One-Electron Reduction of 2- and 6-Methyl-1,4-naphthoquinone Bioreductive Alkylating Agents

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The semiquinones, $Q^{\cdot-}$, of derivatives of 2- and 6-methyl-1,4-naphthoquinones, some incorporating leaving groups with substituents such as CH_2Br or $CH_2OCONHCH_3$, have been produced by radiolytic reduction of Q by $(CH_3)_2\dot{C}OH$ radicals. The absorption spectra and decay kinetics of $Q^{\cdot-}$ were all closely similar to that produced from 2-methyl-1,4-naphthoquinone, with no evidence for unimolecular elimination of a leaving group in the semiquinone form, but immediate loss of leaving group upon two-electron reduction of Q to the hydroquinone. The redox equilibria between $Q/Q^{\cdot-}$ and $O_2/O_2^{\cdot-}$ were characterized, and reduction potentials of the couples $Q/Q^{\cdot-}$ in water at pH 7.6 were calculated. The implications of these observations for the use of these compounds as bioreductive alkylating agents or as radiosensitizers with potential selective activity toward hypoxic cells are discussed.

Derivatives of 2- and 6-methyl-1,4-naphthoquinones with appropriate substitutions are potential bioreductive alkylating agents, and such agents have been shown to possess antitumor activity;[1] the redox chemistry of adriamycin[2,3] and 5,8-dihydroxy-1,4-naphthoquinone[4] has been investigated in some detail. Semiquinones have been reported[5] as intermediates in the metabolism of several quinones and hydroquinones including unambiguous evidence from electron spin resonance measurements that reductive activation of the clinically active quinone antibiotic mitomycin C can occur via its semiquinone.[6,7] A free-radical mechanism can be postulated to be responsible for the selective toxicity of mitomycin C,[8] 2,3-bis(dichloromethyl)-1,4-naphthoquinone,[9] and several anthraquinones[10] toward hypoxic cells if the redox equilibrium (eq 1) is to the right so that the presence of oxygen inhibits

$$Q^{\cdot-} + O_2 \rightleftharpoons Q + O_2^{\cdot-} \quad (1)$$

the formation of activated, reduced hydroquinone in oxygenated cells only:

$$2Q^{\cdot-} + 2H^+ \rightleftharpoons Q + QH_2 \quad (2)$$

(assuming $Q^{\cdot-}$ is not itself the active species).

The reduction potential of the couple $Q/Q^{\cdot-}$ not only defines the position of equilibrium 1 but is likely to be reflected in the rate of reduction by NADPH-cytochrome c reductase.[11] Antineoplastic activity is well-correlated with polarographic half-wave potentials of some benzo- and naphthoquinone derivatives.[12-14] In the present work, we have applied pulse radiolysis to generate $Q^{\cdot-}$ and have observed directly the approach to, and the position of, equilibrium 1 for some selected 1,4-naphthoquinones, thereby estimating the reduction potential of $Q/Q^{\cdot-}$. We have also examined the stability (reaction 2) of the semiquinones of compounds bearing substituents with leaving groups. Intramolecular electron transfer in the radical anions of several nitrobenzyl halides and tosylates and naphthalene analogues results in elimination of the leaving group with the formation of a carbon-centered radical.[15] The time scale of these processes varies from microseconds to seconds, and it was of interest to search for the possible presence of an analogous intramolecular electron transfer in these naphthoquinones that could provide the basis for a radical mechanism of hypoxic cell-specific alkylation.

