# Mechanism of the Oxidation of Dopamine by the Hydroxyl Radical in Aqueous Solution

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**Abstract:** The hydroxyl radical (HO·) reacts with dopamine (4-(2-aminoethyl)-1,2-benzenediol) via one-electron oxidation producing *o*-semiquinone and *o*-semiquinone anion radicals, $k = 5.9 \times 10^9$ $M^{-1}$ $s^{-1}$. Reaction of HO· with protonated dopamine ($H^+QH_2$) proceeds via addition to the aromatic ring, while reaction with deprotonated dopamine ($H^+QH^-$) proceeds via direct, one-electron oxidation. The isomeric hydroxycyclohexadienyl radicals formed via addition of HO· to $H^+QH_2$ yield three kinetically distinguishable groups (1- and 2-, or 3- and 6-, or 4- and 5-hydroxycyclohexadienyl radicals) with regard to rates of water elimination to produce semiquinone radicals; dehydration is "very fast" (addition of HO· ipso to an OH group), "fast", or "slow". The fast and slow reactions are acid and base catalyzed, with minimal rates at pH 4-5. Acid catalysis appears to be specific, while base catalysis is general. Spectra were determined for the initial products of HO· reaction with $H^+QH_2$ at pH 3.1 and 4.7. Deprotonation of the HO· adducts is the rate-controlling step in the base-catalyzed water loss at pH ≤8.5. For the slow water elimination, rate constants for proton transfer from the adducts to $H_2O$, $HPO_4^{2-}$, $HO^-$, and $PO_4^{3-}$ were $1.7 \times 10^2$, $6.5 \times 10^8$, $\leq 1.5 \times 10^{11}$, and $\leq 7.0 \times 10^{11}$ $M^{-1}$ $s^{-1}$, respectively; for the fast reaction, rate constants for $H_2O$ and $HPO_4^{2-}$ were $1.1 \times 10^3$ and $2.2 \times 10^8$ $M^{-1}$ $s^{-1}$, respectively.

## Introduction

Since the first report of the characteristic color reactions of catecholamines (contained in aqueous extracts of biological samples) by Vulpian in 1856,[1] interest in this class of biogenic amines has fluorished.[2] The discovery that Parkinson's disease is accompanied by a specific deficit of dopamine (4-(2-aminoethyl)-1,2-benzenediol) in the nigro-striatal dopamine neuron system of the brain has led to the successful application of a metabolic precursor of this neurotransmitter, i.e., L-Dopa (3-hydroxy-L-tyrosine), in the treatment of the disease.[3-5] In addition, considerable evidence suggests that levels of brain dopamine are significant in psychotic disorders, especially schizophrenia.[3,5,6] The pathologic significance of dopamine and its functioning as a neurotransmitter have stimulated interest in its chemistry. The general features of the oxidative chemistry of the catecholamines are well known.[7] Recent studies have focused on elucidation of the characteristics of the radical intermediates in the oxidation. Methods employed in the studies of catecholamines and related *o*-dihydroxybenzenes have included pulse radiolysis,[8-15] photolysis,[16,17] and electrochemical oxidation.[18]

The mechanism of production of phenoxyl radicals (i.e., the one-electron oxidation product) from the reaction of hydroxyl radical (HO·) with hydroxylated aromatic species in aqueous solution has been extensively studied.[14,19] Reaction proceeds via an initial addition of HO· to the aromatic ring affording isomeric hydroxycyclohexadienyl radicals, which can eliminate water in acid/base-catalyzed reactions to yield their corresponding phenoxyl radicals. In analogy with this general mechanism, the reaction of HO· with dopamine ($H^+QH_2$) is expected to result ultimately in oxidation to the semiquinone radical ($H^+QH$·). The present investigation focuses on the mechanism of the oxidation of dopamine by the hydroxyl radical in aqueous solution, using the technique of pulse radiolysis with detection of transients via optical absorption. The exact paths leading to the one-electron oxidation of dopamine by HO· are established, particularly the nature of the acid/base-catalyzed water-elimination reactions. The results provide significant mechanistic information with general applicability to hydroxyl-radical reactions with hydroxylated aromatic species, and give kinetic and spectral data of special interest in catecholamine chemistry.

## Experimental Section

Dopamine, obtained as the hydrochloride salt (Calbiochem-Behring), was used as received. Water was purified either by passage through a Millipore Milli-Q filtering system, or by distillation from an all-glass Corning Ag-1a still in an oxygen atmosphere with the vapor passing through a quartz chamber at 600 °C. All other chemicals were reagent grade (Baker) and were used without further purification.

Freshly prepared irradiation solutions were deoxygenated by bubbling with $N_2O$. For alkaline solutions, dopamine was added just prior to the beginning of the experiment to minimize autoxidation by traces of $O_2$.

Kinetic spectrophotometric experiments were carried out using a computer-controlled pulse radiolysis system.[20] Computer-controlled averaging of absorbance/time data was used for both kinetic and spectral measurements. The radiation sources used were: (1) an ARCO LP-7 linear accelerator (Radiation Laboratory, University of Notre Dame) which supplies pulses of 7-MeV electrons (pulse width 2-10 ns), or (2) a Van de Graaff accelerator (Radiation Research Laboratories, Carnegie-Mellon University) which provides 2.8-MeV electrons (pulse width 0.5-2 μs). A single-pass flow system with a 5- or 10-mm cell path length

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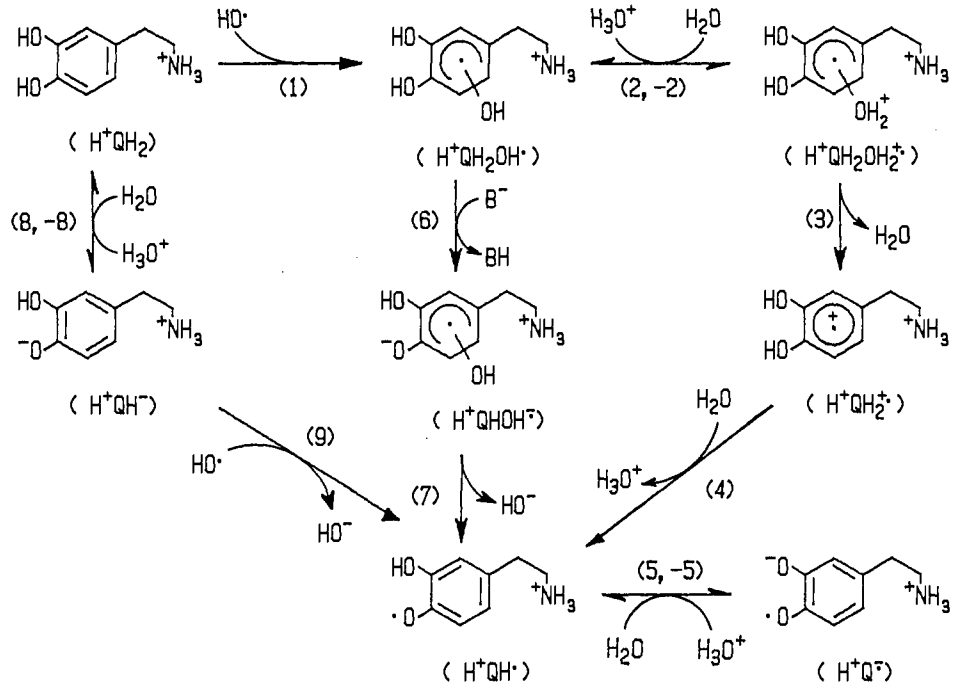
Scheme I




