One-Electron Redox Potentials of Nitro Compounds and Radiosensitizers. Correlation with Spin Densities of Their Radical Anions[1]

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Abstract: One-electron redox potentials for ten nitroaromatic and nitroheterocyclic compounds were determined using the pulse radiolysis technique. These potentials were calculated from experimentally determined equilibrium constants of the electron transfer reaction between a reference semiquinone and the nitro compound. The one-electron half-cell reductions of duroquinone and 9,10-anthraquinone-2-sulfonate were used as references. The redox potentials determined in this study lie in the range of $E_7^1 = -0.19$ V for 4-nitropyridine and $E_7^1 = -0.54$ V for 2-methyl-5-nitroimidazole at pH 7 (relative to NHE). These one-electron redox potentials were shown to correlate linearly with the spin densities on the nitro groups of their radical anions determined from ESR measurements. It was found that the higher the spin density on the nitro group the more negative is the redox potential. The quantitative correlation enables a reasonable prediction of the redox potential of any nitro compound to be made from the nitrogen ESR hyperfine constant of its radical anion. Some nitro compounds are known to be efficient radiosensitizers and it is shown here that their efficiency may be qualitatively correlated with their redox potentials with sensitizers of higher redox potentials generally being found to be more efficient.

One-electron redox potentials for several systems, largely of quinoidic type, were measured using various methods ranging from conventional potentiometric titration to fast reaction techniques. The few one-electron redox potentials measured by potentiometry have been summarized by Clark.[2] Those measurements were confined to such systems where the singly reduced (semiquinoidic) form is sufficiently stable to affect the titration curve. The complex curves were then analyzed mathematically to derive the one-electron potentials as suggested by Elema.[3] In such cases polarography was also used for estimation of redox potentials of the single-electron reduction steps.[4] Two distinct polarographic waves were observed in aprotic solvents (cf. ref 5 and 6) but not in water.

Using the rapid mix technique Yamazaki and Ohnishi[7] were able to determine redox potentials for the benzoquinone/hydroquinone single steps in basic aqueous solutions. The semiquinone formation constants from which the single redox potentials can be calculated were determined by Baxendale and Hardy[8] for duroquinone and by Diebler et al.[9] for benzoquinone. The determination of one-electron redox potential in all those cases was limited to pH ranges where the semiquinoidic forms are relatively stable. Several short-lived organic radicals were studied by the polarographic pulse radiolysis technique,[10] but in most cases only irreversible polarographic waves were observed.

A method for the determination of one-electron redox potentials using kinetic spectrophotometric pulse radiolysis to measure the equilibrium radical concentrations in redox systems has recently been demonstrated.[11] This method was used to determine the potentials of several quinone/semiquinone as well as that of the O_2/O_2^- couples.[12] In the present study we adapt this method to the determination of potentials for reduction of nitro compounds to their radical anions. Electron transfer involving nitro compounds is expected to proceed mainly via the nitro group. Therefore, it is reasonably expected that there will be at least a qualitative correlation between their one-electron redox potentials and the spin density distribution in their radical anions. In order to examine this correlation spin densities were determined from the ESR hyperfine constants measured previously and in the present work.

Several nitroaromatic and nitroheterocyclic compounds were shown to be efficient radiosensitizers (see, e.g., ref 13-17). The model for the sensitization qualitatively related their efficiency with their electron affinity. One-electron redox potentials are expected to provide a close measure of electron affinity and, therefore, to correlate well with radiosensitization. In the present study it is shown that one-electron redox potentials correlate well with the radiosensitization efficiencies and with the spin density distributions in the radical anions.

Experimental Section

The materials used were of the highest purity commercially available and were used without further purification. Duroquinone and 5-nitrouracil were obtained from Sigma Chemical Co., 4-nitropyridine was obtained from Pfaltz and Bauer, nitrobenzene, 2-propanol, and the inorganic compounds were Baker Analyzed Reagents, and the other organic compounds were obtained from Aldrich Chemical Co. The sensitizer Ro07-0582 was kindly supplied by Dr. G. E. Adams. Fresh solutions were prepared immediately before irradiation and were flushed for at least 15 min with prepurified nitrogen. Water was distilled and the vapor passed with oxygen through a silica oven. All solutions contained 0.1-0.2 *M* 2-propanol and were buffered to pH 7 using 5 m*M* phosphate. Irradiation was carried out by 2.8 MeV electrons from a Van de Graaf accelerator. The computer-controlled pulse radiolysis apparatus[18] and the remaining experimental details have been described previously.[11] Details of the in situ radiolysis ESR experiments were also described elsewhere.[19]

