Hydroxylation by Electrochemically Generated OH• Radicals. Mono- and Polyhydroxylation of Benzoic Acid: Products and Isomers' Distribution

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The electrochemical Fenton reaction (simultaneous reduction of dioxygen and ferric ions) permits a controlled production of OH• radicals. These are used for the stepwise hydroxylation of benzoic acid to mono- and polyhydroxylated products. The quantitative distribution of all the hydroxylated products is achieved by use of HPLC. The overall reaction scheme is established and the rate constants of the individual steps are measured.

Introduction

Oxygen radicals are very reactive species which are involved in a number of fields: chemistry (astrochemistry, environmental chemistry), biology, and medicine.[1-7] Among these radicals ($O_2^{\bullet-}$, OH•, $HO_2^{\bullet}$, ROO•, ...), the hydroxyl radical, OH•, is certainly the most reactive. It is a very strong one-electron oxidizing agent: $E°(OH^{\bullet},H^+/H_2O) = 2.72$ V/NHE[8] at pH = 0 and $E°(OH^{\bullet}/OH^-) = 1.89$ V/NHE,[9-10] which however seldom reacts as an electron transfer reagent. On the contrary, it is a very reactive reagent in hydrogen atom abstractions and in electrophilic additions.[11] Some typical rate constants concerning these last reactions are shown in Table 1;[12] they are close to the diffusion limit. If one considers the reactions of OH• with aromatic compounds, addition reactions are observed and not oxidations. Let us consider 1,2,4-trimethoxybenzene as an example. Its oxidation potential, $E° = 1.13$ V/NHE, has been measured[13] by pulse radiolysis in water. Compared with the redox potential given above for the $OH^{\bullet}/OH^-$ couple, one should expect a diffusion-controlled oxidation of the substrate; however, an addition of the hydroxyl radical is observed[14] with a rate constant $k = 8.1 \times 10^9$ M^{-1} s^{-1}. This must be related to the slowness of the electron transfer, which is not unlikely in view of the large solvent reorganization expected to follow this electron transfer.

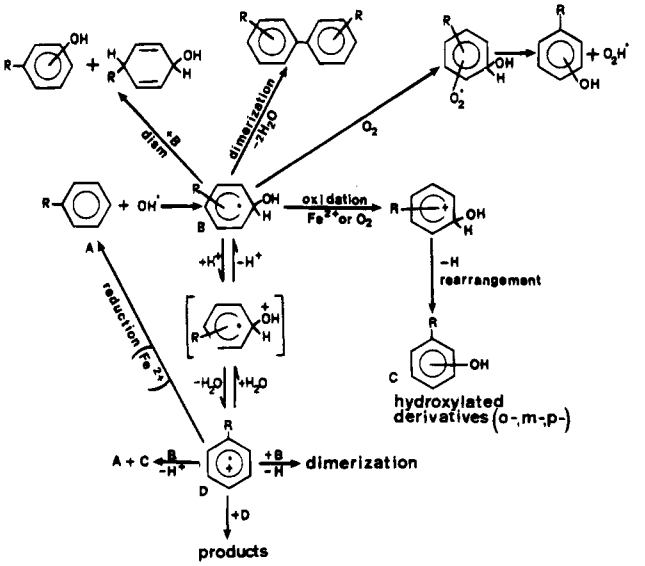
The very complex addition mechanism of OH• on aromatic derivatives has been investigated (benzene,[15-20] toluene,[16,17,21-23] anisole,[22] fluorobenzene,[22] benzonitrile,[22] chlorobenzene,[23] nitrobenzene,[23,24] methoxybenzenes,[14] phenol,[25] benzoic acid and benzoate ion,[27-31] salicylic acid,[29,33,34] 4-hydroxybenzoic acid,[35] phenylacetic acid,[17] diphenylfuran[36]). The first step of this mechanism is a very fast nucleophilic addition[12] ($k = 10^9$ to 10^{10} M^{-1} s^{-1}) of the OH• radical on the aromatic ring, leading to the formation of an intermediate cyclohexadienyl radical (B), which has been detected under different conditions both by UV[14,15,25,35] and ESR[27,37] spectroscopy. This radical undergoes different reactions depending on the medium in which it is formed. These reactions are summarized in Scheme 1.

In the absence of an oxidizing reagent the main reactions are dimerization[14,16,17,22] and/or dismutation.[16,22] In the presence of an oxidizing agent such as Fe^{3+} or Cu^{2+}, the radical (B) is rapidly oxidized to the hydroxylated derivatives.[16-24,26,32-35] In an acidic medium, the hydroxycyclohexadienyl radical (B) gives a radical cation (D) through an acid-catalyzed water elimination.[17,18,22,25,32] The radical cation can be reduced back to the starting material or undergo further reactions. In the presence of oxygen[15,17,18,20,33,34,36,38] one observes the formation of the final hydroxylated aromatic either by formation of an intermediate peroxy radical (Dorfman mechanism) or through the formation of an intermediate dihydro diol in nonpolar solvents. The hydroxycyclohexadienyl peroxyl radicals obtained by addition of dioxygen on the cyclohexadienyl radical may again react with dioxygen to furnish endoperoxyl radicals which lead to ring-opened compounds.[20] Therefore, the fate of the cyclohexadienyl radical depends to a large extent on the medium in which it is formed and therefore on the way hydroxyl radicals are generated. The production of hydroxyl radicals can also be achieved by the Haber−Weiss reaction:[1,39,40]