was used. A Corning 9-54 filter (90% cutoff at 250 nm) was placed between the analyzing light and the sample cell to prevent photolysis of dopamine, and a shutter was employed so that solutions were completely shielded between pulses. All experiments were carried out at room temperature (22–23 °C). Radical concentrations and molar absorptivities were determined relative to thiocyanate dosimetry using $\epsilon_{490} = 7600$ $M^{-1}$ $cm^{-1}$ for $(SCN)_2^-$ and $G[(SCN)_2^-] = 6.0$.[21]

Radiolysis of water produces hydroxyl radicals (HO·), solvated electrons ($e_{aq}^-$), and hydrogen atoms (H) with $G$ values (number of the species produced per 100 eV of absorbed energy) of 3.2, 2.8, and 0.5, respectively. In $N_2O$-saturated solutions, $e_{aq}^-$ is rapidly converted to HO· ($e_{aq}^- + N_2O + H_2O \rightarrow N_2 + HO^- + HO\cdot$, $k = (9.1 \pm 0.2) \times 10^9$ $M^{-1}$ $s^{-1}$)[22] or H ($e_{aq}^- + H^+ \rightarrow H$, $k = (2.3\text{–}2.4) \times 10^{10}$ $M^{-1}$ $s^{-1}$)[23] so that only HO· and H remain to react with dopamine. At the pH used for spectral measurements, the contribution of electron neutralization is negligible and $G(HO\cdot) = 6.0$ is used for computation of molar absorptivities of product radicals; $G(-H^+QH_2) = 6.5$ is used in corrections for bleaching to account for reaction of H with the parent compound. Since 1 rd is equivalent to an absorbed dose of $6.24 \times 10^{13}$ eV/g, a dose of 1000 rd produces 6.3 $\mu$M of a species with $G = 6$.

## Results and Discussion

The anticipated sequence of reactions in the oxidation of dopamine ($H^+QH_2$) to the semiquinoid state by the hydroxyl radical is: (1) addition of HO· to the benzene ring yielding hydroxycyclohexadienyl radicals ($H^+QH_2OH\cdot$), (2) elimination of $H_2O$ from the adducts in acid/base-catalyzed reactions to produce the semiquinone radical ($H^+QH\cdot$), and (3) equilibration of the semiquinone radical with the semiquinone anion radical ($H^+Q^-\cdot$) where $pK_a = 4.7$.[24] Under appropriate conditions, absorbance changes corresponding to HO· addition, water elimination, and the subsequent bimolecular decays of the semiquinone/semiquinone anion radicals are observed, and are sufficiently time resolved so that each process can be examined (Figure 1). The rate of the initial reaction between dopamine and HO·, spectrum of the species present immediately following the HO· reaction, pH dependence of the water-elimination reaction, and effect of phosphate buffer and ionic strength on the water-loss reactions have been examined. Scheme I is a mechanistic summary.

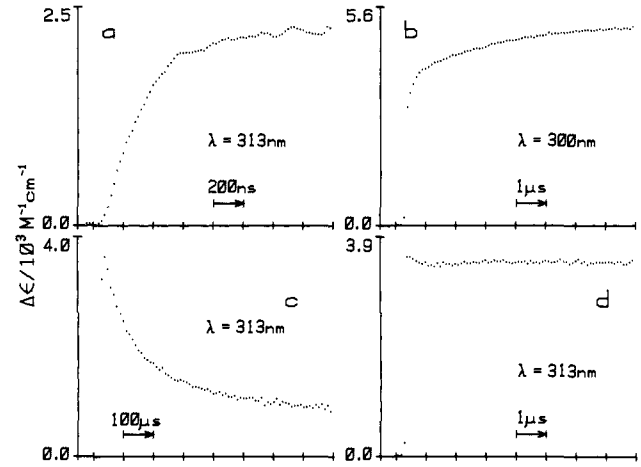



**Figure 1.** Absorbance changes following pulse irradiation of dopamine solutions at pH 3.1: (a) reaction of HO· with dopamine, (b) water-loss reactions, (c) bimolecular radical decay, and (d) water-loss reactions. $N_2O$-saturated solutions contained initially dopamine, 1.0 mM (except for (a) which had 0.2 mM); phosphate, 5.0 mM (except (a) which had no phosphate); $HClO_4$ for pH adjustment; and HO·, 2–3 $\mu$M.

The structure shown for $H^+QH_2OH\cdot$ denotes the presence of the six possible HO· adducts. The initial phenolic group deprotonation (shown as deprotonation of the 1-hydroxy for $H^+QH^-$, $H^+QHOH^-\cdot$, and $H^+Q^-\cdot$) probably occurs statistically between the 1- and 2-hydroxy groups.[25] The main features of the mechanism are: (1) HO· reacts with $H^+QH_2$ by ring addition, producing isomeric hydroxycyclohexadienyl radicals (reaction 1); (2) HO· reacts with deprotonated dopamine ($H^+QH^-$; the $pK_a$ of the phenolic group is 8.9[25]) via direct electron transfer affording a semiquinone radical (reaction 9); (3) acid- and base-catalyzed water elimination from $H^+$ $QH_2OH\cdot$ yields semiquinone radical, with minima in the rates at pH 4–5; (4) the adducts fall into three kinetically distinguishable groups with regard to water elimination (i.e., elimination is "very fast", "fast", or "slow"); and (5) reaction of HO· with dopamine results ultimately in the production of

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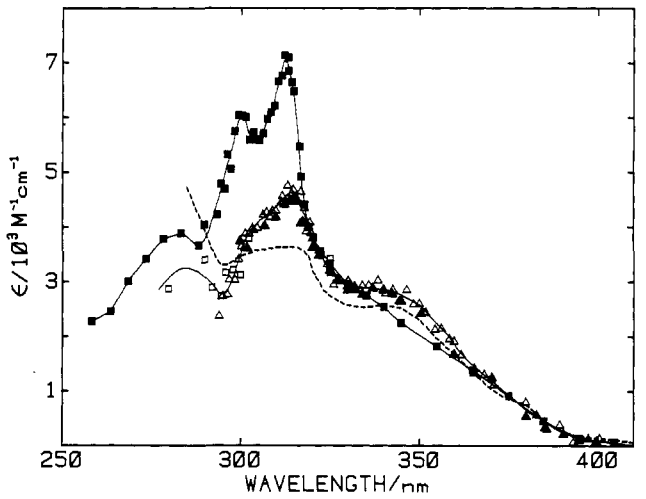


**Figure 2.** Spectra of transients at pH 4.7. (▲, □, △) Spectrum of products present immediately following reaction of HO· with dopamine, obtained at 1.2 μs (▲, 0.9–1.45 μs av), 3.4 μs (□, 2.9–3.9 μs av), and 3.8 μs (△, 2.8–4.8 μs av) after the pulse from three different series of measurements. (■) spectrum of products present following all water-loss reactions, obtained at 294 μs (276–312 μs av). $N_2O$-saturated solutions contained: dopamine, (△, ▲) 1.0 mM, (□) 0.2 mM, or (■) 0.1 mM; and phosphate buffer, 5 mM. Doses of 220–370 rd/pulse were delivered with a 10-ns (□, ▲) or 1-μs (■, △) wide pulse. Dashed line is spectrum of products present immediately following HO· reaction at pH 3.1 (Figure 3).