Method

Equilibrium constants for the electron transfer reaction between nitro substrates (S) and a reference acceptor (Q) were

$$\dot{S}^- + Q \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S + \dot{Q}^- \qquad (1)$$

determined using the spectrophotometric pulse radiolysis technique. The presence of 0.1-0.2 *M* 2-propanol ensured that at the end of the pulse all the radicals produced by water radiolysis (eq 2) were converted into reducing radi-

$$H_2O \longrightarrow e_{aq}^-, \dot{H}, \dot{O}H, H_2, H_2O_2 \qquad (2)$$

cals by reaction 3. The reducing radicals thus produced

$$\dot{H} \text{ or } \dot{O}H + (CH_3)_2CHOH \longrightarrow H_2 \text{ or } H_2O + (CH_3)_2\dot{C}OH \quad (3)$$

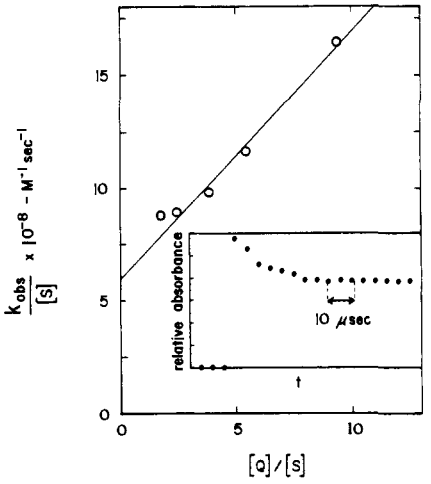

Figure 1. Dependence of $k_{obsd}/[S]$ on $[Q]/[S]$ for the electron transfer between 4-nitropyridine (S) and duroquinone (Q). The intercept yields k_{-1} for $Q^- + S$ and the slope is k_1 for $Q + S^-$. Insert: computer processed kinetic data for the electron transfer from durosemiquinone to 4-nitropyridine. All solutions contain 0.1 *M* 2-propanol at pH 7 deaerated with pure nitrogen. [Q] = 2.9×10^{-4} *M*. [S] variable (1.14×10^{-4} *M* for the insert).

(e_{aq}^- and $(CH_3)_2\dot{C}OH$) subsequently react with either Q or S to produce $\dot{Q}^-$ and $\dot{S}^-$ with initial relative yields dependent on the rate constants for reactions 4–7 and the concentration ratio of Q and S. In general, for all substrates used here reactions 4–7 are very fast (rate constants $\geq 1 \times 10^{10}$ M^{-1} sec^{-1} for e_{aq}^- and $\geq 1 \times 10^9$ M^{-1} sec^{-1} for $(CH_3)_2\dot{C}OH$; cf. ref 20–22). In any case we have experimentally verified that reactions 4–7 were complete within 3 μsec after the pulse.

$$e_{aq}^- + Q \longrightarrow \dot{Q}^- \quad (4)$$

$$e_{aq}^- + S \longrightarrow \dot{S}^- \quad (5)$$

$$(CH_3)_2\dot{C}OH + Q \longrightarrow \dot{Q}^- + (CH_3)_2CO + H^+ \quad (6)$$

$$(CH_3)_2\dot{C}OH + S \longrightarrow \dot{S}^- + (CH_3)_2CO + H^+ \quad (7)$$

Two types of behavior were encountered while measuring the equilibrium constant K_1. In the simplest cases the electron transfer (reaction 1 forward or reverse) could be observed and its rate determined directly. An example is shown in the insert of Figure 1 where the durosemiquinone radical anion is shown to transfer an electron to 4-nitropyridine long after reactions 2–7 are complete. In order to ensure that the only reaction occurring in such cases is an electron transfer, the spectrum after completion of the reaction was recorded and compared with that of the radical anion. For example, Figure 2 shows the spectrum of the 9,10-anthraquinone-2-sulfonate radical anion obtained directly and via electron transfer from the 5-nitrouracil radical anion. The spectra are identical and closely resemble that reported previously.[23] The dependence of the long term absorption on concentrations of the two solutes is in accordance with the achievement of equilibrium 1 as will be shown later. In all cases it was verified that the decay of each of the radicals by itself is much slower than the electron transfer. The kinetics of the approach to equilibrium in those cases where the electron transfer reaction could be followed were also studied. The rate always followed a pseudo-first-order rate law and the observed rate constant was analyzed in terms of eq 8. Figure 1 shows the dependence of $k_{obsd}/[S]$ on the concentration ratio $[Q]/[S]$