TABLE 1: Rate Constants

	subsrate	k (M^{-1} s^{-1})	conditions
H• abstraction	C_2H_5OH	1.9×10^9	pH = 6−7
	CH_2OHCH_2OH	1.8×10^9	pH = 7
addition	benzoate ion	5.9×10^9	pH = 6−7
	benzoic acid	4.3×10^9	pH ≤ 3
	p-aminobenzoate	1.1×10^{10}	pH = 7−9
	p-hydroxybenzoate	8.9×10^9	pH = 7−9
	phenol	1.4×10^{10}	pH = 7.4−7.7

SCHEME 1. Mechanism of the Addition Reaction of the OH• Radical on an Aromatic and Further Reactions of the Cyclohexadienyl Radical



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$$O_2^{\bullet -} + H_2O_2 \rightarrow HO^{\bullet} + OH^- + O_2 \quad (1)$$

(but its rate constant is too slow (k = 0.13 L mol^{-1} s^{-1}) to account for a significant production in biological sytstems), by radiolysis,[15,20-29,35] by photolysis,[31,32,38,41] and by the Fenton reaction,[42] which produces hydroxyl radicals[17-19,33,34,36] through the reduction of hydrogen peroxide by Fe^{2+}:

$$H_2O_2 + Fe^{2+} \rightarrow HO^{\bullet} + OH^- + Fe^{3+} \quad (2)$$

As indicated in Scheme 2, electrochemistry permits production of hydrogen peroxide directly in the solution by reduction of oxygen and at the same time to regeneration of Fe^{2+}, which can thus be used in a catalytic fashion.[19,33,43-50] Setting the potential of the electrode at a potential (E_1) sufficient for the reduction of oxygen permits triggering of the formation of hydroxyl radicals.

Besides its simplicity, a particularly interesting point regarding this method is that it permits a controlled production of hydroxyl radicals; it is then possible to follow the formation of the different products as a function of the amount of electricity which has been used, i.e., as a function of the radicals which have been produced.

This paper deals with the stepwise hydroxylation of benzoic acid by hydroxyl radicals. The monohydroxylation reaction has been previously investigated by radiolysis,[26-30] and by photochemistry.[31,32] Radiolysis and the Fenton reaction have also been used for the investigation of 2- or 4-hydroxybenzoic acid.[33-35] However, in all these preceding investigations, the only formation of the primary hydroxylation products was observed and discussed. In the following we shall focus our attention on the formation of polyhydroxylated products by following their formation and consumption and also on the differences between the Fenton reaction and other methods used for the production of hydroxyl radicals.

Experimental Section

All the products are of commercial origin and were used without further purification, except benzoic acid, which was recrystallized, and mercury, which was redistilled. Benzoic acid (BA); the monohydroxybenzoic acids (-HBA) 2-HBA, 3-HBA, and 4-HBA; the dihydroxybenzoic acids (-dHBA) 2,3-dHBA, 2,4-dHBA, 2,5-dHBA, and 2,6-dHBA; the trihydroxybenzoic acids (-tHBA) 2,3,4-tHBA and 2,4,6-tHBA; benzoquinone; resorcinol (1,3-dihydroxybenzene); and catechol (1,2-dihydroxybenzene) were obtained in the highest purity available from Aldrich. 3,4-dHBA and 3,5-dHBA as well as diethylenetriaminepentaacetate (DETAPAC) were "puriss" quality from Fluka. Ferric chloride, hydroquinone, phenol (Rectapur quality), and the 0.1 M aqueous HCl solution were obtained from Prolabo.

Electrolyses were performed in a three-electrode electrochemical cell. The working electrode was a 15 cm^2 mercury pool. The platinum counter electrode was placed in the anode compartment separated from the cathode compartment by a no. 4 glass frit. The reference electrode was a saturated calomel electrode (SCE). The volume of the electrolyzed solutions was 75 mL. These solutions were prepared by dissolution of 0.375 mmol (c = 5 mM) of the product to be electrolyzed in 75 mL of a 0.1 M HCl solution (pH $\approx$ 1). The central anodic compartment contained only the 0.1 M HCl solution. Prior to the electrolysis, dioxygen was bubbled for 15 min and then 0.012 g of $FeCl_3$ was introduced ([Fe^{3+}] = 1 mM). When solutions with a pH lower than 2 are used, there is no necessity to introduce a complexing agent such as EDTA or DETAPAC in the solution—at such pHs the Fe^{2+} and Fe^{3+} do not precipitate as their hydroxides. At higher pHs (when benzoic acid is dissolved in water without buffering the solution) DETAPAC is introduced as a complexing agent to prevent the precipitation of these ions. Under such conditions, 0.1 M $LiClO_4$ is added to the anolyte and to the catholyte. In every case the solution is stirred magnetically.

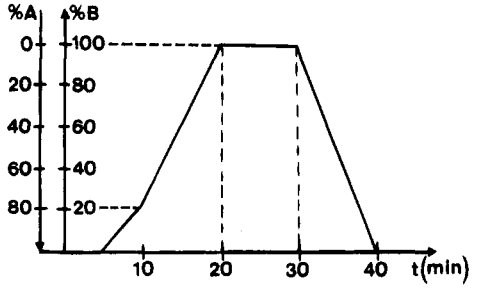


Figure 1. Gradient program.