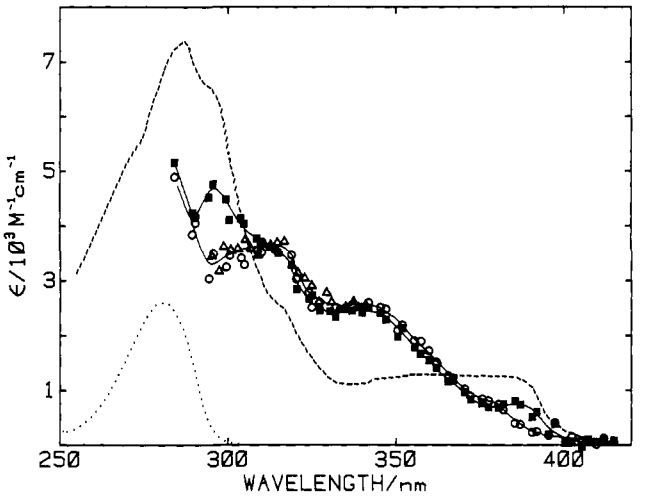


**Figure 3.** Spectra of transients at pH 3.1. (△, ○) Spectrum of products present immediately following reaction of HO· with dopamine, obtained at 370 ns (△, 270–470 ns av) and 900 ns (○, 0.6–1.2 μs av). (■) Spectrum of products present following the fast water-loss reaction obtained at 10.7 μs (10.2–11.2 μs av). $N_2O$-saturated solutions contained: dopamine, (△) 2.4 mM or (○, ■) 1.0 mM; phosphate buffer, (△) 0 mM or (○, ■) 5 mM; and $HClO_4$ for pH adjustment. Dashed line is the spectrum of the dopamine semiquinone radical;[24] dotted line is parent compound.

*o*-semiquinone and *o*-semiquinone anion radicals.

**Reaction of HO· with Dopamine.** The rate of the reaction of $H^+QH_2$ with HO· was determined by varying $[H^+QH_2]$ at pH 4.7, where the rate of water loss is minimized. The reaction was observed as an absorbance increase to a plateau at 325 nm, an isosbestic wavelength for $H^+QH_2OH$· and subsequent water elimination products. Bimolecular rate constants of $5.8 \times 10^9$, $6.3 \times 10^9$, and $5.5 \times 10^9\ M^{-1}\ s^{-1}$ were obtained for $[H^+QH_2] = 9.4 \times 10^{-5}$, $2.07 \times 10^{-4}$, and $1.00 \times 10^{-3}$ M, respectively, confirming the assignment of the observed pseudo-first-order rate constants to the reaction between HO· and dopamine and yielding $k_1 = 5.9 \times 10^9\ M^{-1}\ s^{-1}$. Essentially complete scavenging of HO· was accomplished; $G(\epsilon_{325})$ values of $2.00 \times 10^4$, $1.99 \times 10^4$, and $2.02 \times 10^4\ M^{-1}\ cm^{-1}$, respectively, were obtained. Thus, HO· reacts with dopamine essentially on every collision, as it does with other aromatic species.[25-28]

The switch in mechanism from addition of HO· to direct electron transfer (reaction 9) when the dopamine phenolic group is deprotonated is apparent from the decreased $\Delta A$ values associated with $H_2O$ loss which are observed in alkaline solution with increasing pH. This was not due simply to shifts in the reactant/product spectra since the decreasing $\Delta A$'s were observed over a broad wavelength region. At pH 9, where ~50% of the dopamine is present at $H^+QH^-$, $\Delta A$ at 313 nm of the slow reaction is reduced by ~50% from the value near pH 8: this correlates well with the $pK_a$ of the phenolic group. At pH 11, the semiquinone anion appeared to be formed "instantaneously" upon reaction of HO· with dopamine. Direct electron transfer from $H^+QH^-$ to HO· is not surprising since $H^+QH^-$ is oxidized directly even by $O_2$.[29] If reaction of HO· with $H^+QH^-$ proceeded via an initial addition to the ring, the product would be $H^+QHOH^-$·, i.e., the radical which is produced by base-catalyzed deprotonation of HO· adducts of $H^+QH_2$ (reaction 6). Thus, the rate of the "water elimination" reaction in alkaline pH would be determined by reaction 7. Since the spectra of $H^+QHOH^-$· and $H^+QH$· should be substantially different, absorbance changes would be observed; however, no such changes occurred, and reaction of HO· with $H^+QH^-$ is assigned to reaction 9 (vide infra).

**Spectra of the Initial Products of HO· Reaction.** Since the rate for water loss is minimized at pH 4–5, this pH range should be optimum for determination of the optical absorption spectrum of the initial products of the reaction of HO· with dopamine. For $\lambda \geq 300$ nm, the spectrum of the transients present 1.2 μs after the pulse was determined with a 1.0 mM dopamine solution (Figure 2). Measurements below 300 nm require the use of more dilute solutions ($\lambda_{max}$ 280 nm, $\epsilon_{280}$ 2600 $M^{-1}\ cm^{-1}$); the time required for completion of the HO· reaction and the earliest possible time for spectral analysis increase correspondingly. All measurements were obtained under conditions where the HO· reaction was ≥99% complete, and where negligible water loss could have occurred. Bimolecular radical–radical reactions do not interfere with spectral measurements. Comparison of the 1.2- and 3.4–3.8-μs spectra shows only a slight increase in absorbance in certain wavelength regions, so that Figure 2 accurately depicts the spectrum of the transients present immediately after reaction with HO·. There are maxima at 338 and 314 nm and a shoulder at 300–306 nm. The products of the water-loss reactions have absorption maxima at 300 and 313 nm, corresponding to the semiquinone and semiquinone anion radicals,[24] respectively (Figure 2). Isosbestic points were observed at 320 and 365 nm. The spectrum of the initial products is similar to reported spectra for hydroxycyclohexadienyl radicals of other aromatic species:[26,30] broad peaks in the 300- to 450-nm region are typical. However, contributions from the 288- and 313-nm maxima of the semiquinone and semiquinone anion ($pK_a \sim 4.7$[24]) are clearly visible.

