extraction with $CHCl_3$ and removal of the solvent the residual yellow oil was stirred in CH_2Cl_2 (50 mL) at room temperature for 48 h. Workup gave 1.2 g (58%) of **8l** as a yellow oil: HRMS (CI; CH_4) for $C_8H_{16}PO_4$ ($M^+ + H$) calcd 207.0786, found 207.0771.

***tert*-Butylethynyl Dimethyl Phosphate (8l). Method B.** A solution of $PhIOH{\cdot}OTs$[13] (3.9 g, 10 mmol) and $NaO_2P(OMe)_2$ (1.48 g, 10 mmol) in methanol (135 mL) was stirred at room temperature under argon for 12 h. Removal of the precipitated NaOTs and evaporation of the solvent gave 3.5 g of $PhIOH{\cdot}O_2P(OMe)_2$: IR (neat, cm^{-1}) 3400–2050 (br, shallow, OH), 3060 (m), 2990 (m), 2950 (s), 2850 (s), 1570 (m), 1465 (s), 1440 (s), 1230–1170 (vs), 1060–980 (vs); ^1H NMR ($CDCl_3$, δ) 3.57 (d, $^3J_{P,H}$ = 11 Hz, CH_3), 7.17–7.50 (m, ArH), 7.83–7.93 (m, ArH), 12.57 (br s, OH); ^{13}C NMR ($CDCl_3$; δ) 53.26 (d, $^2J_{P,C}$ = 6 Hz, CH_3), 124.94, 130.57, 131.33, 132.93 (Ar C). A solution of $PhIOH{\cdot}O_2P(OMe)_2$ (10 mmol), 3,3-dimethyl-1-butyne (2.5 g, 30 mmol), and t.h.e. desiccant (5g) in CH_2Cl_2 (50 mL) was refluxed for 21 h. After removal of the desiccant and evaporation of the solvent chromatographic workup of the residue on silica gel (CH_2Cl_2 as eluent) gave 0.76 g (37%) of **8l**.

1-Octynyl Dimethyl Phosphate (8m). Method A. A mixture of 1-(trimethylsilyl)-1-octyne (1.72 g, 10 mmol), iodosobenzene (2.2 g, 10 mmol), and $BF_3{\cdot}OEt_2$ (1.2 mL, 10 mmol) in $CHCl_3$ (20 mL) was stirred at room temperature for 18 h and then reacted with a solution of $NaO_2P(OMe)_2$ (5.92 g, 40 mmol) in water (40 mL). After extraction with $CHCl_3$ with removal of the solvent the resulting yellow oil was stirred in CH_2Cl_2 (50 mL) at room temperature for 24 h. Workup gave 0.90 g (38%) of **8m** as a yellow oil: HRMS (CI; CH_4) for $C_{10}H_{20}PO_4$ ($M^+ + H$) calcd 235.1099, found 235.1108.

***tert*-Butylethynyl(phenyl)iodonium Diphenyl Phosphate (5: R = *t*-Bu, R′ = C_5H_5). Method C.** A diphenyl phosphate-loaded resin (50 mL) was prepared in a manner described above for the diethyl phosphate system. A solution of *tert*-butylethynyl(phenyl)iodonium tosylate (2.28 g, 5 mmol) in $CHCl_2$ (25 mL) was placed on the column and eluted with 200 mL of CH_2Cl_2. Evaporation of the CH_2Cl_2 gave a yellow oil that crystallized upon standing giving 2.40 g (88%) of *tert*-butylethynyl(phenyl)iodonium diphenyl phosphate as an off white powder: mp 108–110 °C (dec); IR (KBr, cm^{-1}) 2970, 2170, 2140, 1585, 1480, 1250–1200, 1070; ^1H NMR ($CDCl_3$, δ) 1.15 (s, *t*-Bu), 6.80–7.50 (m, ArH), 7.85–8.00 (m, Ar H); ^{13}C NMR ($CDCl_3$, δ) 29.30 ($C(CH_3)$), 30.90 (CH_3), 31.71 (C-1), 114.10 (C-2), 119.53, 120.17, 122.86, 128.84, 130.69, 130.99, 132.74, 152.47 (d, $^2J_{P,C}$ = 7 Hz).