$$k_{obsd} = k_1|Q| + k_{-1}|S| \quad (8)$$

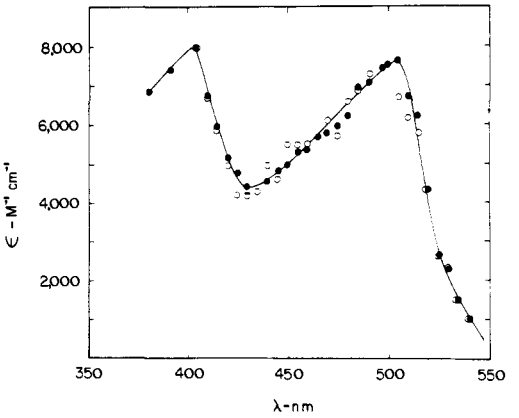

Figure 2. Optical absorption spectra of 9,10-anthraquinone-2-sulfonate. (●) Recorded with pulse irradiated solution of 1×10^{-3} *M* AQS and 0.1 *M* 2-propanol at pH 7. (○) After electron transfer from 5-nitrouracil radical anion (recorded with solution of 2×10^{-5} *M* AQS, 0.1 *M* 2-propanol, and 1×10^{-3} *M* 5-nitrouracil).

Table I. Determination of Equilibrium Constant for (4-Nitropyridine)$^-$ + DQ ⇄ 4-Nitropyridine + DQ^-

[DQ],[a] *M*	[S],[b] *M*	*A*[c]	$\frac{[DQ^-]}{[S^-]}$	$\frac{[S]^d}{[DQ]}$	*K*
0	1×10^{-3}	555			
2.91×10^{-4}	0	7500			
2.91×10^{-4}	3.17×10^{-5}	4830	1.604	0.107	0.172
2.89×10^{-4}	5.36×10^{-5}	4000	0.984	0.182	0.179
2.87×10^{-4}	7.7×10^{-5}	3370	0.680	0.254	0.173
2.85×10^{-4}	1.14×10^{-4}	2720	0.454	0.396	0.180
2.82×10^{-4}	1.52×10^{-4}	2380	0.356	0.539	0.192
2.57×10^{-5}	1×10^{-3}	890	0.050	3.89	0.195
4.0×10^{-5}	1×10^{-3}	1030	0.074	2.50	0.185
					$K_1 = 0.18 \pm 0.01$
					$k_1/k_{-1} = 0.19$[e]
					$E_7^1 = -0.191$

[a] All solutions contained 0.15 *M* 2-propanol and 5 m*M* phosphate buffer at pH 7 and were deoxygenated by bubbling with pure nitrogen. [b] S = 4-nitropyridine. [c] Relative absorbance given in units of $\epsilon \times G_R/G_R^0$. [d] Corrected for depletion. [e] k_1 and k_{-1} independently determined as shown in Figure 1.

where S is 4-nitropyridine and Q is duroquinone. The slope of the line yields $k_1 = 1.12 \times 10^8$ M^{-1} sec^{-1} and its intercept gives $k_{-1} = 5.9 \times 10^8$ M^{-1} sec^{-1}. The ratio of the slope to the intercept is $K_1 = 0.19$ in agreement with the value of 0.18 obtained by measuring the yields at equilibrium. In most cases only one of the rate constants for reaction 1 could be determined directly from that type of plot, while the other one was too small for accurate determination.

The equilibrium constant K_1 was determined by measuring the residual absorption *A* after equilibrium 1 was achieved as a function of [S]/[Q] using eq 9. A_S and A_Q

$$K_1 = \frac{|Q^-|}{|S^-|}\frac{|S|}{|Q|} = \frac{(A - A_S)}{(A_Q - A)}\frac{|S|}{|Q|} \quad (9)$$

are the absorbances of S^- and Q^- produced in the absence of the other component. In all cases A_S and A_Q were measured under the same conditions as those where K_1 is measured so that dosimetry is not involved in the calculation. However, dosimetry was carried out for determination of extinction coefficients. Whenever possible the residual absorption was measured at two wavelengths where both increase in $[Q^-]$ and decrease in $[S^-]$ or vice versa could be recorded as a function of [S]/[Q]. In some cases the initial [Q] or [S] had to be corrected for their depletion upon production of the corresponding radical anion. This correction was done whenever it amounted to more than 3% of the ini-

Table II. Determination of Equilibrium Constant for $MNAP^- + AQS \rightleftarrows MNAP + AQS^-$