Absorption Spectra and Decay Kinetics of Semiquinones. Pulse radiolysis of N_2O-saturated solutions containing 2-propanol (1.0 M) results in the formation of $(CH_3)_2\dot{C}OH$ radicals less than 1 μs after the end of the pulse (0.2-μs duration); only a few percent of $(\dot{C}H_2)(CH_3)CHOH$ radicals are formed, and these are unreactive toward oxidants on the time scale of the present experiments.[16] In the presence of a quinone, at, e.g., 50 μM, the exponential formation of the semiquinone, $Q^{\cdot-}$, is complete in 20 μs, since for typical naphthoquinones, $k_3 \approx 4 \times 10^9$ M^{-1} s^{-1} (a typical 2-Gy pulse generates about 1.2 μM radicals, so $[(CH_3)_2\dot{C}OH] \ll [Q]$ and "pseudo-first-order" kinetics are obeyed); see eq 3.

$$(CH_3)_2\dot{C}OH + Q \rightarrow (CH_3)_2CO + H^+ + Q^{\cdot-} \quad (3)$$

Previous studies[17] have shown that the semiquinone of 1,4-naphthoquinone and its 2-methyl derivative (menadione) have absorption maxima at 390 nm. The spectra shown in Figure 1 confirm this value for menadione and demonstrate that the semiquinones of compounds **1**, **2**, **5**, **7**, and **8** (Table I) have similar spectral characteristics to that of menadione, **9**. At longer times the absorption

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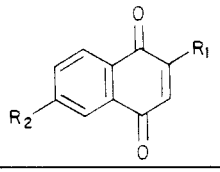
Table I. Reduction Potentials of Naphthoquinones and Redox Equilibria with Oxygen



compd	R_1	R_2	K_1[a]	$E(Q/Q^{\bullet-})$[b]/V	$10^{-8}(2k_2)$[c]/M^{-1} s^{-1}
1	H	CH_2Br	0.084	−0.092	2.2
2	H	CH_2Cl	0.091	−0.094	2.3
3	H	CH_2OCOCH_3	0.092	−0.094	
4	H	$CH_2OCONHCH_3$	0.114	−0.099	
5	H	CH_2OH	0.115	−0.100	2.0
6	CH_2OCOCH_3	H	0.150	−0.106	1.9
7	$CH_2OCONHCH_2CH_2Cl$	H	0.27	−0.122	
8	CH_2OH	H	0.88	−0.152	0.9
9	CH_3	H	6.5	−0.203	2.0
10	thiodione[d]	H	4.2	−0.192	
11	CH_2OCH_3	H	0.37	−0.129	

[a] Mean of measurements using three to five different concentrations of quinone; range of values ca. ±10%. [b] Potentials vs. NHE at pH 7.67 (will be the same at pH 7): uncertainty ca. ±0.003 V plus uncertainty in $E(O_2/O_2^{\bullet-})$, taken as −0.155 V (1 M $O_2/O_2^{\bullet-}$). [c] Uncertainty ±10–20%. [d] 3-*S*-Glutathionyl conjugate of menadione.