Measurements at pH 3.1 show that the intensity of the absorption maximum at 338 nm in the initial products is constant, while that of the 313-nm peak is reduced substantially with an accompanying hypsochromic shift toward 300 nm (Figure 3). These spectral changes are consistent with the conversion of the semiquinone anion to semiquinone which would occur with a pH reduction from 4.7 to 3.1. Thus, the formation of semiquinone and/or semiquinone anion radicals prior to completion of HO· addition[31] is confirmed by: (1) absorption peaks in the initial

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(28) Farhataziz; Ross, A. B. *Natl. Stand. Ref. Data Ser., Natl. Bur. Stand.* **1977**, No. 59.
(29) Acid solutions of dopamine are very stable and unaffected by oxygen. Alkaline solutions, however, must be rigorously protected from $O_2$; if not, the characteristic red color of the dopamine quinone rapidly appears.
(30) O'Neill, P.; Steenken, S.; Schulte-Frohlinde, D. *J. Phys. Chem.* **1975**, *79*, 2773–9.

product spectra with maxima near those of the semiquinone and/or semiquinone anion radicals, and (2) correspondence of pH-dependent shifts in these maxima with those of the semiquinone/semiquinone anion radicals. This can result if direct H-atom abstraction by HO· occurs, or if the water-loss reaction of one or more of the HO· adducts is rapid relative to HO· addition (i.e., water elimination is very fast).

Since at pH 3.1 the rate constants of the fast and slow water-loss reactions differ by a factor of ca. 20, a spectrum of the species present following the fast water loss could be obtained, with little contribution from the slow reaction (Figure 3). The resulting spectrum clearly shows development of features associated with the semiquinone radical; namely, the intensity of the peak near 300 nm increases and the semiquinone radical shoulder at 350–400 nm develops.

**Water-Loss Reactions of the HO· Adducts of Dopamine.** Following the addition of HO· to dopamine, conversion of $H^+$-$QH_2OH$· to the semiquinone/semiquinone anion radicals is observed, the rates of which are independent of initial dopamine and radical concentrations. The identification of the radicals produced as the *o*-semiquinone/*o*-semiquinone anion pair is confirmed by spectral comparison with radicals obtained from the solvated electron reduction of 4-*tert*-butyl-1,2-quinone and HO· oxidation of 4-*tert*-butyl-1,2-dihydroxybenzene.[13,24] The semiquinone and semiquinone anion maxima at 288 and 313 nm,[24] respectively, lie in the wavelength region typical of *o*-semiquinones; *m*- and *p*-semiquinones have absorption maxima in the 420–450-nm region.[9,12,15] It is virtually impossible for *m*- or *p*-semiquinones to be produced, since the added hydroxyl group is chemically distinct from the native phenolic groups (except in the case of addition ipso to a phenolic group); the induced aliphatic character of the carbon atom at which addition occurs causes the added OH to be lost in the subsequent water-elimination process.

The semiquinone/semiquinone anion radicals are not produced from the HO· adducts in a single first-order reaction. The intermediacy of fast and slow processes is obvious at some wavelengths (Figure 1) and is also apparent from attempts to fit the absorbance increases. That is, the total absorbance growth (following the initial reaction with HO·) cannot be fit with a single exponential; however, the data could be fit well by assuming *two concurrent first-order reactions*. The rate constants thus obtained were independent of the analysis wavelength. The slow and fast reactions were very sensitive to pH: with increasing pH, the rate constants first decreased and then increased, with minima occurring in the region of pH 4–5 (Figure 4). At pH 4.7, the water-loss reaction is so slow that extremely low doses (30 rd per pulse) were required for separation from the ensuing radical–radical reactions. The improvement with decreasing dose was visible by a decrease in the slow first-order rate constant and an increase in $G(\epsilon_{313})$; when the dose was decreased from 280 to 30 rd per pulse, the rate constant decreased from $1.62 \times 10^4$ to $0.96 \times 10^4$ $s^{-1}$, while $G(\epsilon_{313})$ increased from $4.4 \times 10^4$ to $5.2 \times 10^4$ $M^{-1}$ $cm^{-1}$. Similar observations were made at other pH values: below a critical pH-dependent dose, the rate constants and $G(\epsilon)$ values were independent of dose.[32]

The observation of the presence of $H^+QH$·/$H^+Q^-$· immediately after HO· reaction and the apparent occurrence of two concurrent water-loss reactions leading to $H^+QH$·/$H^+Q^-$· suggest that the six possible adducts of dopamine are divided into three groups with distinct rate constants for elimination of water, i.e., very fast,

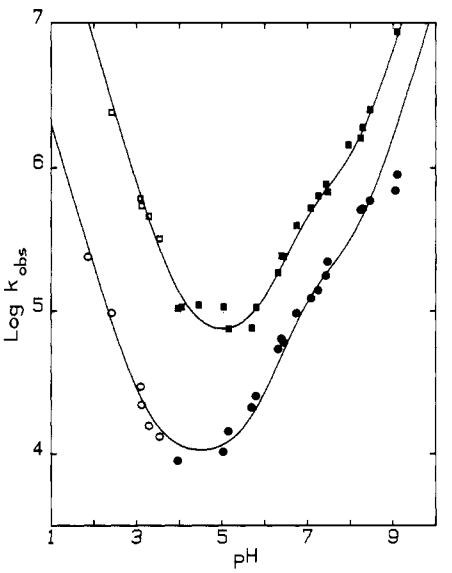
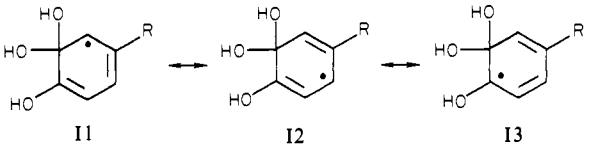



**Figure 4.** Dependence of the observed water-elimination rate constants on pH. Method for obtaining the fast (□, ■) and slow (○, ●) rate constants from $A$ vs. $t$ data is given in text. $N_2O$-saturated solutions contained: dopamine, 0.2–5.0 mM; phosphate buffer, (□, ○) 0 mM or (■, ●) 5 mM; and $HClO_4$ at pH ≤4.5 for pH adjustment. Lines drawn were generated using eq 19 with the values given in Table I ($k_{6e} \equiv 0$).

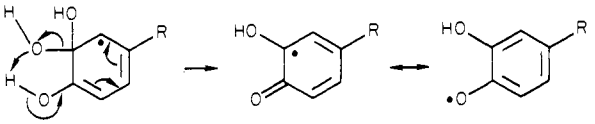
fast, and slow elimination. An obvious division would be three groups of two each, where HO· addition occurs ipso, ortho, or para to a phenolic group, i.e., groups containing 1- and 2-, or 3- and 6-, or 4- and 5-hydroxycyclohexadienyl radicals. Three resonance structures contribute to each of the six adducts. For the ipso adduct (ring position 2, R = $-(CH_2)_2NH_3^+$)) these structures are **I1**, **I2**, and **I3**. It is probable that ipso addition produces the "very




(10)

I1 I2 I3

fast" water loss since a concerted reaction via formation of a five-membered-ring transition state can be drawn from any resonance form, i.e., reaction 2a. Also, it is probable that the




(2a)

gem-diols produced by ipso addition would be the most reactive in an acid/base catalyzed elimination.