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Mechanism of Autoxidation of 5,7-Dihydroxytryptamine: ^{18}O Is Incorporated on C-4 during Oxidation with $^{18}O_2$

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Abstract: Oxidation of 3-[2-((ethoxycarbonyl)amino)ethyl]-5,7-dihydroxyindole (**12**) with $^{18}O_2/H_2O$ (pH ~8) at 25 °C gave the corresponding unlabeled 5-hydroxyindole-4,7-dione **13** and ^{18}O-labeled isotopomer **14** in a ratio of 32:68 as indicated by mass spectral data. An ^{18}O-isotope effect (of 0.05 ppm) on the ^{13}C chemical shift for C-4 of **14** (vs unlabeled **13**) confirmed that the ^{18}O label of **14** was attached to C-4. Oxidation of **12** with $O_2/H_2{}^{18}O$ as above gave **13** and ^{18}O-labeled **13** in a ratio of 75:25. Treatment of **13** with $H_2{}^{18}O$ under identical conditions gave **13** and ^{18}O-labeled **13** in a ratio of 76:24. These results were interpreted to suggest that during the autoxidation of 5,7-dihydroxytryptamine (**1**) to 5-hydroxytryptamine-4,7-dione (**6**), virtually all of the incorporated oxygen on C-4 is derived from O_2 and not from H_2O.

The neurodegenerative effects of 5,7-dihydroxytryptamine (5,7-DHT, **1**, Scheme I), a selective serotonergic neurotoxin,[7] are believed to be the result of the cytotoxic effects of its products of autoxidation.[1-3] Consequently, much effort has been directed toward characterizing the mechanism and the products of autoxidation of 5,7-DHT. 5,7-DHT, which exhibits pronounced phenol–keto tautomerism[4] with **2** being the predominant keto tautomer[5] at pH 7.4, undergoes rapid autoxidation at the same pH. On the basis of kinetic and various circumstantial evidence, we proposed[5] that 5,7-DHT reacts with O_2 to produce initially hydroperoxide **4** via the carbon radical–superoxide complex **3**. The secondary hydroperoxide **4** then breaks down to quinone **5**, which rearranges to produce more stable para quinone **6**. It was postulated that these quinones in turn may decompose to other products. Among the postulated products of autoxidation, so far only quinone **6** has been isolated[6] and its structure has been confirmed by an unambiguous synthesis.[7]

An alternate mechanism, in which *p*-quinoneimine **7** (Scheme II) is the initial product of autoxidation of 5,7-DHT, has not yet been ruled out. *p*-Quinoneimine **7**, long regarded[8] as the product of autoxidation of 5,7-DHT, appears to be the initial, transient product of electrochemical oxidation of 5,7-DHT under acidic pH. When generated electrochemically, **7** undergoes addition of H_2O followed by electrochemical oxidation to produce quinone **6**

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[1] For selected reviews see: (a) Jacoby, J. H.; Lytle, L. D., Eds. Serotonin Neurotoxins. *Ann. N.Y. Acad. Sci.* **1978**, *305*, 1–702. (b) Baumgarten, H. G.; Klemm, H. P.; Sievers, J.; Schlossbarger, H. G. In *Biology of Serotonergic Transmission*; Osborne, N. N., Ed.; Wiley: New York, 1982; Chapter 10. (c) Jonsson, G. In *Handbook of Chemical Neuroanatomy*; Bjorklund, A., Hokfelt, T., Eds.; Elsevier: Amsterdam, 1983; Vol. 1, Methods in Chemical Neuroanatomy, Chapter XII. (d) Shallert, T.; Wilcox, R. E. In *Neuromethods*; Boulton, A. A., Baker, G. B., Eds.; Humana Press: Clifton, 1985; Vol. 1, General Neurochemical Techniques, pp 343–387.

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[5] Sinhababu, A. K.; Borchardt, R. T. *J. Am. Chem. Soc.* **1985**, *107*, 7618.

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[8] (a) Baumgarten, H. G.; Klemm, H. P.; Lachenmayer, L.; Bjorklund, A.; Lovenberg, W.; Schlossberger, H. G. *Ann. N.Y. Acad. Sci.* **1978**, *305*, 3. (b) Creveling, C. R.; Rotman, A. *Ibid.* **1978**, *305*, 57.