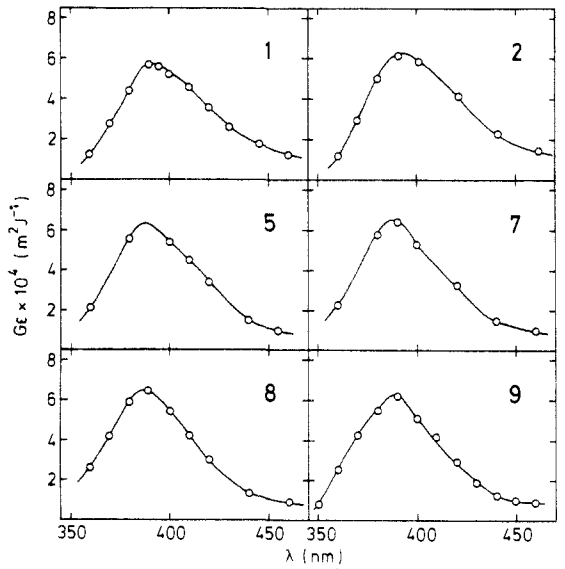


Figure 1. Transient differential absorption spectra observed upon one-electron reduction of substituted 1,4-naphthoquinones by pulse radiolysis (2.0-Gy dose in 0.2 μs). Solutions contained quinone (100–200 μM), 2-propanol (1 M), and sodium phosphate buffer (4 mM, pH 7.6) and were N_2O saturated. The numbers correspond to the structures in Table I. Spectra were measured upon completion of reaction of quinone with $(CH_3)_2\dot{C}OH$ (25 μs). Absorption is given as the product of G, the radiation chemical yield measured in mol J^{-1}, and ϵ, the extinction coefficient. For all quinones studied, assuming $G = 0.62$ μmol J^{-1}, then $\epsilon_{max} = 1 \times 10^3$ m^2 mol^{-1} (=1 × 10^4 M^{-1} cm^{-1}) at 390 nm.

decayed according to second-order kinetics, reaction 2, with $-d[Q^{\bullet-}]/dt = 2k_2[Q^{\bullet-}]^2$. From plots of A^{-1} vs. time using a variety of radiation doses (i.e., initial concentrations of radicals), estimates of the disproportionation rate constants $2k_2$ at pH 7.6 were obtained for representative compounds and are collected in Table I.

The "natural" decay of the semiquinones, reaction 2, has a typical first half-life of about 5 ms (= $^1/_2k_2[Q^{\bullet-}]_0$) at an initial radical concentration of $[Q^{\bullet-}]_0 \approx 1$ μM. No evidence for any first-order component attributable to unimolecular elimination of a leaving group in the semiquinone was observed, for example, by comparing the decay of the absorptions of the semiquinones of 1 and 2 with that of 5.

Redox Equilibria between the Semiquinones and Oxygen. Equilibrium 1 is established in a few tens of microseconds with the semiquinones of menadione and other simple quinones in aerated or oxygenated aqueous solutions.[17-19] Hence, the equilibrium constant K_1 can be estimated from the absorption of the equilibrium concentration at $Q^{\bullet-}$, measured at these short (microsecond) times before significant decay occurs via reaction 2 (milliseconds).[17-19] Equilibrium concentrations of $Q^{\bullet-}$ (from which the ratio $[O_2^{\bullet-}]/[Q^{\bullet-}]$ can be calculated, since $[O_2^{\bullet-}] + [Q^{\bullet-}]$ = a constant at a fixed radiation dose) were estimated for 3–5 concentrations of Q for each compound using air- or O_2-saturated solutions. In the case of menadione, the saturating gases were air or 2:98 O_2/N_2O. Estimates of K_1 are listed in Table I. Since the reduction potential $E(Q/Q^{\bullet-}) = E(O_2/O_2^{\bullet-}) - (RT/F) \log K_1$, it is possible to calculate[17-19] $E(Q/Q^{\bullet-})$ using the value $E(O_2/O_2^{\bullet-}) = -0.155$ V (nonstandard state of 1 M O_2).[18,19] These values are listed in Table I. An independent check on $E(Q/Q^{\bullet-})$ for menadione was performed by using benzyl viologen as a redox indicator ($E = -0.354$ V),[20] giving $E(Q/Q^{\bullet-}) = -0.199$ V, both estimates being in excellent agreement with a published value (−0.20 V).[19]

Within experimental error, the naphthoquinone 8 had a reduction potential similar to that of O_2, while compounds 1–7 and 11 had higher reduction potentials (equilibrium 1 was to the left), and menadione was significantly lower in potential than oxygen. Dr. G. M. Cohen kindly provided a sample of the menadione/glutathione conjugate ("thiodione"), and this enabled us to demonstrate that glutathione conjugation had little effect on the reduction potential (Table I).

Halide Ion Release from Quinones 1 and 2. γ-Radiolytically reduced N_2O-saturated solutions containing quinone 1 (60 μM) and 2-propanol (0.5 M) at pH 7.4 were analyzed for bromide ion release. Measurements prior to irradiation indicated a slow release of halide upon standing (approximately 15 μM Br^- in 1 h), and hence all solutions were used immediately after preparation to minimize this effect. A radiation dose of 64 Gy (equivalent to 40 μM radicals) resulted in generation of 20 μM bromide ion. Additional irradiations gave further halide release but in reduced yield, until eventually all bromide (i.e., 60 μM) was liberated.