The resonance structures corresponding to **I3** (where the radical center and OH group are located at one carbon) of the two ipso and the two ortho adducts have conjugated systems. Corresponding structures for the para adducts exhibit a "crossed" conjugation and therefore would be expected to have absorptions at significantly shorter wavelengths. In Figure 3, conversion of the "fast" adduct to semiquinone has essentially no effect on the 338-nm absorption band (i.e., 338 nm is an isosbestic wavelength for the "fast" adduct and the semiquinone); however, conversion of the "slow" adduct to semiquinone causes a dramatic decrease in the absorbance at 338 nm. Thus, the species having a maximum at 338 nm (seen at both pH 3.1 and 4.7) may be reasonably assigned to the ortho adducts. The "fast" adducts, which do not absorb at 338 nm, are then thought to be the para adducts. The normally expected preference[33] of the HO· radical for electrophilic attack at ring positions activated by the phenolic OH is inoperable with dopamine since each of the remaining ring positions is either ortho or para to one or the other of the phenolic groups. The

(31) At pH 4.7, the observed first-order rate constant for the fast water-loss reaction is $\sim 7.5 \times 10^4$ $s^{-1}$. Thus, at 1.2 μs (the time of the "adduct" spectrum in Figure 2) the fast reaction is only 9% complete. Assuming that ≤50% of the adducts lose water via the fast reaction predicts that ≤4.5% of the adducts will have been converted to semiquinone/semiquinone anion radicals when the spectrum was taken; this is not large enough to account for the intensities of the shoulder and peak at 300 and 313 nm, respectively. Furthermore, the similarity of the 1.2- and 3.8-μs spectra support the assignment of the spectrum to the initial products.

(32) At high radiation doses, i.e., high initial radical concentrations, bimolecular radical–radical reactions can compete with water elimination (adduct + adduct or adduct + semiquinone). The possible reaction paths include dimerization or disproportionation, which could produce parent compound, dopamine quinone, *benzenetriols*, and/or *trihydroxycyclohexadienes*.

(33) Raghavan, N. V.; Steenken, S. *J. Am. Chem. Soc.* **1980**, *102*, 3495–9.

relative yields of ipso, ortho, and para addition may be estimated from Figure 3 by assuming that the band shape of the absorption peaking at 338 nm is Gaussian. In this case, the absorbances at 385 nm may be attributed solely to the semiquinone, and relative yields of ipso:ortho:para are 1.15:1.38:1.0. The assumption of three groups of adducts, where the adducts within a given group lose water at nearly the same rate, successfully explains the experimental observations. The dehydration of isomeric HO· adducts at different rates were recognized as a probability in the earliest studies of HO· reactions with phenolic species.[8,9] Recent investigations[33,34] have confirmed this at selected pH, and the present results document large differences in rate constants for the isomeric dopamine/HO· adducts over a wide pH range.

**Acid-Catalyzed Water-Loss Reactions.** The sequence of reactions (Scheme I) producing acid-catalyzed loss of water from the HO· adducts is:[35,36] (1) protonation of the adduct (reaction 2); (2) elimination of $H_2O$ from this protonated adduct, producing a phenyl-centered radical cation (reaction 3; the reverse reaction, i.e., hydration of the radical cation to yield hydroxycyclohexadienyl radicals, does not appear to occur in radical cations having a labile proton[36]); and (3) loss of a labile, phenolic proton from the cation (reaction 4), yielding a semiquinone radical. The initial step is presumably protonation of the more basic added hydroxyl group (reaction 2),[35] since the p$K_a$ of protonated hydroxyl groups on aliphatic carbons is near −2,[37] while the p$K_a$ of the protonated hydroxyl groups at positions 1 and 2 should lie between −2 and the −7 associated with protonated phenols.[37]

In acid solution, phosphate provides two potential proton donors, $H_3PO_4$ and $H_2PO_4^-$ (with p$K_a$'s of 2.12 and 7.20,[38] respectively). However, below pH 5, addition of phosphate ions had a negligible effect on the slow and fast reactions. At pH 2.3, 0 and 50 mM phosphate ($[H_3PO_4]$ = 20 mM and $[H_2PO_4^-]$ = 30 mM) yielded slow rate constants which were essentially identical. This lack of dependence suggests that the acid catalysis is specific, i.e., solution pH is the rate-controlling factor.[39] Thus, the equilibration of the protonated/deprotonated adducts (reactions 2 and −2) must be rapid with respect to the subsequent reactions 3 and 4, so that either reaction 3 or 4 is the rate-determing step. ESR[35,36] investigations have indicated that the deprotonation of phenyl-centered radical cations possessing labile protons (such as $H^+QH_2^+\cdot$) is rapid with respect to the preceding water-loss reaction, i.e., $k_4[H_2O] \gg k_3$.

If reaction 3 is the rate-controlling step in the acid-catalyzed reaction, there will be no primary ionic-strength ($\mu$) effect on the observed rate. However, a secondary ionic strength effect occurs via equilibrium 2. Using the formulation of the Debye–Hückel limiting law given in eq 11[38,40] to include this secondary effect on the rate and assuming sufficiently dilute solutions so that molarity = molality, one obtains eq 12 for the observed first-order rate constant. Since p$K_2 \sim -2$ and pH ≥1.9, the exponential term in the denominator is ≫1, giving eq 13. Thus, at a given pH,

$$-\log \gamma_i = AZ_i^2\sqrt{\mu}\Big/(1 + Ba_i\sqrt{\mu}) - \beta\mu \qquad (11)$$

$$k_{obsd} = k_3\Big/\left(1 + \exp\left(-pK_2 + pH - 1.52\sqrt{\mu}\Big/(1 + 1.25\sqrt{\mu})\right)\right) \qquad (12)$$

$$\log k_{obsd} = \log (k_3/K_2) - pH + 1.52\sqrt{\mu}\Big/(1+ 1.25\sqrt{\mu}) \qquad (13)$$

a plot of log $k_{obsd}$ vs. $\sqrt{\mu}/(1 + 1.25\sqrt{\mu})$ should have a slope of +1.5; this is consistent with measurements made at pH 3.1 (Figure 5).[41] In addition, at constant ionic strength, a plot of log $k_{obsd}$ vs. pH should be linear with a slope of −1.0. In the acid region, the slopes obtained are essentially −1.0 for both the slow and fast reactions (Figure 4). Thus, the effect of the very low value of the p$K_a$ of the protonated adducts is that the log of their concentration increases essentially linearly with the decrease in pH, and that the plateau region where the adducts are completely protonated is not approached at experimental pH.