[MNAP],[a,b] M	[AQS],[c] M	[NB],[d] M	Rel absorbance A[e]	$\frac{[AQS^-]}{[MNAP^-]}$	$\frac{[AQS^-]}{[NB^-]}$	$\frac{[MNAP]}{[AQS]}$[f]	K_1
0	2×10^{-3}		7600				
1×10^{-3}	0		175				
1×10^{-3}	1.04×10^{-5}		820	0.095		100	9.50
1×10^{-3}	2.12×10^{-5}		1410	0.199		48	9.55
1×10^{-3}	3.39×10^{-5}		1980	0.321		30	9.60
1×10^{-3}	4.81×10^{-5}		2415	0.432		21	9.10
1×10^{-3}	7.79×10^{-5}		3130	0.661		13	8.60
							Av $K_1 = 9.3 \pm 0.5$
1×10^{-3}	7.79×10^{-5}	1.9×10^{-3}	2910	0.755[g]	2.5[h]	13	9.80
1×10^{-3}	1.22×10^{-4}	1.9×10^{-3}	3600	1.103[g]	3.9[h]	8.2	9.05

[a] All solutions contained 0.15 M 2-propanol and 5 mM phosphate buffer at pH 7 and were deoxygenated by bubbling with pure nitrogen. [b] MNAP = *m*-nitroacetophenone. [c] 9,10-Anthraquinone-2-sulfonate. [d] Nitrobenzene. [e] Given in units of $\epsilon \times G_R/G_R^0$. [f] Corrected for depletion. [g] Corrected for $[NB^-]$ which remains in equilibrium. [h] Calculated from $K_1 = 61$ for the $NB^- + AQS$ system, determined independently.

tial concentration. In none of the cases did the total concentration of radicals exceed 10% of the lowest concentration of the substrates. Table I is an example of a detailed calculation of K_1 for the case where Q is duroquinone and S is 4-nitropyridine.

The more complicated cases occur when the electron transfer could not be observed directly. Actually, only two such cases were encountered, namely the transfer from *m*-nitroacetophenone (MNAP) and *p*-nitroacetophenone (PNAP) radical anions to 9,10-anthraquinone-2-sulfonate (AQS). In these cases a third component was used to examine the achievement of equilibrium. For example, when 0.1 M 2-propanol and 1 mM MNAP solution was irradiated and increasing concentrations of AQS were added the absorption at 505 nm (λ_{max} for AQS^-) increased with increasing [AQS] (Table II). Since the absorption 2 μsec after the pulse was equal to that 50 μsec later, it is not immediately clear whether the effect of [AQS] is a kinetic competition effect or an equilibrium situation. The rate constants for reactions 4–7 for this system are not sufficient to explain the results in Table II, yet it was felt that experimental evidence for equilibrium would increase our confidence in the mechanism. In order to decide whether equilibrium exists 2 mM nitrobenzene was added. Under our experimental conditions (Table II) about $\frac{2}{3}$ of the reducing radicals should initially react with nitrobenzene. The equilibrium constant of reaction 1 for the nitrobenzene + AQS system was determined separately and found to be 61. Therefore, a transfer from the nitrobenzene radical anion to AQS (and/or MNAP) should be observed. If rapid equilibrium exists between AQS^- and MNAP the ratio of $[AQS^-]/[MNAP^-]$ should not be affected by the addition of nitrobenzene. This was found to be the case as can be seen from Table II and, therefore, it may be concluded that equilibrium 1 is rapidly achieved between $MNAP^-$ and AQS.

The potential for one of the half-cell reactions can be calculated from the equilibrium constants provided the potential of the other half-cell is known, using eq 10. The redox

$$\Delta E = 0.059 \log K_1 \qquad (10)$$

potentials which we use as references are those of the DQ/DQ^- and AQS/AQS^-. The former potential was calculated[11] from previous data[8] and experimentally verified[11] while the latter was determined in the present study against the DQ/DQ^- couple. It should be emphasized that the redox potential E_7^1 determined by this method applies only to the pH of measurement (pH 7 in all cases). However, knowledge of the pK_a values of all the species involved enables the calculation of the pH dependence of E^1 for some of the systems studied. All values of potentials reported here are against NHE. Values for potentials which are given in the literature vs. SCE are quoted here after transformation to NHE. The IUPAC convention for reduction potentials is applied.

