/deprotonation of reactants and intermediates.

The complexity of the system implies that is not possible to establish a general mechanism for the process, and only partial conclusions can be obtained. In the present work, most of the mechanistic and kinetic considerations are referred to the reaction of 4-methoxyphenol (1 mM) with nitrite (5 mM) at pH 2.3

in open reaction cells. Kinetic considerations are based on initial reaction rates obtained by extrapolation of reactants (oxygen, phenol, and HONO) consumption and products formation to zero reaction time.

At high oxygen concentrations, several oxygen molecules (nine for 4-methoxyphenol) are consumed by each reacted HONO molecule, suggesting that the main process in the reaction of phenols with HONO is oxidation and not nitration [4] and that a large fraction of reacted phenols does not incorporate nitrogen atoms. HONO behaves then as a catalyst of phenol oxidation. Several reaction paths can explain these results:

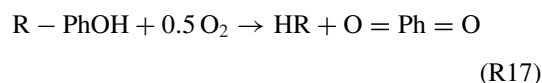
1. Reaction (R8) can be followed by recombination of two phenoxyl radicals with partial oxidation of NO molecules to NO_2 and N_2O_3 and, hence, to HONO.
2. Reaction (R8) can be followed by disproportionation of the initial phenoxyl radical with NO_2 to give back HONO and the corresponding quinone in compounds with two phenolic groups in ortho- or para-positions [2]
3. A mechanism similar to that proposed by [4] for the reaction of 4-methoxy phenol with HONO, where the initial step (reaction (R8)) is followed by



and



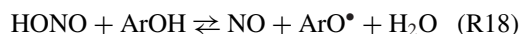
This leads to a total stoichiometry as follows:



The occurrence of these processes leads to the predominance of phenols oxidation and reduced rates of HONO consumption.

The relevant role of volatile compounds in the reaction of nitrite with phenols makes the rate of the process extremely dependent on the factors that determine the

accumulation of these intermediates during the reaction, such as the size of the dead volume, closing of the reaction cell, or fluxing of gases [4,10]. This is evidenced by the data given in Table II. These data show that both the rate of 4-methoxyphenol and HONO consumption follow the following trend: close cell with minimum dead volume < open cell \ll continuous air fluxing, emphasizing the role of phase transfer of the intermediates upon the rate of the process [24]. The reversibility of the first step



and/or



can explain these results and the noticeable decrease in the rate of the process observed when NO is the flushing gas [4].

A peculiar characteristic of the interaction of the phenol derivatives with HONO is the protection afforded by the aromatic compound toward HONO consumption. It can be proposed that a process such as



could explain the reduction in the rate of HONO consumption in the presence of the phenol derivatives.

It is interesting to note the difference in the pH effect when the process is carried out at high pHs with a NO₂ continuous input or at low pHs with HONO as the initial nitrogen reactive compound. In fact, in acidic conditions the rate of the process decreases when the pH increases. On the other hand, when the reaction takes place by NO₂ fluxing of the phenol solution, the rate of the process at pH 7.4 is considerably faster than that at pH 5.0. This difference could mean that under atmospheric conditions the initial step is reaction (R18), whereas in stomach conditions it can be represented by (R19). The similar rates of phenol nitration at pH <2 and >10 reported by Patnaik and Khoury [16] can be ascribed to the occurrence of different mechanisms under the two employed experimental conditions.

Results given in Table I and in Fig. 1 show that 4-methoxyphenol reacts with HONO in acidic conditions and with NO₂ in basic conditions, faster than 4-nitrophenol. At low pH, this difference should be related to the effect of the substituent on the strength of the phenolic H–O bond if the initial step is represented by (R20) and (R21):

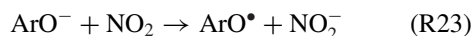


This process can take place directly by hydrogen transfer or by electron transfer [13]:



followed by deprotonation of the aromatic radical cation. The rate of reaction (R22) must depend on the charge density in the aromatic ring and hence on the electron donor capacity of the substituent. Thus, an initial step such as that depicted in (R8) and/or reaction (R21) or (R22) are in agreement with the data plotted in Fig. 2 that show that the rate of reaction of para-substituted monophenols follows a Hammett-type relationship with a slope equal to –1.23. However, it has to be considered that a fast rate of reaction (R21) is unlikely due to higher bond dissociation energies of the phenols and hence at low pH the main initial step of phenols nitration/oxidation promoted by HONO should be that represented by (R8) [3,4].

NO₂ is a potent one-electron oxidant with a standard potential of 0.99 V at room temperature. At basic pH, phenols are partially deprotonated, and a likely reaction path to produce the phenol-derived initial intermediate can be represented by (R23):



This reaction has been directly studied by pulse radiolysis with hydroxycinnamic derivatives [25], tyrosine [13] and tryptophane, at pH below the phenol pK_a, and its rate decreases when the pH of the solution decreases. Regarding the reaction of para-substituted phenols, the rate of the process fits a Hammett-type relationship with a slope of ca. 3.0 [22]. As expected, this value is considerably larger than that obtained in the present work for the rate of p-substituted phenols promoted consumption by nitrite at low pH. Furthermore, reaction (R23) is very fast, reaching near diffusion control ($1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) for 4-hydroxyphenol). The high rate of this electron transfer and its dependence on the electron donor character of the substituent support the proposal that it is the initial step in the nitration of phenols at high pH and that it can be of relevance to atmospheric hydrometeors

CONCLUSIONS

The initial reaction associated with the oxidation/nitration of 4-substituted phenols promoted by HONO/NO₂ depends on the pH of the solution. At low pH, the initial step involves the reaction between HONO and phenol, whereas at basic conditions it involves an electron transfer from the phenoxy anion to

NO₂. The former reaction should be relevant to the processing of nitrite by stomach fluids, whereas the electron transfer should be the dominant process in atmospheric hydrometeors. The rate of both processes is determined by the donor capacity of the substituent at the 4-position of the phenol. The partition of the gaseous intermediates (NO and NO₂) between the solution and the gas phase leads to a dependence on the rate of the HONO-mediated oxidation of phenols with their gas-liquid distribution. At low pH, the main process is the phenol oxidation, even in oxygen-free conditions. The presence of any 4-substituted phenol decreases the rate of HONO auto-oxidation.

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