Chloride ion release by γ-radiolytic reduction of quinone

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2 (200 μM) in the presence of 2-propanol (0.5 M) was also observed, although results appeared more complex. Initial rapid generation of chloride ions was accompanied by precipitation of products from solution. A maximum yield of only 120 μM chloride ion was obtained upon continued irradiation. Again, very slow release of halide was observed prior to irradiation.

Biological Implications. The overall efficiency of oxygen in inhibiting the formation of hydroquinones via reactions 1 and 2 depends upon a number of factors in addition to $E(Q/Q^{\bullet-})$ or K_1. At first sight, one might expect that naphthoquinones with $E(Q/Q^{\bullet-}) > E(O_2/O_2^{\bullet-})$, i.e., $K_1 < 1$, would exhibit less selectivity toward reduction only in hypoxic cells than those of lower potential. In practice, there is no such clear-cut boundary. Neglecting other potential electron acceptors for $Q^{\bullet-}$ or $O_2^{\bullet-}$ such as cytochrome c,[21] it is instructive to consider the time scales of the various reactions involved in the semiquinone/O_2 equilibrium 1 and competing radical decay processes (eq 2 and 4).

$$2O_2^{\bullet-} + 2H^+ \rightarrow O_2 + H_2O_2 \quad (4)$$

In biological systems, the steady-state concentrations of the radicals $Q^{\bullet-}$ and $O_2^{\bullet-}$ will be very much less than those of Q and O_2, and the approach to equilibrium 1 will be described by "pseudo-first-order" kinetics; i.e., they will be exponential with half-life given by $t_{1/2} = \ln(2)/k_{obsd}$, where

$$k_{obsd} = k_1[O_2] + k_{-1}[Q]$$

In the case of menadione,[19] $k_1 = 2.4 \times 10^8$ and $k_{-1} = 3.8 \times 10^7$ M^{-1} s^{-1}, and corresponding values for other quinones can be readily predicted from the values of $E(Q/Q^{\bullet-})$.[22] As examples, with 10 μM Q and either 100 μM O_2 (well-oxygenated cells) or 10 μM O_2 ("partially hypoxic" in radiobiological terms), the relaxation time of equilibrium 1 with menadione will be about 30 or 250 μs, respectively. The steady-state concentration of $Q^{\bullet-}$ in even partially hypoxic biological systems is most unlikely to exceed 0.1 μM, at which concentration the first half-life of disproportionation (eq 2) is about 5 ms for typical naphthoquinones. Hence, equilibrium 1 is maintained very much faster than the time scale of disproportionation of $Q^{\bullet-}$.

Oxygen can effectively inhibit the reduction of quinones of somewhat higher potential than the $O_2/O_2^{\bullet-}$ couple because the efficient removal of $O_2^{\bullet-}$ from the system serves to drive reaction 1 over to the right even when $K_1 < 1$.[21] At typical intracellular concentrations of superoxide dismutase (SOD) of 10 μM, steady-state concentrations of $O_2^{\bullet-}$ are likely to be <1 nM, so the spontaneous disproportionation (eq 4) is unimportant,[23] and the first-order disappearance of $O_2^{\bullet-}$ via the catalyzed reaction will have a half-life of the order of 30 μs. Thus, $O_2^{\bullet-}$ will be removed via the superoxide dismutase catalyzed disproportionation about as fast as the establishment of equilibrium 1 even in partially hypoxic tissue, serving to push the reaction to the right to reduce the concentration of $Q^{\bullet-}$ and inhibit hydroquinone formation via reaction 2.