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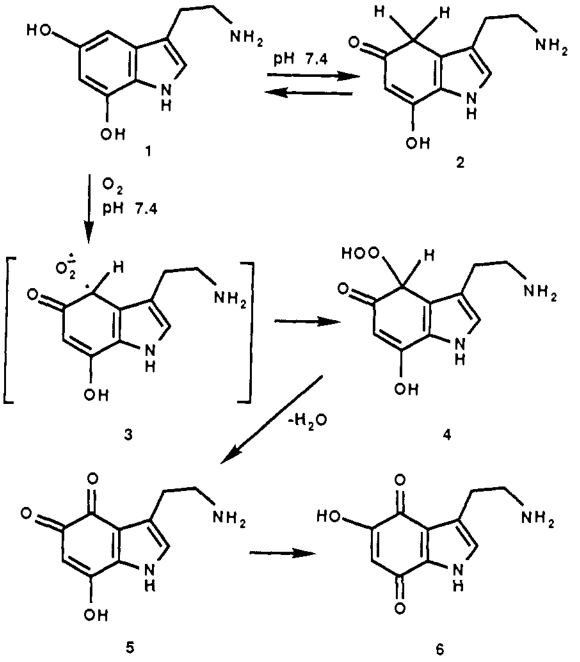
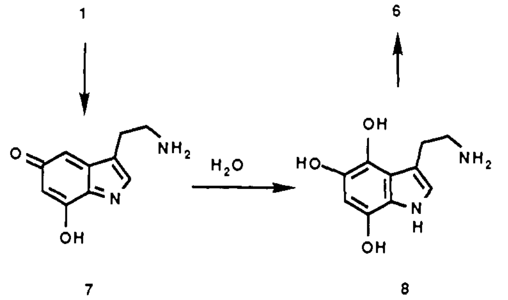
Scheme I



Scheme II



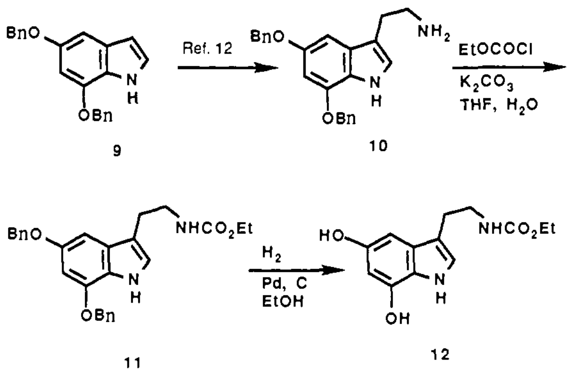
(Scheme II). The results of the electrochemical studies indicate that, in principle, it is possible for 5,7-DHT to undergo oxidation to the same quinone **6** via **7**.

One of the distinguishing features between the two possible mechanisms of autoxidation of 5,7-DHT is that the source of the oxygen atom on C-4 of the common product **6**, is O_2 in Scheme I and H_2O in Scheme II.[9] We thought that by carrying out oxidation of 5,7-DHT with $^{18}O_2/H_2O$ and $O_2/H_2{}^{18}O$, it should be possible to obtain the first, direct evidence regarding the extent to which O_2 and/or H_2O is the source of the incorporated oxygen. We now report the results of these studies.

Results and Discussion

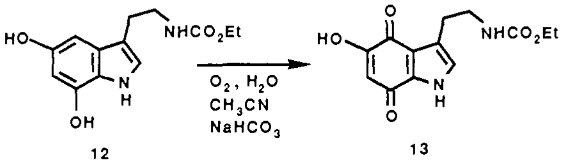
In designing the experimental protocol for the ^{18}O-labeling studies, we felt it would be desirable (and more convenient) to use a suitable amino-protected derivative of 5,7-DHT rather than 5,7-DHT itself for the following reasons. First, it has been reported that the isolation of quinone **6** (as its HCl salt) after the autoxidation of 5,7-DHT required repeated chromatography under acidic conditions.[6] We felt that much of the incorporated ^{18}O-label may be lost during isolation of **6** using such conditions. Second, it was thought that the protection of the amino group of 5,7-DHT would not only improve the solubility of the products in organic solvents but also minimize any side reactions involving the amino group.[5] Among the protecting groups tried were *tert*-butyloxycarbonyl, acetyl, and ethoxycarbonyl. The latter turned out to be the most suitable in rendering **1** and **6** optimally soluble in both organic and aqueous solvents.