SCHEME 2. Electrochemical Generation of Hydroxyl Radicals

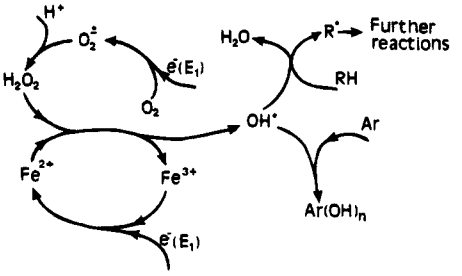


TABLE 2: Composition of HPLC Solvents

	composition by volume		
eluent	H_2O	CH_3OH	CH_3COOH
eluent A	92	4	4
eluent B	61	35	4

The potential is maintained at −0.5 V/SCE with a homemade potentiostat, a potential where both O_2 and Fe^{3+} are reduced respectively to $O_2^{\bullet -}$ and to Fe^{2+}. The current remains constant (70 mA), which permits a constant production of hydroxyl radicals. The amount of charge passed through the solution is measured with a Tacussel IG5-N, and samples are withdrawn at regular charge intervals: 0, 50, 100, ... C. These samples are analyzed in a liquid chromatographer (Gilson) equipped with a UV detector set at 280 or 313 nm and a Hypersil BDS C8 5 mm column (25 cm × 4.6 mm) from Shandon HPLC. In order to obtain a good separation with a reasonable elution time, a gradient of solvents was programmed with a Gilson HPLC System Manager. The composition of the solvents is shown in Table 2, and the rate was v = 0.8 mL/min. The gradient program is shown in Figure 1.

Qualitative and quantitative analyses were performed with authentic samples. The calibration curves were established in a concentration range from 0.1 to 2 mM. Most of the compounds under examination absorb at λ = 313 nm with a reasonable absorption coefficient; however, some only absorb at 280 nm. Therefore, two standards were prepared: standard 1 and standard 2 (Figure 2). Therefore the analyses performed during the electrolysis were duplicated at 313 and 280 nm and the concentration was calculated from the appropriate calibration curves.

Results and Discussion

The electrochemical reduction of dioxygen leads to superoxide ion,[51] which is stable in an aprotic medium such as

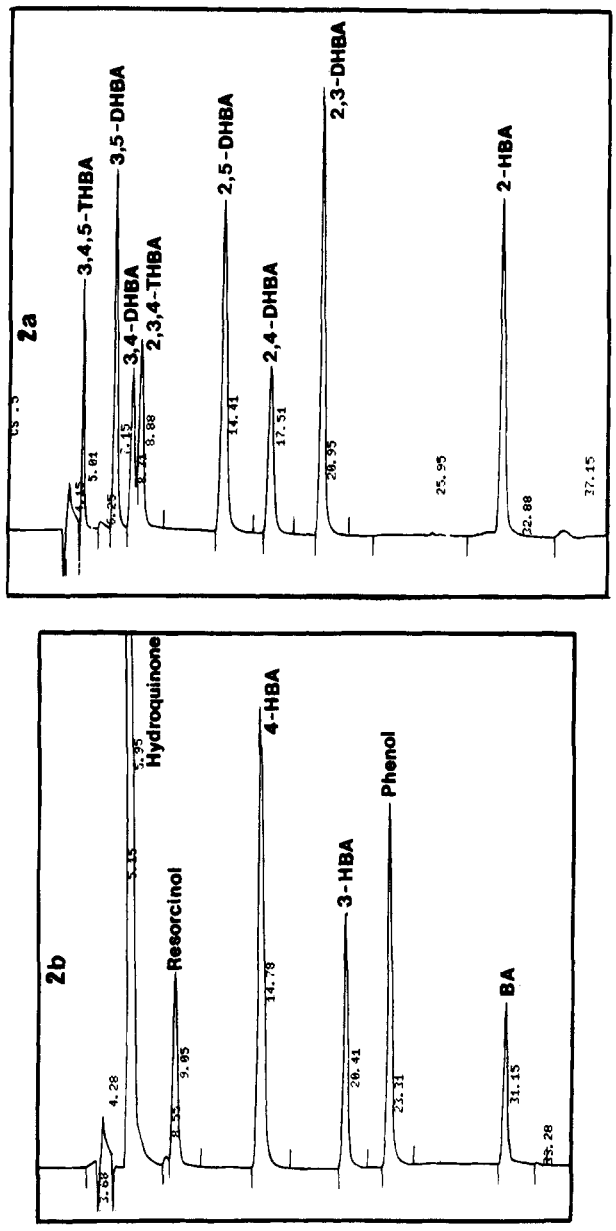


Figure 2. (A) Standard 1 (λ = 313 nm). (B) Standard 2 (λ = 280 nm). Concentration of the compounds: 0.5 mM each.

acetonitrile (ACN), dimethylformamide (DMF), or dimethyl sulfoxide (DMSO) and in strongly basic aqueous solutions; the redox potential $E°(O_2/O_2^{\bullet -}) = -0.75$ V/SCE in DMSO has been measured. In a protic medium, $O_2^{\bullet -}$ reacts rapidly with H^+ to give an unstable peroxyl radical $HO_2^{\bullet}$, which disproportionates to H_2O_2:[52-54]

$$O_2 + e^- \rightleftharpoons O_2^{\bullet -} \quad E° = -0.33 \text{ V/NHE} = -0.572 \text{ V/SCE} \quad (3)$$

$$O_2^{\bullet -} + H^+ \rightleftharpoons HO_2^{\bullet} \quad pK_a = 4.69 \quad (4)$$

$$HO_2^{\bullet} + HO_2^{\bullet} \rightarrow O_2 + H_2O_2 \quad k_5 = 8.3 \times 10^5 \text{ M}^{-1} \text{ s}^{-1} \quad (5)$$

$$HO_2^{\bullet} + O_2^{\bullet -} + H_2O \rightarrow O_2 + H_2O_2 + OH^- \quad k_6 = 9.7 \times 10^7 \text{ M}^{-1} \text{ s}^{-1} \quad (6)$$

These reactions can be summed up as a reaction leading to the formation of H_2O_2:

$$2HO_2^{\bullet} + 2O_2^{\bullet -} + H^+ + H_2O \rightarrow 2O_2 + 2H_2O_2 + OH^- \quad k = 6 \times 10^{12}[H^+] \quad \text{pH} > 6$$

In a strongly acidic medium (pH = 0), equilibrium 4 is displaced to the right, therefore facilitating the reduction of dioxygen.[51]

$$O_2 + H^+ + e^- \rightarrow HO_2^{\bullet} \quad E°_7 = -0.046 \text{ V/NHE} = -0.287 \text{ V/SCE} \quad (7)$$

As the redox potential of the Fe^{3+}/Fe^{2+} couple is equal to +0.77 V/NHE (+0.53 V/SCE) when a potential (−0.5 V) is applied to the cathode under the conditions described in the experimental section, the following reactions take place:

$$O_2 + 2H^+ + 2e^- \rightleftharpoons H_2O_2 \quad (8)$$

$$Fe^{3+} + e^- \rightleftharpoons Fe^{2+} \quad (9)$$

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^- \quad (2)$$

The hydroxyl radical thus produced can undergo several reactions in an aqueous medium,[49,55,56] among which are

$$OH^{\bullet} + H_2O_2 \rightarrow H_2O + HO_2^{\bullet} \quad k_{10} = 3.3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1} \quad (10)$$

$$OH^{\bullet} + Fe^{2+} \rightarrow Fe^{3+} + OH^- \quad k_{11} = 3.0 \times 10^8 \text{ M}^{-1} \text{ s}^{-1} \quad (11)$$

$$OH^{\bullet} + OH^{\bullet} \rightarrow H_2O_2 \quad k_{12} = 5.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1} \quad (12)$$

which are in competition with the addition on benzoic acid:

$$OH^{\bullet} + BA \rightarrow BA(OH)^{\bullet} \quad k_{13} = 4.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1} \quad (13)$$

The rate constant of reaction 13 is larger than that of reactions 10 and 11 but of the same order of magnitude as that of reaction 12. However, due to the low concentration of hydroxyl radicals, the hydroxylation of benzoic acid (reaction 13) will take place.

The results of the hydroxylation of benzoic acid by the Fenton reagent (Fe^{2+} + H_2O_2) and by the electrochemical Fenton reaction (O_2 + $3e^-$ + $2H^+$ + catalytic amounts of Fe^{3+}) are gathered in Table 3 and 4 and Figure 3. In the case of the chemical Fenton reaction the *o*-, *m*-, and *p*-isomers are in the ratio 1:1:0.5 and the yield of hydroxylated products is low (13% by reference to initial BA). On the contrary, during the electrochemical Fenton reaction at pH = 1, the yields of the different hydroxylated products vary during the electrolysis. Rather high yields of mono-, di-, or trihydroxylated products can be obtained at different times during the electrolysis (Table 4). A slight variation of the *o*:*m*:*p* ratio is observed from 1:1:1 at the beginning to 1:1.17:1.17 at the end of the electrolysis. These ratios can be compared with the ratios found by different authors (Table 5).

Examination of Table 5 indicates some variations in the relative yields of the three isomers. These variations can be assigned, in part, to the different conditions under which the experiments were performed—more acidic conditions should favor the acid-catalyzed dehydration of the hydroxycyclohexadienyl radical (Scheme 2), and there may be variations of the rate of the reoxidation of the different isomeric radicals with the oxidant but also some uncertainty in the determination of the different isomers, at a time when analytical methods were not as reliable as modern HPLC. Anyhow, even under these different conditions, the relative ratio of two isomers never

TABLE 3: Starting Material and Product Distribution (in mM) at the End of Reaction for the Fenton Reagent Hydroxylation of Benzoic Acid[a]

BA	2-HBA	3-HBA	4-HBA	2,3-dHBA	2,5-dHBA	3,4-dHBA	2,3,4-tHBA	3,4,5-tHBA
3.85	0.10	0.12	0.04	0.11	0.15	0.09	<0.01	0.02

[a] Reaction conditions: V = 100 mL of H_2O; $[BA]_0$ = 5.0 mM; [DETAPAC] = 20 mM; $[H_2O_2]$ = 10 mM; $[Fe^{2+}]$ = 10 mM. Ratio of Fenton reagent to initial BA was equal to 2. Yield of hydroxylated products against BA consumed (1.15 mM) = 55%. Yield of hydroxylated products against initial BA (5 mM) = 13%.