**Base-Catalyzed Water-Loss Reactions.** At pH >4.5, the onset of a base-catalyzed process is observed. O'Neill and Steenken[35] have proposed that base catalysis of phenoxyl formation proceeds via deprotonation of one of the more acidic, native phenolic groups of the HO· adduct, followed by loss of hydroxide from the deprotonated adduct, reactions 6 and 7. Reaction 6 would be slow with respect to reaction 7 at sufficiently low concentrations of base, $B^-$, and the observed rate would depend on base concentration:

$$k_{obsd} = k_6[B^-] \qquad (14)$$

At sufficiently high $[B^-]$, reaction 6 would become fast with respect to reaction 7, and $k_{obsd}$ would be independent of further increases in $[B^-]$:

$$k_{obsd} = k_7 \qquad (15)$$

Alternatively, specific base catalysis would be obtained if the deprotonation/protonation of the adducts were rapid with respect to reaction 7. However, this alternative can be discounted since the slope of the log $k_{obsd}$ vs. pH plots is ≲0.5 over a very broad pH range, while specific base catalysis predicts a slope of +1.0.

For the data shown in Figure 4, all experiments with pH ≥4 contained phosphate buffer so that the species available for base catalysis of water loss via reaction 6 are $H_2O$, $HO^-$, $H_2PO_4^-$, $HPO_4^{2-}$, and $PO_4^{3-}$. In the regions of transition from acid to base catalysis, where the phosphate buffer is present mostly as $H_2PO_4^-$, both the slow and fast rate constant plots exhibit plateaus. Both $H_2O$ (reaction 6a) and $H_2PO_4^-$ (reaction 6b) could contribute in

$$H^+QH_2OH\cdot + H_2O \rightarrow H^+QHOH^-\cdot + H_3O^+ \qquad (6a)$$

$$H^+QH_2OH\cdot + H_2PO_4^- \rightarrow H^+QHOH^-\cdot + H_3PO_4 \qquad (6b)$$

this region. However, at pH 4.45, asorbance growths for solutions containing 10 or 83 mM phosphate buffer were essentially identical, so that the effect of $H_2PO_4^-$ is negligible. Thus, the plateaus must be attributed to base catalysis by $H_2O$ (reaction 6a) which contributes a pH-independent term to the overall rate of water loss:

$$k_{obsd} = k_{6a}[H_2O] \qquad (16)$$

In the absence of such a reaction, the plots of log $k_{obsd}$ vs. pH would have a pronounced "V" shape, rather than the observed plateau or "U" shapes.

As the pH is increased beyond the plateau regions, the rate constants begin to increase; it is immediately apparent that the bimolecular rate constants calculated on the basis that the increases are due solely to $HO^-$ catalysis are much too large in the region pH 5–7. The participation of phosphate ions in the catalysis is

(34) Steenken, S.; Raghavan, N. V. *J. Phys. Chem.* **1979**, *83*, 3101–7.
(35) O'Neill, P.; Steenken, S. *Ber. Bunsenges. Phys. Chem.* **1977**, *81*, 550–6.
(36) Zemel, H.; Fessenden, R. W. *J. Phys. Chem.* **1978**, *82*, 2670–6.
(37) March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; pp 227–9.
(38) Bates, R. G.; Acree, S. F. *J. Res. Natl. Bur. Stand.* **1943**, *30*, 129–55.
(39) Application of the Brønsted relationship to $H_3O^+$ and $H_3PO_4$ as acid catalysts shows that $k_6$ could be as much as $10^4$ times the corresponding rate constant for $H_3PO_4$. Thus, even though $[H_3PO_4] = 4[H_3O^+]$, the lack of effect of added phosphate on the rate may result from a larger value for $k_6$ and not from specific acid catalysis.
(40) Robinson, R. A.; Stokes, R. H. "Electrolytic Solutions"; Butterworths: London, 1959; pp 230–6, 468. Robinson and Stokes tabulate values for $A$ and $B$ of water at various temperatures. $a_i$ = 3.8 A is taken from Bates and Acree.[38]

(41) In the ionic-strength-effect experiments, the only acid species available is $H_3O^+$. Thus, an assumption of generalized acid catalysis yields, in place of eq 13:

$$\log k_{obsd} = \log k_6^\circ + \log [H_3O^+] + 1.02\sqrt{\mu}\Big/(1 + \sqrt{\mu}) \qquad (13')$$

Thus, the assumption of generalized acid catalysis also predicts a positive correlation between reaction rate and ionic strength where the expected slope of log $k_{obsd}$ vs. $\sqrt{\mu}/(1 + \sqrt{\mu})$ plots is 1.02. The data in Figure 5 are not of sufficient precision to conclusively establish whether the catalysis is specific or generalized. Rather, the data support the conclusion, based on other evidence, that the catalysis is specific. Note also that eq 13′ predicts the same pH dependence for $k_{obsd}$ as does eq 13.

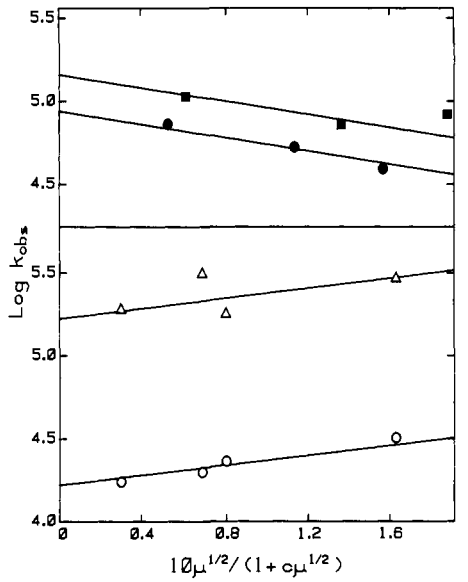



**Figure 5.** Dependence of the observed water elimination rate constants on ionic strength. Rate constants of the slow reaction were determined at pH 7.0 (●) and 7.35 (■) with $N_2O$-saturated solutions containing dopamine, 1 mM, and phosphate buffer, 1 mM. Solid lines have a slope of −2.0; value of $c$ = 1.0. Rate constants of the (△) fast and (○) slow reactions at pH 3.1 were determined with $N_2O$-saturated solutions containing dopamine, 0.2 or 0.5 mM, and $HClO_4$ for adjustment of pH. Solid lines have a slope of +1.5; value of $c$ = 1.25. Ionic strength was increased by addition of perchlorate ion.

clear from the following. Near neutral pH, the rate constants decreased upon addition of $NaClO_4$ to solutions buffered with 1 mM phosphate (Figure 5); the rate constants obtained were substantially below values found with 5 mM buffer present, comparing experiments with equivalent ionic strength (Figure 4). Thus, the $HPO_4^{2-}$ ion, whose concentration is increasing rapidly in this pH region, contributes to the base-catalyzed water-loss processes via the reaction:

$$H^+QH_2OH\cdot + HPO_4^{2-} \rightarrow H^+QHOH^-\cdot + H_2PO_4^- \quad (6c)$$

If $H_2O$ and $HPO_4^{2-}$ were the only base catalysts, the rate constants could not exceed twice its value at pH 7.2 with further pH increase (at pH 7.2, ~50% of buffer is present as $HPO^{2-}$); however, the rate constants do exceed this limit so that at pH >7 contributions from base catalysis by $HO^-$ (reaction 6d) and by

$$H^+QH_2OH\cdot + HO^- \rightarrow H^+QHOH^-\cdot + H_2O \quad (6d)$$

$PO_4^{3-}$ (reaction 6e) become important. Land and Ebert[8] observed

$$H^+QH_2OH\cdot + PO_4^{3-} \rightarrow H^+QHOH^-\cdot + HPO_4^{2-} \quad (6e)$$

that the dehydration of HO· adducts of phenol was catalyzed by both $HPO_4^{2-}$ and $HO^-$.