Scheme III



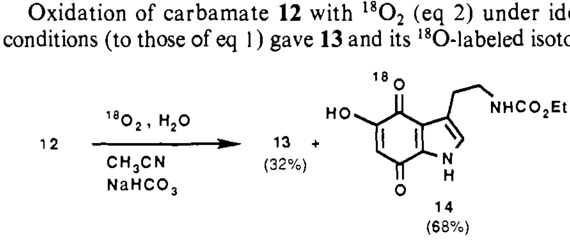
The synthesis of the aminoethoxycarbonyl derivative, which is **12**, is shown in Scheme III. Indole **9**[11] was converted to tryptamine **10** via the corresponding glyoxalamide.[12] The crude tryptamine was then protected as its ethoxycarbonyl derivative to give **11**, which upon catalytic debenzylation furnished the target carbamate **12**. Carbamate **12** was found to discolor even in the solid state and, consequently, it was utilized for the autoxidation reactions immediately after its synthesis.

It was found that the autoxidation of carbamate **12** (eq 1) was complete in 24 h at 25 °C when **12** was exposed to air in H_2O-CH_3CN in the presence of $NaHCO_3$ (pH of the solution in the beginning of the reaction was <8). The product could be precipitated by simply diluting the reaction mixture with H_2O and subsequently acidifying (to pH 2) with HCl with cooling. This minimized exposure of the product to aqueous, acidic solvents. The product was quinone **13**, produced in 83% yield and characterized with MS, ^1H and ^{13}C NMR, and UV-visible spectroscopic techniques.



(1)

Oxidation of carbamate **12** with $^{18}O_2$ (eq 2) under identical conditions (to those of eq 1) gave **13** and its ^{18}O-labeled isotopomer in a ratio of 32:68 as determined by mass spectrometry. The ^{13}C NMR spectrum displayed three resonances for the three types of quinone carbonyls of **13** and its isotopomer ($C_7{=}O$, $C_4{=}O$, and $C_4{=}{}^{18}O$) at 178.50, 178.75, and 178.70 ppm downfield from internal Me_4Si. Observation of this ^{18}O-isotope effect[13] of 0.05 ppm on the chemical shift of C-4 confirmed that the ^{18}O-isotopomer was quinone **14** (eq 2). The observed ^{18}O-isotope effect



(2)

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(9) Another distinguishing features between the two mechanisms is that the autoxidation of 5,7-DHT, according to Scheme II, would require the formation of reduced oxygen species, such as H_2O_2, at both stages of oxidation (**1** to **7** and **8** to **6**). It has been reported (Cohen, G.; Heikkila, R. *Ann. N.Y. Acad. Sci.* **1978**, *305*, 74) that very little or no H_2O_2 is detectable during the autoxidation of 5,7-DHT. As H_2O_2 is not always produced in stoichiometric amounts during the autoxidation of related phenols,[10] these results do not rule out the possibility that small fraction of 5,7-DHT undergoes autoxidation according to Scheme II.

(10) For example, the autoxidation of 5,6-dihydroxytryptamine at pH 7.4, which proceeds with autocatalytic promotion, yields 40–60 mol % of H_2O_2: cf. ref 1b.

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is comparable to those reported in the literature for some simple aldehydes and ketones.[14]

It is of interest to note that in an initial experiment, in which **12** was reacted with $^{18}O_2$ under conditions similar to that described in eq 2, except that EtOH was used in place of CH_3CN and the reaction was terminated after 5.5 h, the ratio of **14** to **13** formed was 82:18. (The product mixture in this case also contained ~10% of the starting material as determined by MS.) These results indicate that the amount of ^{18}O incorporated during autoxidation with $^{18}O_2/H_2O$ is not an accurate reflection of the extent to which O_2 (Scheme I) or H_2O (Scheme II) is the source of the incorporated oxygen. In addition to the possibility that H_2O is a minor source of the incorporated oxygen, the reasons for less than quantitative incorporation of ^{18}O may have been the exchange of ^{18}O of **14** with H_2O during reaction and during workup, partial oxidation of **12** by atmospheric O_2 prior to its exposure to $^{18}O_2$, and the incomplete removal of $^{16}O_2$ from the reaction mixture. Thus, the percent ^{18}O incorporated reflects the minimum extent to which autoxidation proceeds by the incorporation of dioxygen.