One-Electron Redox Potentials

Using the method described in the previous section one can measure redox potentials which differ by up to ~0.15 V from that of the reference half-cell reaction. In order to extend the accessible range of potentials it was felt that an additional reference system was needed for which the potential is more negative than that of the duroquinone system ($E_7^1 = -0.235$ V).[11] For this purpose 9,10-anthraquinone-2-sulfonate was chosen. The equilibrium constant K_1 for the system containing duroquinone (Q = DQ) and the anthraquinone-2-sulfonate (S = AQS) was measured directly by following the electron transfer from AQS^- to DQ at both 505 and 445 nm, the absorption peaks of AQS^- and DQ^-, respectively. The value obtained for K_1 is 255 which yields $E_7^1 = -0.380$ V for the AQS/AQS^- system. The redox potential for this system was measured previously[4] using polarography and the Elema type calculations. The value given by these authors is $E_{9\text{-}13}^1 = -0.360$ V (in the pH range 9–13). These authors also report $pK_a = 9$ for the semiquinone but Hulme et al.[23] using pulse radiolysis found $pK_a = 3.2$ which must be the correct value. This latter value leads to $E_7^1 = -0.36$ V from the study of Gill and Stonehill,[4] which is in good agreement with the value obtained in this study considering the variance in the techniques employed.

The rest of the compounds studied, all of which contain a nitro group, were tested against either DQ/DQ^- or AQS/AQS^- or both. The results are summarized in Table III in order of decreasing potentials. The compounds with potentials between −0.19 and −0.39 V were measured against duroquinone and those with potentials down to −0.54 V were determined against the anthraquinone sulfonate. In two cases, *p*-nitroacetophenone and 2-nitrothiophene, the potentials were measured against the two reference quinones and found to be identical (within ±5 mV). This agreement supports our determination of E_7^1 for the AQS/AQS^- system. With PNAP the transfer from AQS^- could not be observed but the transfer from $PNAP^-$ to DQ was observed. The agreement between the potentials determined independently with each of the references validates our method for K_1 determination when electron transfer is not observed directly.

We know of no other work where one-electron redox po-

Table III. Equilibrium Constants, One-Electron Redox Potentials,[a] and Rate Constants for $S^- + Q \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} S + Q^-$

No.	S	Q	λ,[b] nm	K_1	E_7^1, V	k_1, M^{-1} sec^{-1}	k_{-1},[c] M^{-1} sec^{-1}	a^N,[d] G
1	4-Nitropyridine	DQ	445	0.18	−0.191	1.1×10^8	6.1×10^8	9.75
2	5-Nitro-2-furaldoxime (nifuroxime, anti)	DQ	445	2.02	−0.253			11.43[e]
3	5-Nitro-2-furoic acid (NFA)	DQ	445 375	25.0	−0.317	5×10^8	2×10^7	12.20[e]
4	*p*-Nitroacetophenone (PNAP)	DQ	445 350	125	−0.358	7×10^8	5.6×10^6	11.57
		AQS	505	0.35	−0.353			
5	1-(2′-Hydroxy-3′-methoxypropyl)-2-nitroimidazole (Ro07-0582)	DQ	445	150	−0.363	3×10^8	2×10^6	14.05[f]
		AQS	505	2.01	−0.398			
-	9,10-Anthraquinone-2-sulfonate (AQS)	DQ	505 445	255	−0.380	4×10^8	1.6×10^6	
6	2-Nitrothiophene	AQS	505	1.78	−0.395			13.10[g]
		DQ	445	420	−0.390	8×10^8	1.9×10^6	
7	*m*-Nitroacetophenone (MNAP)	AQS	505	9.3	−0.437			13.66
8	Nitrobenzene (NB)	AQS	505	61.5	−0.486	5.4×10^8	8.8×10^6	14.20[h]
9	5-Nitrouracil	AQS	505	313	−0.527	1.3×10^9	4.1×10^6	17.4[i]
10	2-Methyl-5-nitroimidazole	AQS	505	551	−0.542	1.0×10^9	1.8×10^6	15.87[f]
11	Nitromesitylene				(−0.86)[j]			21.95
12	Nitromethane				(−1.06)[j]			25.55[k]

[a] DQ/DQ$^-$ was chosen as primary reference assuming $E_7^1 = -0.235$ V (ref 11). [b] Wavelength studied. [c] Calculated from k_1/K_1. [d] Hyperfine splitting constants for the nitro group nitrogen in the radical anions S^-, determined in the present study unless otherwise indicated. [e] From ref 22. [f] From ref 27. [g] From ref 28. [h] From ref 19. [i] From ref 26. [j] Estimated from the line of Figure 4. [k] From ref 29.