Because of the positive charge (via the protonated amine) of the reacting hydroxycyclohexadienyl radicals, the rate constants $k_{6c}$,$k_{6d}$, and $k_{6e}$ should exhibit primary ionic strength effects as described by the Brønsted equation:

$$\log k = \log k^0 + 1.02Z_aZ_b\sqrt{\mu}/(1+\sqrt{\mu}) \quad (17)$$

$$\log k_{obsd} = \log k_{6c}{}^0 - 2.04\sqrt{\mu}/(1+\sqrt{\mu}) + \log [HPO_4^{2-}] \quad (18)$$

Thus, in the pH region where base catalysis is dominated by $HPO_4^{2-}$, a plot of log $k_{obsd}$ vs. $\sqrt{\mu}/(1+\sqrt{\mu})$ at constant phosphate concentration should give a slope of −2.0 (eq 18). From Figure 5, it may be seen that a plot of pH 7 data in this format is consistent with a slope of −2.0, supporting the assignment of reaction 6 as the rate-controlling step.

**Water-Loss Rate Constants.** The contributions of reactions 3, 6a, 6c, 6d, and 6e can be summed to yield an expression for the observed water-loss rate constant which covers the entire experimental pH range:

Table I. Rate Constants Obtained from Fitting of log $k_{obsd}$ vs. pH Data

| $H_2O$-loss rxn | $(k_3/K_2)/10^8$ $M^{-1}$ $s^{-1}$ | $k_{6a}/10^3$ $M^{-1}$ $s^{-1}$ | $k_{6b}/10^4$ $M^{-1}$ $s^{-1}$ | $k_{6c}{}^0/10^8$ $M^{-1}$ $s^{-1}$ | $k_{6d}{}^0/10^{11}$ $M^{-1}$ $s^{-1}$ | $k_{6e}{}^0/10^{11}$ $M^{-1}$ $s^{-1}$ | $k_7/10^6$ $s^{-1}$ |
|---|---|---|---|---|---|---|---|
| fast | 7.5 | 1.1 | $\leq 7.3^a$ | 2.2 | $(\leq 6.0)^{b,c}$ | $(\leq 28)^{b,c}$ | $c$ |
| slow | 0.20 | 0.17 | $\leq 1.1^a$ | 0.65 | $\leq 1.5^b$ | $\leq 7.0^b$ | ~1.8 |

[a] Values for base catalysis by $H_2PO_4^-$ are computed by assuming that catalysis by $H_2O$ is at least 10-fold faster than catalysis by $H_2PO_4^-$ with $[H_2PO_4^-]$ = 83 mM. [b] The values given for $k_{6d}{}^0$ and $k_{6e}{}^0$ are maxima since virtually identical theoretical curves are obtained when either of the tabulated values is used, with the other rate constant set equal to zero. [c] Rate constant is high or could not be determined owing to overlap (in time) with the very fast water-loss reaction.

$$k_{obsd} = (k_3/K_2)/\exp\left(pH + 1.52\sqrt{\mu}/(1+1.25\sqrt{\mu})\right) + k_{6a}[H_2O] + k_{6c}[HPO_4^{2-}] + k_{6d}[HO^-] + k_{6e}[PO_4^{3-}] \quad (19)$$

The ionic-strength dependence of $k_{6c}$, $k_{6d}$, and $k_{6e}$ are given by eq 17. The contribution of each reaction will be most noticeable in a different pH region: (1) reaction 3 will predominate at pH <4; (2) reaction 6a at pH 3.5–5 for the slow reaction and at pH 4–6 for the fast reaction; (3) reaction 6c at pH 5–7.5; and (4) reactions 6d and 6e at pH >7.5. Values of $k_3/K_2$, $k_{6a}$, $k_{6c}{}^0$, $k_{6d}{}^0$, and $k_{6e}{}^0$ for the two sets of data in Figure 4 were determined using eq 19 (Table I).

Assuming that $K_2 = 10^2$ M ($pK_a \sim 2$ for $H^+QH_2OH_2^+\cdot$), the best-fit values of $k_3/K_2$ give values for $k_3$ of $7.5 \times 10^{10}$ and $2.0 \times 10^9$ $s^{-1}$ (fast and slow reactions, respectively). Thus, to satisfy the initially assumed condition that equilibrium 2 is established rapidly with respect to reaction 3 (acid catalysis is specific), $k_{-2}$ must be $\geq 1.3 \times 10^{10}$ or $3.6 \times 10^8$ $M^{-1}$ $s^{-1}$ (fast and slow reactions; 10-fold advantage for reaction −2). Similarly, to satisfy the condition that reaction 4 is rapid with respect to reaction 3, $k_4$ also must be $\geq 1.3 \times 10^{10}$ or $3.6 \times 10^8$ $M^{-1}$ $s^{-1}$ (fast and slow reactions). Reactions −2 and 4 are both proton transfers to $H_2O$ from dopamine radicals, the values calculated for the rate constants are large for proton transfers and thus reflect the high reactivity of the radicals.[42,43]

On the basis of $pK_a$ values,[44] the Brønsted correlation[45] predicts that the rate constant for proton transfer from $H^+QH_2OH\cdot$ to acceptors would follow the order $H_2O < H_2PO_4^- < HPO_4^{2-} < PO_4^{3-} < HO^-$. The observed result was $H_2O$ ($< H_2PO_4^-$?) $< HPO_4^{2-} < PO_4^{3-}$, $HO^-$. Only an upper limit could be obtained for the rate constant for catalysis by $H_2PO_4^-$, since addition of this base had no effect on $k_{obsd}$ at the highest concentration examined. The individual contributions of $PO_4^{3-}$ and $HO^-$ cannot be determined: virtually identical fits could be obtained in the high pH regions using either species independently. In view of the large values found for the slow reaction, it is clear that both species must be contributing to the catalysis (concentrations of both bases are increasing linearly in the pH region of interest). The high values obtained from the rate constants result from positive-ion/negative-ion interaction: correspondingly high values have been reported for other ion–ion reactions.[43,45]

(42) Alternatively, if the acid catalysis were general, the data fits would give $k_6 = 7.5 \times 10^8$ $M^{-1}$ $s^{-1}$ (fast reaction) or $2.0 \times 10^7$ $M^{-1}$ $s^{-1}$ (slow reaction). These values are only slightly smaller than those obtained by Raghavan and Steenken[33] for acid-catalyzed dehydration of HO· adducts of phenol based on an *a priori* assumption of general catalysis: two kinetically distinguishable isomers gave $k \sim 1 \times 10^9$ and $\sim 1 \times 10^8$ $M^{-1}$ $s^{-1}$, and were assigned to the para and ortho HO· adducts, respectively.