Oxidation of carbamate **12** with $O_2/H_2{}^{18}O$ under identical conditions (eq 3) gave quinone **13** and its ^{18}O-labeled isotopomer

$$12 \xrightarrow[\mathrm{CH_3CN\ ,\ NaHCO_3}]{\mathrm{O_2\ ,\ H_2{}^{18}O}} \underset{(75\%)}{13} + \underset{(25\%)}{[^{18}\mathrm{O}]\text{-}13} \tag{3}$$

in a ratio of 75:25 as determined by mass spectrometry. The site at which ^{18}O was incorporated has not yet been determined. As mentioned above, it was suspected that the formation of [^{18}O]-**13** under these conditions may at least in part be due to the exchange of ^{18}O with the carbonyl groups of starting carbamate **12** and the unlabeled products as they form. To determine the extent of this exchange with preformed quinone **13**, the latter was exposed to $H_2{}^{18}O$ under identical conditions (eq 4). The product was a mixture of **13** and [^{18}O]-**13** in a ratio of 76:24.

$$13 \xrightarrow[\mathrm{CH_3CN\ ,\ NaHCO_3}]{\mathrm{H_2{}^{18}O}} \underset{(76\%)}{13} + \underset{(24\%)}{[^{18}\mathrm{O}]\text{-}13} \tag{4}$$

The fact that oxidation of **12** in $H_2{}^{18}O$ and the exchange reaction of **13** with $H_2{}^{18}O$ (eq 3 and 4, respectively) resulted in the formation of **13** and [^{18}O]-**13** in almost the same ratio must be fortuitous. In the absence of precise data on the rate of autoxidation of **12** and the rate of exchange of oxygen of various carbonyls of **13** with $H_2{}^{18}O$ it is not possible to estimate accurately the fraction of [^{18}O]-**13** formed in eq 3 that arose solely by exchange reaction with $H_2{}^{18}O$. Another complication is the contribution in eq 3 of the possible exchange of ^{18}O with the hydroperoxide intermediate of **12** (analogous to **4** of Scheme I). However, the fact that the reaction of **12** in EtOH–H_2O was ~90% complete in 5.5 h suggests that the majority of quinone **13** to be formed was exposed to $H_2{}^{18}O$ for the major part of the reaction time (24 h). Thus, the majority (and if not all) of the [^{18}O]-**13** formed, when the oxidation was done in $H_2{}^{18}O$ (eq 3), arose from simple exchange reaction and not by the addition of $H_2{}^{18}O$ to the *p*-quinoneimine analogous to **7** (cf. Scheme II).

Circumstantial evidence that strengthens the above conclusions is derived from the results of oxidation of **12** with $^{18}O_2$ in EtOH–H_2O described above. In this reaction, evidence for the formation of 4-ethoxy-5,7-dihydroxy-3-[2-((ethoxycarbonyl)amino)ethyl]indone (**15**, structure not shown) could not be derived by TLC, MS, or ^1H NMR. If the *p*-quinoneimine derivative of **12** (analogous to **7** of Scheme II) was a significant intermediate during oxidation, then autoxidation of **12** in EtOH–H_2O should have produced detectable amounts of **15**.

In conclusion the results of these ^{18}O-labeling studies confirm the proposal that the autoxidation of 5,7-DHT proceeds with the incorporation of oxygen on C-4 and that the major source of this oxygen is O_2 and not H_2O. Because of the complex isotope dilution during reaction with $^{18}O_2$ and during workup it was not possible to quantitate the contribution, if any, of H_2O as the source of incorporated oxygen. However, the ^{18}O-labeling data as well as the circumstantial evidence strongly suggest that this contribution is probably negligible.

Experimental Section

General Materials and Methods. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian FT-80A or Varian XL-300 spectrometer while ^{13}C NMR spectra (broad-band proton-noise decoupled) were recorded on a Varian XL-300 spectrometer. The chemical shifts are reported in parts per million (ppm) relative to internal Me_4Si (0.00 ppm). UV–visible spectra were recorded on a Shimadzu-260 recording spectrometer. Electron impact mass spectra (EIMS) and chemical ionization mass spectra (CIMS) were recorded on a Nermag R10-10 quadrupole mass spectrometer with ammonia as the ionizing gas. High-resolution mass spectra (HRMS) were recorded on a ZAB mass spectrometer. Melting points were detected on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Chromatography was performed on a 60–200 mesh silica gel. $^{18}O_2$ containing 97 atom % ^{18}O and $H_2{}^{18}O$ containing 50 atom % ^{18}O were purchased from Cambridge Isotope Laboratories (Woburn, MA).

5,7-Bis(benzyloxy)-3-[2-((ethoxycarbonyl)amino)ethyl]indole (11). To a stirred solution of tryptamine **10**[12] (500 mg, 1.34 mmol) in tetrahydrofuran (7 mL) were added at 25 °C a solution of K_2CO_3 (207 mg, 1.5 mmol) in H_2O (4 mL) followed by EtOCOCl (0.26 mL, 2.7 mmol). The mixture was stirred at 25 °C for an additional 1.25 h and then concentrated in vacuo. The concentrate was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed on a column of silica gel (15 g) with 95:5 CH_2Cl_2–Et_2O as the eluent. Recrystallization of the chromatographed material form cyclohexane–toluene gave 523 mg (88%) of carbamate **11** as a colorless amorphous solid: mp 87 °C; ^1H NMR ($CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 3 H, CH_3), 2.89 (t, 2 H, $\mathit{CH}_2\mathrm{CH_2N}$), 3.47 (q, 2 H, CH_2N), 4.11 (q, J = 7.1 Hz, 2 H, $\mathit{CH}_2\mathrm{CH_3}$), 4.66 (br s, 1 H, $NHCO_2$), 5.08 (s, 2 H, OCH_2Ph), 5.14 (s, 2 H, OCH_2Ph), 6.52 (d, J = 1.9 Hz, 1 H, H-6), 6.73 (d, J = 1.9 Hz, 1 H, H-4), 6.95 (d, J = 2.3 Hz, 1 H, H-2), 7.25–7.50 (m, 10 H, Ph), 8.13 (br s, 1 H, H-1). Anal. ($C_{27}H_{28}N_2O_4$) C, H, N.

5,7-Dihydroxy-3-[2-((ethoxycarbonyl)amino)ethyl]indole (12). A mixture of carbamate **11** (222 mg, 0.5 mmol), 5% Pd on C (70 mg), and deoxygenated EtOH (20 mL) was shaken in a Parr shaker at 40 psi of H_2 for 5 h at 25 °C. The mixture was then filtered under an Ar atmosphere. Evaporation of the solvent in vacuo from the filtrate gave 120 mg (90%) of **12** as a light gray solid which was shown to be pure by ^1H NMR standards and was used in the next step immediately without further purification: mp 101 °C dec; ^1H NMR (Me_2SO-d_6) δ 1.15 (t, J = 7.0 Hz, 3 H, CH_3), 2.64 (t, 2 H, $\mathit{CH}_2\mathrm{CH_2N}$), 3.05–3.24 (m, 2 H, CH_2N), 3.98 (q, J = 7.0 Hz, 2 H, $\mathit{CH}_2\mathrm{CH_3}$), 6.08 (d, J = 1.9 Hz, 1 H, H-6), 6.28 (d, J = 1.9 Hz, 1 H, H-4), 6.89 (d, J = 2.3 Hz, 1 H, H-2), 7.07 (br s, 1 H, $NHCO_2$), 8.35 (s, 1 H, OH), 9.28 (s, 1 H, OH), 10.18 (br s, 1 H, H-1); HRMS (EI) *m/e* calcd for $C_{13}H_{16}N_2O_4$ 264.1109, found 264.1103.