Table IV. ESR Parameters of Some Nitroaromatic Radical Anions[a]

Compd	*g* factor	$a^N_{NO_2}$	*a* (ortho)	*a* (meta)	*a* (para)
4-Nitropyridine	2.00492	9.75	3.37 (2H)	1.16 (2H)	3.98 (N)
p-Nitroacetophenone	2.00470	11.57	3.24 (2H)	1.08 (2H)	0.43 (CH_3)
m-Nitroacetophenone	2.00448	13.66	3.38 (2H)	1.12 (1H) <0.1 (CH_3)	3.60 (1H)
Nitromesitylene	2.00501	21.95	0.59 ($2CH_3$)[b]	0.30 (2H)[b]	0.89 (CH_3)[b]

[a] Determined in irradiated aqueous solutions containing $1-5 \times 10^{-4}$ *M* nitro compounds, 0.1 *M* 2-propanol, and 2 m*M* phosphate buffer at pH 7 and deoxygenated by bubbling with pure nitrogen. The hyperfine constants *a* are given in gauss and are accurate to ±0.03 G. The *g* factors were determined relative to the signal from the silica cell and are accurate to ±0.00005. Second-order corrections have been made. [b] These assignments are based on the experimental observation of groups of 14 lines with relative intensities of about 1:2:4:6:7:10:11:11:10:7:6:4:2:1 separated by 0.295 G. The calculated pattern should consist of 24 lines, the five outermost lines on each side having relative intensities between 0.5 and 0.02 which are within the noise level.

tentials for the nitro compounds were measured in aqueous solutions. The half-wave potentials reported by Greenstock et al.[17] for some of the systems studied here differ considerably from ours and are probably four-electron redox potentials. One-electron redox potentials of nitrobenzene derivatives were determined polarographically in acetonitrile.[24]

In those cases where the acid-base ionization constants of all the species involved are known one can calculate the pH dependence of E^1. In the cases where only one ionization constant of the radical is involved (denoted K_{r_1}) E^1 can be calculated from eq 11. Sufficient data are available for

$$E^1 = E_7^1 + 0.059 \log \frac{K_{r_1} + [H^+]}{K_{r_1} + 10^{-7}} \qquad (11)$$

this calculation to be carried out on the DQ/DQ$^-$ ($pK_{r_1} = 5.1$),[25] PNAP/PNAP$^-$ ($pK_{r_1} = 2.6$),[21] AQS/AQS$^-$ ($pK_{r_1} = 3.25$),[23] and NB/NB$^-$ ($pK_{r_1} = 3.2$)[20] systems. For the 5-nitrofuroic acid system, where two ionization constants of the radical ($pK_{r_1} = 1.22$, $pK_{r_2} = 3.77$)[22] and one ionization constant of the oxidized parent compound ($pK_0 = 2.1$) are involved, we used eq 12. The results of our calculations are

$$E^1 = E_7^1 + 0.059 \log \frac{(K_{r_1}K_{r_2} + K_{r_1}[H^+] + [H^+]^2)(K_0 + 10^{-7})}{(K_{r_1}K_{r_2} + K_{r_1} \times 10^{-7} + 10^{-14})(K_0 + [H^+])} \qquad (12)$$

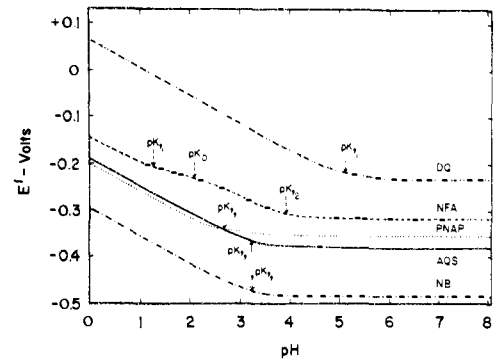

Figure 3. Dependence of the first reduction step potential (E^1) on pH for: duroquinone (- - - - -), 5-nitro-2-furoic acid (- - -), PNAP (· · ·), AQS (—), and nitrobenzene (- · -).

presented in Figure 3. It is evident from the figure that while AQS$^-$ should transfer an electron to PNAP (when [AQS] = [PNAP]) at pH >2.6, the reverse reaction should be favored at pH <2.6.

Electron Spin Resonance and Spin Densities

The one-electron redox potentials for the series of nitroaromatic and nitroheterocyclic compounds can be correlated with the spin densities on the nitro groups of their radical anions. These spin densities can be derived to a good approximation from the nitrogen hyperfine constants. Most of the compounds examined in the present work have