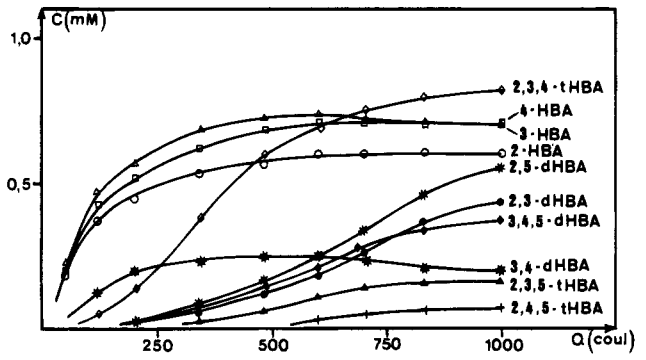
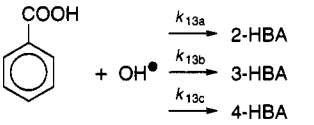


Figure 3. Formation of products during the hydroxylation of benzoic acid by electrochemically generated OH• radicals.

exceeds two, except in one case,[30] indicating a very low selectivity both in the addition of the hydroxyl radical and in the further oxidation of the hydroxycyclohexadienyl radical. This is in agreement with the ESR measurements of Schuler et al.,[27] who found at pH = 13 a ratio of *o*-, *m*-, and *p*-isomers of the hydroxycyclohexadienyl radical equal to 1:1.3:1.4. This low selectivity can be rationalized by considering the electrophilic character of the hydroxyl radical.[21-25,33,55,57,58] In the case of electrophilic substitution, electron donating (+M) substituents (R) are *o*-, *p*-directing and -activating.[59,60] The electrophilic hydroxyl radical will selectively react with the *o*- and *p*-positions; this is observed in the case of anisole[22] (R = OCH_3) in the presence of an oxidant, where the ratio *o*:*m*:*p* of hydroxyanisoles reaches 1:0.07:0.57, and also in the case of phenol,[25] where the ratio of the three diphenols is *o*:*m*:*p* = 1:0.17:0.75. In the case of strongly accepting substituents, Eberhardt and Yoshida[23] have shown that the very low lying SOMO of the OH• radical interacts mainly with the HOMO of nitrobenzene, which has very small coefficients in the aromatic ring. Because of this small overlap in all ring positions, there is little selectivity in the initial addition reaction, and in the presence of a strong oxidizing agent a close to statistical distribution is observed (*o*:*m*:*p* = 1:0.86:0.4). The COOH group being slightly accepting (−I),[60] there will be little selectivity in the hydroxylation of benzoic acid, in agreement with the literature data of Table 5 and with the results reported in this paper.

As can be observed in Figure 3, the concentration of the monohydroxylated derivatives increases rapidly (5×10^{-3} mM/C) at the beginning of the electrolysis to reach a stationary concentration ([2-HBA] ≅ 0.6 mM, [3-HBA] ≅ 0.7 mM, [4-HBA] ≅ 0.7 mM) at about 400 °C, at which point the net rate of formation of these compounds becomes nearly zero. At the end of the electrolysis the yield of the three HBAs starts decreasing. This can be rationalized in the following way: at the beginning of the electrolysis the main reaction is



(13)

When the concentration of monohydroxybenzoic acids reaches a sufficient value, reactions 14−16 come into play. As the OH group is *o*-, *p*-directing and -activating, the following reactions should be considered:

$$\text{2-HBA} + \text{OH}^\bullet \xrightarrow{k_{14}} \text{2,3-dHBA} + \text{2,5-dHBA} \quad (14)$$

$$\text{3-HBA} + \text{OH}^\bullet \xrightarrow{k_{15}} \text{2,3-dHBA} + \text{2,5-dHBA} + \text{3,4-dHBA} \quad (15)$$

$$\text{4-HBA} + \text{OH}^\bullet \xrightarrow{k_{16}} \text{3,4-dHBA} \quad (16)$$

The values of the rate constants k_{14}, k_{15}, and k_{16} have been measured previously; they are gathered in Table 7. These rate constants are somewhat higher than k_{13} (4.3×10^9 L mol^{-1} s^{-1}), the rate constant of hydroxylation of benzoic acid. The stationary state is reached when

$$k_{13a}[\text{BA}][\text{OH}^\bullet] = k_{14}[\text{2-HBA}][\text{OH}^\bullet]$$

$$k_{13b}[\text{BA}][\text{OH}^\bullet] = k_{15}[\text{3-HBA}][\text{OH}^\bullet]$$

$$k_{13c}[\text{BA}][\text{OH}^\bullet] = k_{16}[\text{4-HBA}][\text{OH}^\bullet]$$

At the end of the electrolysis when the concentration of BA becomes low, the concentration of 2-, 3-, and 4-HBA decreases. Considering the values of k_{14}, k_{15}, and k_{16}, it should be remarked

TABLE 4: Mono- and Polyhydroxylated Product Distribution during Electrolysis of O_2 (To Generate OH•) in the Presence of Benzoic Acid[a]

		hydroxylated product concentrations in 10^{-3} mol·L^{-1} (mM)													
entry	Q_{exp} (C)	2-HBA	3-HBA	4-HBA	phenol	2,3-dHBA	2,4-dHBA	2,5-dHBA	2,6-dHBA	3,4-dHBA	hydroquinone	2,3,4-tHBA	2,4,5-tHBA	2,3,5-tHBA	3,4,5-tHBA
1	50	0.18	0.22	0.20											
2	120	0.38	0.47	0.43						0.12		0.05			
3	202	0.45	0.57	0.52	trace	0.02		0.02	<0.01	0.20		0.14			0.03
4	340	0.53	0.68	0.62	trace	0.06	trace	0.08	0.01	0.23	trace	0.38		0.02	0.08
5	480	0.56	0.72	0.69	<0.01	0.12	trace	0.17	0.015	0.25	<0.01	0.60	0.01	0.06	0.14
6	600	0.60	0.75	0.72	<0.01	0.18	<0.01	0.25	0.015	0.25	0.01	0.69	0.03	0.11	0.20
7	702	0.60	0.73	0.71	<0.01	0.26	<0.01	0.34	0.01	0.22	0.03	0.75	0.05	0.14	0.28
8	830	0.61	0.71	0.70	0.01	0.37	<0.01	0.46	trace	0.20	0.05	0.80	0.06	0.15	0.34
9	1000	0.60	0.69	0.70	0.01	0.43	trace	0.57	trace	0.19	0.05	0.82	0.06	0.16	0.37

[a] See Experimental Section for conditions (initial concentration of BA = 6 mM). Only traces of 3,5-dHBA were detected. No detection of 2,4,6-tHBA, resorcinol, and catecol.

TABLE 5: Ratio of *o*-, *m*-, and *p*-Isomers in the Monohydroxylation of Benzoic Acid[a]

o:*m*:*p* ratio	ref	pH	oxidant	method of production
1:1:0.5	this paper	3.5	O_2	Fenton reaction
1:1:1	this paper	1	O_2	electrochemical Fenton reaction
1:0.6:0.6	26	6.5	O_2	γ-radiolysis
1:1.3:0.7	27	7	$Fe(CN)_6^{3-}$	γ-radiolysis
1:0.6:0.5	28	6.8−8.3	O_2	γ-radiolysis
1:0.4:2	30	3	O_2	200 kV X-rays
1:0.6:0.4	29	unbuffered	O_2	γ-radiolysis, 45 kV X-rays
1:1:0.5	31	2	none	$Fe(ClO_4)_3 + h\nu$

[a] The relative amount of the ortho isomer was always taken as unity for the sake of comparison.

TABLE 6: Relative Rate Constants for the Hydroxylation Reaction of Some Di- and Trihydroxybenzoic Acids by Reference[a] to k_{14}

hydroxylated derivative	$k_{rel} = k/k_{14}$
2-HBA	$k_{14} = 1$
2,3-dHBA	$k_{17} = 0.6$
2,5-dHBA	$k_{18} = 1.1$
3,4-dHBA	$k_{19} = 1.0$
2,3,4-dHBA	1.2
3,4,5-dHBA	2.5

[a] $k_{14} = 2.2 \times 10^{10}$ L mol^{-1} s^{-1} (ref 12c).

that k_{15} is the lowest, which explains the excess of 3-HBA at the expense of 2-HBA at the beginning of the electrolysis. From the above relations and the values of k_{14}, k_{15}, and k_{16} it is possible (see Table 7) to obtain k_{13a}, k_{13b}, and k_{13c}. The stationary state for 2- and 3-HBA is reached at about 800 C, and that for 4-HBA, at about 600 C; at these points the concentrations of BA are respectively 4.46 and 3.96 mM and the concentrations of the HBAs measured from Figure 3 are [2-HBA] = 0.60 mM, [3-HBA] = 0.70 mM at 800 C, and [4-HBA] = 0.73 mM at 600 C. The sum $k_{13a} + k_{13b} + k_{13c} = 5.7 \times 10^9$ L mol^{-1} s^{-1} is close to the known value of 4.3×10^9 L mol^{-1} s^{-1} given in the literature.[12c]

The dihydroxybenzoic acids, in their turn, are hydroxylated, and they reach a stationary state at the end of the electrolysis (1000 C). Comparison of the experimental results (2,3,6-tHBA cannot be detected and the concentration of 2,4,5-tHBA remains very low) with the *o*-, *p*-directing effect of the OH group and with the weak *m*-directing effect of the COOH group permits us to describe the further hydroxylation by reactions

TABLE 7: Rate Constants for the Hydroxylation of Benzoic Acid and Hydroxybenzoic Acids

rate constant (L mol^{-1} s^{-1})	obtained from
$k_{13} = 4.3 \times 10^9$	ref 12c at pH < 3
$k_{13a} = 3.0 \times 10^9$	ST[a] on 2-HBA, Figure 3 at 800 C
$k_{13b} = 1.2 \times 10^9$	ST[a] on 3-HBA, Figure 3 at 800 C
$k_{13c} = 1.6 \times 10^9$	ST[a] on 4-HBA, Figure 3 at 800 C
$k_{14} = 2.2 \times 10^{10}$	ref 12c, pH = 2
$k_{14a} = 1.8 \times 10^{10}$	ST[a] on 2,3-dHBA, ref 33, Table 3 at 400 C
$k_{14b} = 0.5 \times 10^{10}$	ST[a] on 2,5-dHBA, ref 33, Table 3 at 400 C
$k_{15} = 7.8 \times 10^9$	ref 27
$k_{15a} \cong k_{15c} \ll k_{15b} \cong k_{15}$	ST[a] on 2,5-dHBA, Figure 3 at 1000 C
$k_{16} = 8.5 \times 10^9$	ref 12c, at pH 7−9
$k_{17} = 1.3 \times 10^{10}$	Table 6 and the value of k_{14}
$k_{17a} = 0.75 \times 10^{10}$	ST[a] on 2,3,4-tHBA, ref 33, Table 4 at 500 C
$k_{17b} = 0.6 \times 10^{10}$	k_{17} and k_{17a}
$k_{18} = 2.4 \times 10^{10}$	Table 6 and the value of k_{14}
$k_{19} = 2.2 \times 10^{10}$	Table 6 and the value of k_{14}
$k_{19a} = 2.2 \times 10^{10}$	ST[a] on 2,3,4-tHBA, ref 33, Table 8 at 500 C
$k_{19d} = 2.2 \times 10^{10}$	ST[a] on 3,4,5-tHBA, ref 33, Table 8 at 500 C
$k_{20} = 2.2 \times 10^{10}$	Table 6 and the value of k_{14}
$k_{23} = 5.5 \times 10^{10}$	Table 6 and the value of k_{14}