Oxidation of 12 with O_2 in H_2O. A mixture of **12** (53 mg, 0.2 mmol), $NaHCO_3$ (76 mg, 0.9 mmol), H_2O (2.5 mL), and CH_3CN (4 mL) was stirred at 25 °C for 24 h in a stoppered flask containing at least 60 mL of air above the solution. The mixture was concentrated to ~1 mL in vacuo and then acidified at 0–5 °C to pH ~2 with 6 N HCl. The precipitate was collected by filtration and recrystallized from EtOAc–cyclohexane to give 46 mg (83%) of 3-[2-((ethoxycarbonyl)amino)ethyl]-5-hydroxyindole-4,7-dione (**13**) as a red solid: mp 180 °C dec; UV–visible max (0.05 M phosphate buffer, pH 7.4) 527 (ϵ 1100), 302 (ϵ 11 000), 235 nm (ϵ 12 000); UV–visible max (0.05 M HCl–KCl buffer, pH 2.0) 466, 339, 286, 226 nm; ^1H NMR δ (Me_2SO-d_6) 1.12 (t, J = 7.1 Hz, 3 H, CH_3), 2.77 (t, J = 6.8 Hz, 2 H, $\mathit{CH}_2\mathrm{CH_2N}$), 3.06–3.40 (m, 2 H, CH_2N), 3.95 (q, J = 7.1 Hz, 2 H, $\mathit{CH}_2\mathrm{CH_3}$), 5.64 (s, 1 H, H-6), 6.90 (d, J = 1.9 Hz, 1 H, H-2), 7.04 (br s, 1 H, $NHCO_2$), 11.49 (br s, 1 H, OH), 12.35 (br s, 1 H, H-1); ^{13}C NMR (Me_2SO-d_6) δ 14.58 (CH_3), 25.71 (CH_2CH_2N), 38.55 (CH_2N), 59.33 (OCH_2), 106.27 (C-6), 119.41 (C-3), 122.64 (C-2), 123.13 (C-3a), 132.01 (C-7a), 156.10 (CO_2), 159.50 (C-5), 178.50 (C-7), 178.75 (C-4); CIMS *m/e* (rel intensity) 278 (100.0 MH^+), 280 (16.0), 281 (4.8); HRMS (EI) *m/e* calcd for $C_{13}H_{14}N_2O_5$ 278.0902, found 278.0913. Anal. ($C_{13}H_{14}N_2O_5$) C, H, N.

Oxidation of 12 with $^{18}O_2$ in H_2O. A stirred mixture of **12** (98 mg, 0.38 mmol), $NaHCO_3$ (140 mg, 1.67 mmol), deoxygenated H_2O (5 mL), and deoxygenated CH_3CN (9 mL) under an Ar atmosphere was cooled in a dry ice–acetone bath (−78 °C) and evacuated for a few seconds (to ~10 mmHg). Immediately after that, $^{18}O_2$ (containing 97 atom % ^{18}O) was introduced to restore pressure to atmospheric pressure. The mixture was warmed to 25 °C and stirred under excess $^{18}O_2$ (volume of $^{18}O_2$ (gas) above the solution was ~60 mL) for 24 h. Workup as described above

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gave 72 mg of a red solid with mp and ^{1}H NMR properties identical with those of quinone **13**. The ^{13}C NMR spectrum indicated that ^{18}O had been incorporated on C-4 and the CIMS data indicated that the product consisted of 68% of ^{18}O-labeled quinone **14** and 32% of unlabeled quinone **13**: ^{13}C NMR (Me_2SO-d_6) δ 14.60 (CH_3), 25.73 ($\mathit{CH_2}CH_2N$), 38.56 (CH_2N), 59.37 (OCH_2), 106.31 (C-6), 119.43 (C-3), 122.65 (C-2), 123.15 (C-3a), 132.05 (C-7a), 156.11 (CO_2), 159.47 (C-5), 178.50 (C-7), 178.70 (C-4 of **14**, rel intensity 41.6), 178.75 (C-4 of **13**, rel intensity 28.8); CIMS *m/e* (rel intensity) 279 (51.9 MH$^+$), 281 (100.0), 282 (17.2).

Oxidation of 12 with O_2 in $H_2{}^{18}O$. To a stirred mixture of **12** (27 mg, 0.1 mmol), $NaHCO_3$ (38 mg, 0.45 mmol), and CH_3CN (2.5 mL) under an atmosphere of dry air (volume of air above solution was 60 mL) was added $H_2{}^{18}O$ (1 g, containing 50 atom % ^{18}O) and the stoppered reaction mixture was stirred at 25 °C for 24 h. Workup as described above gave 16 mg of a red solid with melting point and ^{1}H NMR properties identical with those of quinone **13**: CIMS *m/e* (rel intensity) 279 (100.0, MH$^+$), 280 (15.5), 281 (18.8). Comparison of these MS data with those of pure **13** indicated formation of **13** and ^{18}O-labeled **13** in a ratio of 87.7:12.3 (or in a ratio of 75:25 based on $H_2{}^{18}O$ containing 100 atom % ^{18}O).