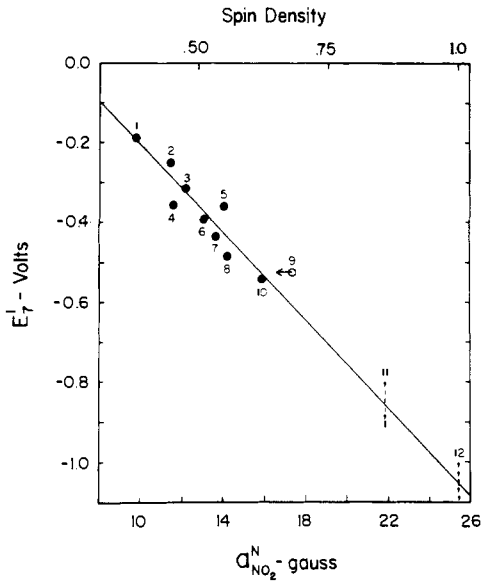

Figure 4. Correlation between E_7^1 with the nitrogen hyperfine constant ($a^N_{NO_2}$, lower scale) or spin density on the nitro group (upper scale). Numbers relate to number of compounds in Table III. Dashed lines for nitromesitylene (no. 11) and nitromethane (no. 12) indicate predicted redox potentials. For 5-nitrouracil (no. 9) $a^N_{NO_2}$ was determined only at high pH. At pH 7 it is expected to be lower (see ref 26). This point was not included in the least-squares treatment of the line.

already been studied by ESR in irradiated aqueous solutions.[19,22,26-28] The remaining compounds were studied during this work using the same technique of in situ radiolysis ESR.[19] The parameters determined in the present study are summarized in Table IV. Of these values only $a^N_{NO_2}$ is useful for correlation with redox potentials. The nitrogen hyperfine constants for all radicals studied are given in the last column of Table III. The value for $CH_3NO_2^-$ (a^N = 25.55 G)[29] can be taken to represent 100% spin density on the nitrogen. By comparison with this value, spin densities varying from 0.38 for 4-nitropyridine to 0.86 for nitromesitylene radical anions can be calculated.

The effect of substituents on the nitrogen hyperfine constants of substituted nitrobenzene radical anions has been treated previously.[30] It is evident from Table III that electron-withdrawing groups such as acetyl or aldoxime decrease the spin density on the nitro group. Similarly electron withdrawal by the heteroatom in pyridines and furans decreases the spin density compared to nitrobenzene. It is further noticed here that the acetyl group exerts a strong effect on the spin distribution when it is located para to the nitro group, i.e., in a high spin position, while its effect is much smaller when it is in the low spin meta position. The effect of the three methyl groups in nitromesitylene is far beyond that which may be expected to result from electron donation by the methyl groups. It is probably due to a steric effect which tends to rotate the nitro group away from the plane of the ring and thus decrease the resonance interaction.

The large difference between the 2-nitro and the 5-nitro derivatives of imidazoles has been discussed previously.[27] Large differences are found also between the 2-nitro and 3-nitro derivatives of thiophene and pyrrole.[28]

Correlation of Redox Potentials with Spin Densities and Radiosensitization

Electron transfer to a nitro compound and from its radical anion is expected to involve the nitro group as the main site of the transfer. It is reasonable, therefore, to correlate the one-electron redox potentials with the spin densities on the nitro groups. This correlation is presented in Figure 4, where the nitrogen hyperfine constants are taken as a measure of spin density. It is seen from the figure that a linear correlation is obtained despite the wide structural variations in the compounds studied. The negative slope in Figure 4 shows that when a lower spin density resides on the nitro group of the radical anion the redox potential is less negative. Resonance between the nitro group and the rest of the molecule lowers the energy level of the first unoccupied orbital available for the electron, i.e. stabilizes the radical anion, and thus increases the redox potential.

Using linear least mean squares analysis the correlation is found to be described by

$$E_7^1 = 0.315 - 0.054 a^N_{NO_2} \qquad (13)$$

Equation 13 should be regarded merely as a representation of our experimental results and although it represents the data fairly well it does not necessarily have a theoretical justification. This equation can be used to estimate the one-electron redox potential for nitro compound from the nitrogen hyperfine constant of its radical anion. The deviations of the points from the straight line do not result to any appreciable extent from experimental errors in the determination of either the hyperfine constants or the potentials but rather are ascribable to structural differences which are neglected in our generalized treatment. Despite the deviations from the straight line, most unknown potentials can be predicted with an accuracy of about ±0.05 V. In Figure 4 the line has been extended to cover the region of the hyperfine constants for nitromesitylene and nitromethane. The potentials for these compounds have not yet been determined because they are outside the range of presently available references. They can be, however, predicted to be −0.86 and −1.06 V, respectively, as shown by the dashed lines in Figure 4.