While a full appreciation of these systems requires more information concerning steady-state concentrations of radicals, other electron-acceptors, etc., than is now available, from our present understanding it seems likely that the naphthoquinones are not of too high a potential for inhibition of reduction by oxygen to be significantly impeded. Recent results[24] indicate that naphthoquinones unprotected by appropriate substitution can undergo rapid conjugation with glutathione. The preliminary measurements of the properties of the menadione–glutathione conjugate reported here indicate thioether formation does not significantly alter the reduction potential. This is in accord with the relatively weak electron-withdrawing power of thioether substituents, which have Hammett constants typically of the order $\sigma_p \approx 0$ and $\sigma_m \approx 0.1$–0.2. Our measurement suggests that the menadione–glutathione conjugate should redox cycle with O_2 in virtually an identical way to menadione itself, as has been recently described.[25] The effects of GSH conjugation upon the bioavailability and intracellular distribution of quinones will be much more profound, and this will also be important in the use of such compounds as radiosensitizers. The values of $E(Q/Q^{\bullet-}) \simeq -0.10$ to 0.20 V for naphthoquinones reported here may be compared with those of typical 9,10-anthraquinones,[20,26] also of interest as bioreductive alkylating agents[27] (probably −0.3 to −0.4 V), and with that of mitomycin C. Although values of −0.24 to −0.27 V[11] have been reported for the one-electron reduction potential of the latter, unpublished work by E. D. Clarke (personal communication) gives an estimate of −0.306 V (determined vs. benzyl viologen), in excellent agreement with a more recent value (−0.310 V).[27]

Finally, no evidence could be found for rapid, unimolecular elimination of a leaving group (in appropriate naphthoquinones) occurring at the semiquinone stage of reduction. While hypoxic-specific reduction of nitrobenzyl halides, probably involving nitro radical anions as obligate intermediates,[5] does generate a radical that rapidly eliminates the leaving group,[15] there seems to be no parallel in the naphthoquinone series discussed here. In fact, γ-radiolytic reduction of naphthoquinones 1 and 2 suggests that loss of the leaving group only occurs upon two-electron reduction to the hydroquinone, in agreement with previous findings.[12] The above results indicate that conditions of low oxygen tension may be sufficient to cause activation of these naphthoquinone alkylating agents.

Experimental Section

Materials. Synthesis of the naphthoquinones employed in this study was carried out as outlined previously.[1] All other chemicals (BDH, AnalaR or AristaR, or Sigma Chemicals) were used as received. Water was distilled and purified by Milli-Q treatment (Millipore Ltd.). Oxygen, air, nitrogen (<5 ppm O_2), and nitrous oxide (<10 ppm O_2) were supplied by B.O.C. Ltd.

Pulse Radiolysis. A 1.8-MeV linear accelerator was used to produce electron pulses of 0.2-μs duration.[28] Solutions were presaturated with the appropriate gas in syringes[29] that were connected to a 2-cm spectrophotometric cell in a flow system to permit sample changing. Spectrophotometric detection techniques were as described earlier[16] using a Philips xenon arc lamp, Hilger-Watts monochromator, Hammamatsu R777 photomultiplier, and Datalab DL 905 digitizer. A PDP11/34 computer was used for analysis of reaction kinetics and transient absorption spectra. Dosimetry was carried out by irradiation of 10 mM KSCN in aerated water,[30] assuming the irradiation product, $(SCN)_2^{\bullet-}$, absorbed at 480 nm with $G\epsilon = 2.13 \times 10^{-4}$ m^2 J^{-1} (where G is the

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radiation chemical yield measured in mol J^{-1}).

γ-Radiolysis. Quinone solutions were first saturated with N_2O gas in syringes as above, before being irradiated by a ^{60}Co source. Dose rates of 36 Gy min^{-1} were used, as measured by Fricke dosimetry.[30] Ion-selective electrodes for bromide (Russell pH Ltd.) and chloride (E.I.L.) were then used to monitor the release of leaving groups from quinones 1 and 2. Upon completion of irradiation, 20-mL aliquots of quinone solution were mixed with an ionic strength adjuster (20 mL of 0.2 M KNO_3 in the case of bromide ion detection, and 2 mL of 0.5 M ammonium acetate with 0.5 M acetic acid for chloride ions), and electrode measurements were carried out with continuous N_2 gassing to minimize reoxygenation. Results were compared with predetermined calibration measurements.