[a] ST: stationary state.

$$2,3\text{-dHBA} + OH^{\bullet} \xrightarrow{k_{17}} 2,3,4\text{-tHBA} + 2,3,5\text{-tHBA} \quad (17)$$

$$2,5\text{-dHBA} + OH^{\bullet} \xrightarrow{k_{18}} 2,3,5\text{-tHBA} + 2,4,5\text{-tHBA} + 2,3,6\text{-tHBA} \quad (18)$$

$$3,4\text{-dHBA} + OH^{\bullet} \xrightarrow{k_{19}} 2,3,4\text{-tHBA} + 3,4,5\text{-tHBA} \quad (19)$$

We had previously[33] determined the values of k_{17} and k_{18} relative to k_{14}, and we have now measured k_{19} by the same method. The results are shown in Table 6. In the same way as before, considering a stationary state on 2,3-dHBA and using the results of the electrolysis of 2-HBA described in Table 2 of ref 33, it is possible to obtain k_{14a} and k_{14b} (Table 7) the sum of which, 2.3×10^{10} L mol^{-1} s^{-1}, is close to the literature[12c] value of 2.2×10^{10} L mol^{-1} s^{-1}. Using the results of Figure 3 and by consideration of the stationary states on the dHBA, one finds that k_{15a} and k_{15c} are very small relative to k_{15b}, which is therefore equal to k_{15}. At the end of the electrolysis, the main product is 2,3,4-tHBA (which has not completely reached a stationary state after consumption at 1000 C), the concentration of which is about twice that of 3,4,5-tHBA; this is related to the fact that (i) the rate of consumption of 3,4,5-tHBA is about twice that of 2,3,4-tHBA (Table 6) and (ii) the rate of formation of 2,3,4-

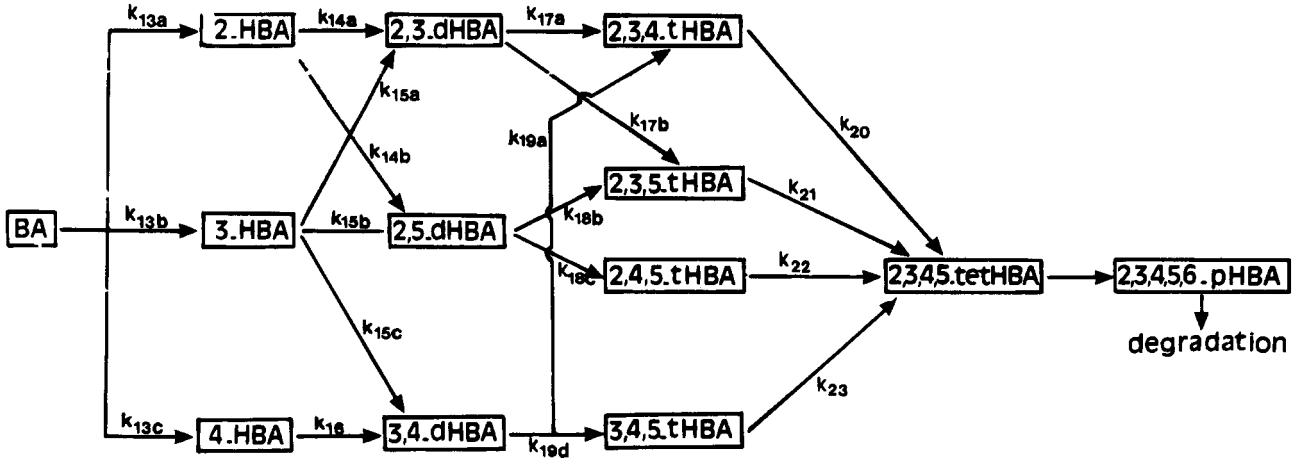


Figure 4. Stepwise hydroxylation of benzoic acid.