(43) Crooks, J. E. In "Proton-Transfer Reactions"; Caldin, E., Gold, V., Eds.; Chapman & Hall: London, 1975; pp 153–77.

(44) $pK_a$ for the acids $H_3O^+$, $H_3PO_4$, $H_2PO_4^-$, $HPO_4^{2-}$, and $H_2O$ are −1.74,[37] 2.21,[38] 7.20,[38] 12.32,[38] and 15.74,[37] respectively.

(45) Weston, R. E., Jr.; Schwarz, H. A. "Chemical Kinetics"; Prentice-Hall: Englewood Cliffs, N.J., 1972; pp 161, 191–5.

Above pH 8.5, $k_{obsd}$ appears to be leveling off. This change can be attributed to the high rate of the base-catalyzed reaction (reactions 6), such that reaction 7 (unimolecular hydroxide loss) becomes the rate-controlling step and $k_{obsd}$ becomes independent of pH (eq 15). Unfortunately, the attainment of a plateau in the log $k_{obsd}$ plot (by measurements at pH >9) cannot be verified because of the increasing influence of reaction 9. If HO· reacted with $H^+QH^-$ via addition, as it does with $H^+QH_2$, a plateau would be obtained, since $H^+QHOH^-$· would be formed from either species: reaction 7 then would be the easily observable rate-controlling step in alkaline solution. However, $H^+QHOH^-$· is produced in ever smaller yields with increasing pH owing to the intervention of reaction 9: when [$HO^-$] has been increased sufficiently that reaction 7 is rate controlling, only a small portion of the HO· radicals produce $H^+QHOH^-$· and small $\Delta A$'s accompany reaction 7. It is interesting to note the maximum value of $k_{obsd}$ for the slow base-catalyzed water loss is $1.8 \times 10^6$ $s^{-1}$ (pH 10.0), i.e., $k_7 \geq 1.8 \times 10^6$ $s^{-1}$; O'Neill and Steenken[35] have stated for methoxylated phenols and hydroxybenzoic acids that $HO^-$ is eliminated from the deprotonated hydroxycyclohexadienyl radicals with $k \geq 10^6$ $s^{-1}$.

The values obtained for $k_{6d}^0$ and $k_{6e}^0$ from the fast base-catalyzed data clearly exceed the possible values for even diffusion-controlled, ion–ion rate constants. These anomalously high values can be attributed to overlap of the fast water elimination with the very fast reaction (which is possibly pH independent): the observed $\Delta A$ for the fast reaction at higher pH did not decrease as sharply as for the slow process, and kinetic fits of data (after completion of the HO· reaction) showed the contribution to have a very fast absorption growth.[46]

## Conclusions

Using time-resolved spectra of the transients generated by the reaction of HO· with dopamine, we are able to document that three HO· adducts are formed which are thought to represent three groups of two each of the six possible adducts. These are assigned as ipso, para, and ortho adducts, which are formed in the near-statistical approximate ratios of 1.15:1.0:1.38. Furthermore, from the spectral data it is clear that each adduct loses water at a different rate. A very fast reaction occurs and is thought to be due to water loss from the ipso adduct. Fast and slow water-loss reactions are observed and are assigned to dehydration of the para and ortho adducts, respectively. The probability of different rates of dehydration for isomeric HO· adducts of aromatic compounds was recognized in early studies[8,9] and has been confirmed at selected pH in recent investigations.[15,33,34] We have now quantitatively demonstrated these different rates over a wide pH range. Indeed, even though the contribution of acid–base catalysis of the dehydration reaction has been recognized,[8,9,15,30,35,36,47] our data afford for the first time rate constants for base catalysis and in particular for catalyses by $H_2O$, $HPO_4^{2-}$, $HO^-$, and $PO_4^{3-}$. Acid catalysis is specific.

These detailed results on the addition of HO· to dopamine and the dehydration of the adducts have bearing upon related work that has been reported for benzoic acids, phenols, and methoxylated benzenes[15,33,35,48,49] in which positional ratios of HO· attack on the aromatic ring indicate the electrophilic nature of the HO· radical. The near-statistical distribution of ipso, para, and ortho adducts that are observed here indicate that the relative reactivity of HO· with specific positions on the aromatic ring are comparable and that groups such as OH and $CH_2CH_2NH_3^+$ do not exert a sufficient steric and/or electronic effect to alter reactivity of 1,2-benzenediols as has been observed with other types of aromatics.

Finally, the reaction of HO· with deprotonated dopamine ($H^+QH^-$; phenolic OH deprotonated) via direct, one-electron transfer is also demonstrated. One-electron oxidation of aromatic species by HO· without the intermediate formation of an adduct is an unusual reaction for the hydroxyl radical: in most nonphenolic species, one-electron oxidation would require direct production of a radical cation (corresponding to $H^+QH_2^+$·), which is energetically unfavorable.[47] Thus, this reaction observed for dopamine would be peculiar to catecholamines and other phenolic species with relatively low p$K_a$ values.

**Acknowledgment.** We thank the Office of Basic Energy Sciences of the Department of Energy, the National Institute of Neurological and Communicative Disorders and Stroke of the National Institutes of Health (Grant NS15850), and The Samuel and Emma Winters Foundation for their support. This is document NDRL- 2399 from the Notre Dame Radiation Laboratory.

**Registry No.** HO·, 3352-57-6; dopamine, 51-61-6.

(46) The kinetic measurements at high pH used 5 mM solutions of dopamine: thus, the initial HO· reaction was very rapid and it was possible to see the very fast water elimination, which could not be observed under the conditions required for spectral measurements ([$H^+QH_2$] ≤ 1 mM). Similarly, at pH 7.5, a slight contribution by the very fast reaction to the fast reaction could be seen with high dopamine concentrations (4 mM). However, the very fast elimination does not appear to be pH dependent (in contrast to the fast reaction) so that the overlap of the fast and very fast reactions is more problematical as pH is increased.

(47) Walling, C. *Acc. Chem. Res.* **1975**, *8*, 125–31. Walling, C.; Johnson, R. A., *J. Am. Chem. Soc.* **1975**, *97*, 363–7. Walling, C.; Camaioni, D. M.; Kim, S. S. *Ibid.* **1978**, *100*, 4814–8.

(48) Klein, G. W.; Bhatia, K.; Madhavan, V.; Schuler, R. H. *J. Phys. Chem.* **1975**, *79*, 1767–74.

(49) Eberhardt, M. K. *J. Phys. Chem.* **1977**, *81*, 1051–7.