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Synthesis and Anti-Herpes-Virus Activity of Acyclic 2′-Deoxyguanosine Analogues Related to 9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine[1,2]

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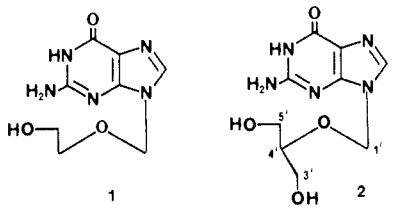
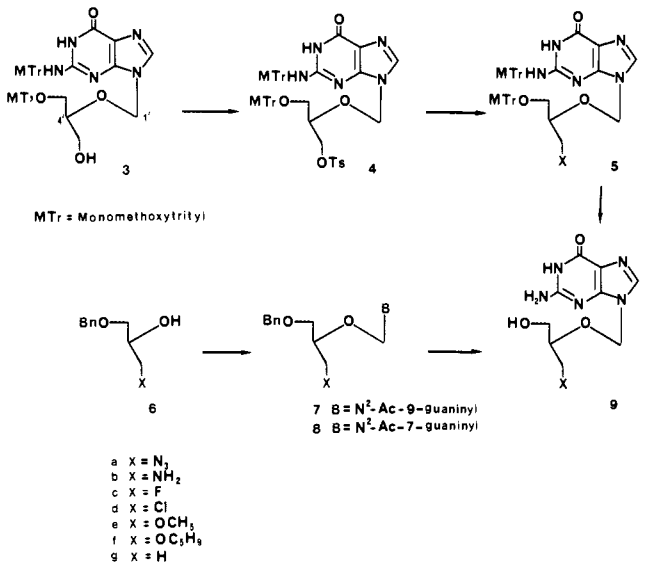
Several "sugar" modified acyclic nucleoside analogues related to 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, **2**) were synthesized and evaluated for antiviral activity. The preparation generally involved the condensation of the acetoxymethyl ether of alcohols **6c–g** and **10–12a** with diacetylguanine to give adducts **7c–g** and **14–16**, which were then deprotected to afford analogues **9c–g** and **17–19**. Alternatively, alcohols **12a** and **13a** were converted to iodides via their tosylates **12b** and **13b** and then reacted with the sodium salt of guanine to afford, after deprotection, analogues **22** and **23**. A crossed aldol–Cannizzaro reaction on aldehyde **27** readily afforded **28**, which was deprotected to give analogue **29**. An in vitro assay against HSV-1 showed that all compounds tested were less active than DHPG, though several were good substrates for the viral thymidine kinase. The more promising acyclic nucleosides **9c**, **19**, and **29** were evaluated in a mouse encephalitis model and proved ineffective at preventing death at a dose of 20 mg/kg.

The report of the anti-herpes-virus activity of acyclovir (**1**)[4] followed more recently by the discovery of the substantially greater in vivo potency of 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, **2**)[5,6] has stimulated a



substantial research effort in the synthesis of acyclic guanosine analogues.[7]

Scheme I



Both acyclovir and DHPG are unusually selective as compared to other nucleoside antiviral agents.[8] The se-

(1) Contribution 206 from the Institute of Bio-Organic Chemistry, Syntex Research.

(2) Presented in part at the 185th National Meeting of the American Chemical Society, Seattle, WA; March 24, 1983; CARB 43.

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(6) The structural formulas of DHPG (**2**) and the related acyclic nucleoside analogues have been depicted in a "ribose-like" conformation only to draw attention to the similarity in structure between these compounds and 2′-deoxynucleosides. In accordance with this representation, the two terminal carbons of the glycerol are referred to as the 3′ and 5′ positions.

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