Treatment of 13 with $H_2{}^{18}O$. To a mixture of **13** (14 mg, 0.05 mmol), $NaHCO_3$ (19 mg, 0.23 mmol), and CH_3CN (2.5 mL) under an Ar atmosphere was added $H_2{}^{18}O$ (1 g, containing 50 atom % ^{18}O) and the stoppered reaction mixture was stirred at 25 °C for 24 h. Workup as described above for the isolation of **13** gave 10 mg of a red solid with melting point and ^{1}H NMR properties identical with those of quinone **13**: CIMS *m/e* (rel intensity) 279 (100, MH$^+$), 180 (17.5), 281 (18.6). Comparison of these MS data with those of pure **13** indicated formation of **13** and ^{18}O-labeled **13** in a ratio of 87.9:12.1 (or in a ratio of 76:24 based on $H_2{}^{18}O$ containing 100 atom % ^{18}O).

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Kinetics and Mechanism of the Bromination of Phenols and Phenoxide Ions in Aqueous Solution. Diffusion-Controlled Rates[1]

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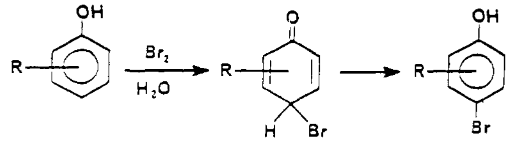
Abstract: Second-order rate constants ($k_2{}^{obsd}$) for the aqueous bromination of various phenols, pyridones, and pyrimidones have been measured in the pH range 0–7. For phenols the acidity dependence follows: $k_2{}^{obsd} = k_2 + k_2'K_a/[H^+]$, where k_2 is for bromine attack on the phenol, k_2' is for the phenoxide ion, and K_a is the phenol acid dissociation constant. Values of k_2 vary widely and systematically ($\rho^+ = -5.2$ for *p*-substituted phenols), but for 16 phenoxide ions the values of k_2' are nearly constant: $(1\text{-}9) \times 10^9$ M^{-1} s^{-1}, at or close to the diffusion-controlled limit. Strong electron withdrawal ($\sigma^+ > 0.9$) is necessary to lower k_2' much below this limit. Since the k_2' values hardly vary, the contribution of the anion route is determined largely by the phenol acidity. The facile tribromination of phenol arises since the mono- and dibromophenols are more reactive than phenol at intermediate pHs. Tribromide ion reacts with phenoxide ion at almost the same rate as Br_2, but its reaction with phenol is insignificant. The mechanism of bromination of phenols via cyclohexadienones is discussed; it appears that the protonated dienone is not a mandatory intermediate. Values of ρ^+ for the bromination of monosubstituted benzenes in water, CF_3COOH, and in CH_3COOH are virtually the same, suggesting that solvent stabilization of the Wheland intermediate is not of primary importance.

Phenols react readily with bromine to undergo electrophilic substitution at positions ortho and para to the hydroxyl group.[2] These reactions proceed via cyclohexadienone intermediates,[3,4] and recent studies in this laboratory have shown that transient 4-bromo-2,5-cyclohexadienones can be observed during the bromination of phenol and alkyl derivatives (eq 1) (and 1-naphthols) in aqueous solution.[5]



(1)

In aqueous solution the bromination of phenol proceeds rapidly,[6] and with sufficient bromine it leads quickly to the formation of 2,4,6-tribromophenol.[7] In fact, controlled mono- or dibromination of phenol is difficult to achieve. Among other things, the present work provides insight into the course of the tribromination and shows how the reaction can be controlled.

There have been few previous kinetic studies of the bromination of simple phenols in aqueous solution, presumably because the reactions are so fast that special techniques are required. Bell and Rawlinson[6] studied six phenols in dilute aqueous perchloric acid by using a potentiometric method. They showed that bromine reacts with the phenol or its anion, depending upon the pH. Phenoxide ions bearing only one electron-withdrawing substituent react with bromine at or near the diffusion-controlled limit,[8] and for some of these anions a small amount of reaction was attributed

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