TABLE 8: Current Yield in Measured OH• Radical

entry	concentrations (mM) of hydroxylated products: monohydroxylated[a] (C_1)	dihydroxylated[b] (C_2)	trihydroxylated (C_3)	Σ[hydroxylated] ($C_1 + C_2 + C_3$)[c] (mM)	C_{OH} measured[d] (mM)	n_{OH} measured[e] (mmol)	theoretical charge[f] (C)	exp charge (C)	current yield (%)
1	0.60			0.60	0.60	0.045	13.0	50	26
2	1.28	0.12	0.05	1.45	1.67	0.125	36.2	125	29
3	1.54	0.24	0.17	1.95	2.53	0.190	55.0	202	28
4	1.83	0.38	0.48	2.69	4.03	0.302	87.4	340	26
5	1.97	0.56	0.81	3.34	5.52	0.414	119.8	475	25
6	2.07	0.70	1.03	3.80	6.56	0.492	142.4	600	24
7	2.04	0.86	1.22	4.12	7.42	0.567	161.1	702	23
8	2.03	1.08	1.36	4.47	8.27	0.620	179.6	830	22
9	1.99	1.24	1.41	4.64	8.70	0.653	189.0	1000	19

[a] Including phenol. [b] Including hydroquinone. [c] Overall concentration of hydroxylated products. [d] Overall concentration of OH measured, $C_{OH} = C_1 + 2C_2 + 3C_3$. [e] Total number of moles of OH measured, $n_{OH} = C_{OH} \times V$. [f] $Q_{theo} = 3 \times n_{OH} \times F$ C.

tHBA is $k_{17a} + k_{19a} = 3.0 \times 10^{10}$ L mol^{-1} s^{-1} higher than its rate of consumption $k_{20} = 2.2 \times 10^{10}$ L mol^{-1} s^{-1} (Table 7). The course of the successive hydroxylations of BA is shown in Figure 4, and the rate constants are given in Table 7.

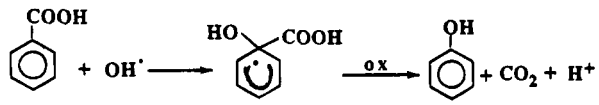
We have also searched for possible decarboxylation products: phenol, catechol (1,2-dihydroxybenzene), resorcinol (1,3-dihydroxybenzene), and hydroquinone (1,4-dihydroxybenzene). Only phenol and hydroquinone were detected in trace amounts. These results are similar to those reported in the literature: the relative yield of phenol/Σ(HBA) was found to be equal to (i) 0.07 in the radiolysis[27] of a pH 7 solution in the presence of ferricyanide as an oxidant and (ii) 0.04 in the radiolysis[26] of a pH 6 solution in the presence of air. As we found less than 1% phenol, it appears that the decarboxylation is somewhat easier in a neutral than an acidic medium. Several reaction paths could explain the formation of phenol: (a) an oxidation of the benzoyloxy radical by OH•

$$OH^\bullet + C_6H_5COO^- \rightleftharpoons OH^- + C_6H_5COO^\bullet$$

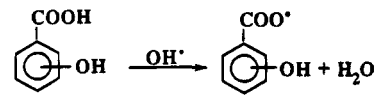
$$C_6H_5COO^\bullet \rightarrow C_6H_5^\bullet + CO_2$$

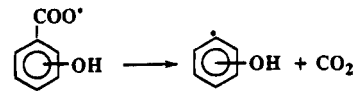
$$C_6H_5^\bullet + OH^\bullet \rightarrow C_6H_5OH$$

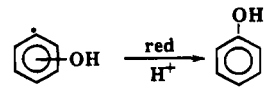
is unlikely, as it would imply a second-order reaction between species in low concentration; (b) an ipso attack on benzoic acid



(c) a decarboxylation of HBA







is also unlikely, as benzoate does not decarboxylate upon electrochemical oxidation (there is no Kolbe reaction from benzoate).[61,62]

Our results can be compared with the results of a recent study of the radiolysis of benzene in aqueous solution.[20] In this investigation, a careful product analysis showed that phenol, the hydroxylation product, amounts to less than 50% of all the identified products. Many of these products arise from ring opening and successive loss of carbon down to formic acid and carbon monoxide. The opening of the benzene ring is assigned to the formation of an endoperoxyalkyl radical. As for benzoic acid, at the end of the electrolysis (Table 4, entry 9), the total amount of identified hydroxylated benzoic acids (HBA, dHBA, tHBA) amounts to 77.5% of the initial benzoic acid. Among the 22.5% of unidentified products, a large part must be assigned tetrahydroxybenzoic acids and pentahydroxybenzoic acid and its degradation products (which could not be quantitized under our conditions, because of their very short retention times). For example, the hydroxylation of 3,4,5-trihydroxybenzoic acid leads to a 44% yield of 2,3,4,5-tetrahydroxybenzoic acid and 4% yield of pentahydroxybenzoic acid.[33] Therefore, the amount of products obtained from the endoperoxyl radical pathway must be quite small.

Finally, we would like to emphasize the high values of the chemical and faradic yields. At the end of the electrolysis, the yield of hydroxylated compounds, by reference to the initial concentration of benzoic acid, comes close to 80%. The faradic yield, which is about 30% at the beginning of the electrolysis, decreases to 19% at the end (Table 8) due to the increasing amount of tetra- and pentahydroxylated compounds, which have very short retention times and are therefore very difficult to quantitize.

Conclusion

Although several authors[26,27] had previously noticed that further hydroxylation of HBAs could be important in the process of the hydroxylation of benzoic acid, this is the first time that this phenomenon of step by step hydroxylation has been evidenced and quantitized. It should not be disregarded in any process involving hydroxyl radicals, as the rates of hydroxylation show a clear tendency to increase with the number of hydroxyl groups already present on the aromatic ring (see Table 7); i.e., the possible activity of polyhydroxylated compounds should be considered in examining the biological effects of hydroxyl radicals. The electrochemical Fenton reaction is well suited for the examination of such reactions, as it allows a controlled production of hydroxyl radicals.

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