Sensitization of cells to radiation damage has been related[31] to the electron affinity of the sensitizer with various parameters being used as a measure of electron affinity. For example, correlations of radiosensitization with Hammett's substituent constants[14] and with polarographic half-wave potentials[17] have been reported. For nitroheterocyclic compounds the nitrogen hyperfine constants of their radical anions have recently been used to explain differences in radiosensitization.[27] It seems now that correlation with the redox potential of the sensitizer is a common factor for both phenomena. The one-electron redox potential is a straightforward measure of electron affinity. When the potentials in Table III are compared with previously reported measurements on sensitization it is found that the compounds with less negative potentials are also the better sensitizers. This is evident from the comparison of nitrofurans with PNAP,[15] of PNAP with MNAP and nitrobenzene,[14] and of the 2-nitro- and 5-nitroimidazoles.[16] According to this observed trend, nitropyridine may be a better sensitizer than the others tested so far. Its practical use is, of course, predicated on finding a derivative that is biologically suitable (low toxicity and resistance to metabolic changes). It should be noted that oxygen, which is the most efficient sensitizer, has a one-electron potential of −0.15 V[11] (1 *M* O_2), more positive than any of the values in Table III. Diamide (diazinedicarboxylic acid bis(dimethylamide)) is also an efficient sensitizer. We have attempted to measure its redox potential but could only determine that it lies between 4-nitropyridine and oxygen. Further increase in potential beyond that of oxygen may limit the sensitization effect because of interference with the biological redox systems. Thus, benzoquinone (E_7^1 = 0.1 V[11]) which is a highly effective radiosensitizer[17] is relatively toxic while vitamin K_3 (menad-

ione, $E_7^1 = -0.20$ V[11]) may be a more favorable sensitizer.[31] The apparent limit of sensitization at the oxygen redox potential may lie in the capability of the cell to dispose of O_2^- radicals by the superoxide dismutase enzyme and consequently of other radicals which transfer electron to oxygen.

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Electrochemical Reactions of Organic Compounds in Liquid Ammonia. II. Nitrobenzene and Nitrosobenzene

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Abstract: The electrochemical behavior of nitrobenzene and nitrosobenzene in anhydrous liquid ammonia was investigated by cyclic voltammetry and controlled potential coulometry. In the absence of added protonating agents, nitrosobenzene and nitrobenzene are both reversibly reduced in two one-electron transfer steps to yield the stable radical anion and stable dianion species. In the presence of the weak acid isopropyl alcohol, the dianion of nitrosobenzene adds a single proton to form the anionic species, which can be reversibly oxidized back to parent compound. The dianion of nitrobenzene also adds a single proton and then rapidly decomposes with the loss of hydroxyl ion to neutral nitrosobenzene, which undergoes further reduction and protonation. The overall reduction process consists of the addition of a single electron to yield a stable radical anion followed by addition of three electrons and two protons to yield the protonated dianion of nitrosobenzene. In the presence of strong acid (ammonium ion), nitrosobenzene is reduced in a single two-electron reduction process to yield phenylhydroxylamine. Nitrobenzene is reduced in two steps, involving the addition of one and three electrons, to yield the same final product, phenylhydroxylamine. Estimates of the equilibrium or rate constants for several of these reactions associated with the electrode reactions are given.

The mechanism of the electrochemical reduction of nitrobenzene to phenylhydroxylamine and aniline has received considerable attention over the past 25 years.[1-14] Most of this work involved the use of aqueous solutions containing alcohol or an ether to aid in the dissolution of the relatively insoluble organic compound. Attempts at elucidating the reduction mechanism were made by correlating changes in electrochemical behavior of the system with changes in pH, which was adjusted through the use of various buffer systems. Some studies have also been undertaken in nonaqueous solvent systems with addition of proton sources of varying proton-donating strength. In aqueous solution, nitrobenzene is reduced to phenylhydroxylamine in a single four-electron reduction step at all pH values. At pH values less than 4.7, nitrobenzene is assumed to be pre-protonated giving the species $C_6H_5NO_2H_2^{2+}$, while analysis of the polarographic wave shows that the rate-determining step involves the addition of two electrons and a single proton.[8,9] The mechanism of reduction is given as:

$$C_6H_5NO_2H_2^{2+} + 2e^- + H^+ \longrightarrow C_6H_5NOH^+ + H_2O \quad \text{(slow)}$$

$$C_6H_5NOH^+ + 2e^- + 2H^+ \longrightarrow C_6H_5NH_2OH^+ \quad \text{(fast)}$$

The reduction product of the rate-determining step ($C_6H_5NOH^+$) is reducible at a less negative potential than the starting compound ($C_6H_5NO_2H_2^{2+}$), which explains why this intermediate has never been detected during the course of an experiment. A second wave at a more negative potential occurs in acid solution corresponding to reduction of the protonated phenylhydroxylamine species $C_6H_5NH_2OH^+$, to yield aniline in a single two-electron transfer step: