Acid–Base Properties of Free Radicals in Solution

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Received August 3, 1973

Following the discovery at the beginning of this century of free radicals as finite chemical entities capable of undergoing chemical reactions, attention was given to establishing the presence and role of such intermediates produced in solution. The high reactivity of these radicals presented a problem before the development of fast-reaction techniques, and recourse to "unreactive" solvents, extremes of acidity or basicity, and/or low-temperature glasses were explored.

One of the first main classes of free radicals to be examined was the semiquinones; the stability and spectral characteristics of these radicals were found to be dependent on the pH. The pioneering work of Michaelis, and others, up to 1935 has been reviewed.[1] The classical work of G. N. Lewis and coworkers[2] on the photochemical generation of free radicals and radical ions in organic glasses, and the later work of Michaelis, opened the gates to present concepts in photochemistry, free-radical chemistry, and the subject matter of this Account.

Studies of free radicals, particularly those involving their direct observation, have progressed during the last two decades with the rapid growth of fast-reaction techniques and new types of detectors. The involvement of free radicals in certain biochemical processes,[3] in enzymatic reactions, in radiation-induced mutation, cancer therapy, ageing, and in photochemical reactions and autoxidation processes has been a major factor in the promotion of research in free-radical reactions. We describe below how the reactivity and the course of free-radical reactions in solution can depend upon their state of protonation (ionization constants).

Generation and Detection of Free Radicals in Solution

This article deals with unstable free radicals in water, with lifetimes well below $\sim 10^{-2}$ sec at room temperature. In order to produce and observe these species, the fast-reaction techniques of flash photolysis, laser photolysis, and pulse radiolysis have been employed.[4,5]

Most of the free radicals presented in this Account have been produced from the pulse radiolysis of dilute aqueous solutions

$$H_2O \longrightarrow e_{aq}^- \ (2.8),\ OH\ (2.8),\ H\ (0.6)$$

where the values in parentheses are the yields (G values) of radicals produced. One-electron reduction of substrates (S) was obtained by reaction with e_{aq}^- or H, usually in the presence of *tert*-butyl alcohol to scavenge the OH radicals[6] (eq 1). Reactions with OH radicals produce free radicals *via* H atom abstraction, addition to unsaturated groups, and/or electron transfer.

$$e_{aq}^- + S \longrightarrow \cdot S^- \qquad (1)$$

Basically, three techniques have been used for the observation, identification, and quantitative study of free radicals in solution:

Spectrophotometry. This is based on the electronic absorption (or emission) properties of free radicals and is the most widely used. The absorption spectra of radicals are usually red shifted compared to those of the parent compounds. Furthermore, the optical absorption of the acid form of the radical is, in most cases, blue shifted compared to that of the conjugate base. The ionization constants (pK_a) of the free radicals are derived on the basis of spectral differences.

Electron Spin Resonance. The protonation or deprotonation of radicals has been observed in a few cases by esr.[7-10] Recent[9,10] improvements make this a very promising technique. The time resolution is still, however, a limitation, and transients with $\tau \ll 100\ \mu$sec cannot be observed.

Conductivity or Polarography. Recently this technique has been used successfully[11,12] in a few studies, and time resolutions of $\leq 2\ \mu$sec have now

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been obtained.[12] Considerable developments of this technique can be predicted.

Inorganic Free Radicals

The hydrated electron, e_{aq}^-, is the smallest and simplest free radical known to undergo acid-base reactions (eq 2 and 3). The exact mechanism of these reactions is not well understood.

$$e_{aq}^- + H_3O^+ \longrightarrow H + H_2O$$
$$k = 2.2 \times 10^{10}\ M^{-1}\ sec^{-1} \qquad (2^{13})$$
$$e_{aq}^- + H_2O \rightleftharpoons H + OH^-$$
$$k_3 = 16\ M^{-1}\ sec^{-1},\ k_{-3} = 2 \times 10^7\ M^{-1}\ sec^{-1} \qquad (3^{13,14})$$

From the equilibrium constant $K = k_3/k_{-3}$, the redox potential of e_{aq}^-, $E^\circ = -2.8$ V, was derived.[15] The H atoms have somewhat higher redox potential, $E^\circ = -2.0$ V.

The reactions of e_{aq}^- and H atoms can result in distinctly different intermediates and final products. H atoms preferentially add to unsaturated bonds and aromatic and heterocyclic rings but are relatively unreactive toward carbonyl groups, esters, peptide bonds, etc., whereas e_{aq}^- reacts at almost diffusion-controlled rates with the latter compounds.[13] Furthermore, H atoms can abstract from C-H bonds, whereas e_{aq}^- cannot. H atoms are believed to protonate to form H_2^+, but this reaction is still not well established.

The hydroxyl radical is a strong oxidizing species ($E^\circ \sim +2$ V). It behaves as a weak acid,[16,17] $pK_a = 11.9$ (eq 4). Its protonation to give H_2O^+ has been suggested and a $pK_a < 0$ proposed.[18] The reactions of OH and O^- radicals with aliphatic molecules and ions are rather similar, but the rate constants of O^- are generally lower. They show distinct differences in their reaction with aromatic and olefinic compounds:[19] the rate of addition of OH is much higher than that of O^-, whereas the rates for hydrogen atom abstraction are comparable.

$$OH + OH^- \rightleftharpoons O^- + H_2O$$
$$k_4 = 1.2 \times 10^9\ M^{-1}\ sec^{-1},\ k_{-4} = 9.2 \times 10^7\ sec^{-1} \qquad (4)$$

The hydroxyl and amino radicals are isoelectronic, but their acidities are quite different (eq 5). $\cdot NH_3^+$

$$\cdot NH_3^+ \rightleftharpoons \cdot NH_2 + H^+ \qquad pK_a = 6.7 \qquad (5)$$

is a much stronger oxidizing agent than $\cdot NH_2$ and can also add to aromatic rings.[18] The chemical and physical properties of substituted amino radicals, $R_1R_2\dot{N}H^+$, vary. While the hydrazine radical $\cdot N_2H_4^+$ and $(CH_3)_2\dot{N}H^+$ have pK_a values of 7.1[20] and 6.5–7.5,[21] respectively, the hydroxyamino[18] $\cdot^+NH_2OH$ and methoxyamino[18] $\cdot^+NH_2OCH_3$ radicals have pK_a values of 4.2 and 2.9, respectively. The nature of the reactions of these radicals is markedly dependent upon their state of protonation.

Oxygen is highly reactive toward free radicals and reacts with e_{aq}^- and H atoms to produce the superoxide radical (eq 6 and 7), and the equilibrium constant is now well established[22,23] (eq 8).

$$e_{aq}^- + O_2 \longrightarrow \cdot O_2^- \qquad k = 2.2 \times 10^{10}\ M^{-1}\ sec^{-1} \qquad (6)$$
$$H + O_2 \longrightarrow \cdot O_2H \qquad k = 2.0 \times 10^{10}\ M^{-1}\ sec^{-1} \qquad (7)$$
$$\cdot O_2H \rightleftharpoons \cdot O_2^- + H^+ \qquad pK_a = 4.85 \pm 0.1 \qquad (8)$$

These radicals are formed in a variety of electron-transfer reactions, *e.g.*, in enzymatic, cellular, and other biochemical redox systems.[3,24] The difference in the reactivity of $\cdot O_2^-$ and $\cdot O_2H$ radicals can now be rationalized on the basis of the recent experimentally determined redox potentials of these radicals.[25,26] The $E^{\circ\prime}$ (at pH 7.0 and 25°) of the $\cdot O_2^-/O_2$ couple is −0.07 V, of the $\cdot O_2H/O_2$ couple ~+0.9 V, and of the O_2^-/H_2O_2 couple +0.22 V. (When a redox reaction equilibrium involves H^+ on one side but not the other, the standard potential at unit activity of H^+ (symbolized E°) differs from the midpoint potential for the redox couple at pH 7 (symbolized $E^{\circ\prime}$) by 0.42 V.) From these redox potentials, it is now clear why O_2^- can reduce cytochrome *c* ($E^{\circ\prime}$ = +0.26 V) and *p*-benzoquinone ($E^{\circ\prime}$ = +0.29 V) but cannot reduce vitamin K_1 ($E^{\circ\prime}$ = −0.05 V) or ascorbic acid ($E^{\circ\prime}$ = +0.04 V). Similarly, hydroquinone ($E^{\circ\prime}$ = +0.28 V) and other *reduced* biochemical systems can[25,26] reduce O_2^- to H_2O_2.

Table I presents the ionization constants of some other inorganic free radicals reported in the literature.[27-31]

Organic Free Radicals

This section deals primarily with free radicals having the odd unpaired electron localized mainly on a carbon atom. The main functional groups which can undergo ionization or protonation are OH, CO_2H, NH, $^+NH_3$, SH, and radical anions and cations. As will soon become evident, the acid-base properties of free radicals are markedly affected only when these functional groups are in an α position to the carbon atom carrying the unpaired electron.

α-Hydroxyalkyl Radicals. This is one of the most thoroughly studied classes of free radicals, usually known as ketyl radicals, and produced *via* reactions 9–11, where $^1(R_1R_2CO)$ and $^3(R_1R_2CO)$ are the sin-

$$R_1R_2CO \xrightarrow{h\nu} {}^1(R_1R_2CO) \xrightarrow{isc} {}^3(R_1R_2CO) \xrightarrow{RH_2} R_1R_2\dot{C}(OH) + RH\cdot \qquad (9)$$

$$e_{aq}^- + R_1R_2CO \longrightarrow R_1R_2\dot{C}(O^-) \xrightleftharpoons{H^+} R_1R_2\dot{C}(OH) \qquad (10)$$

$$OH + R_1R_2CHOH \longrightarrow R_1R_2\dot{C}OH + H_2O \qquad (11)$$

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Table I
Acid–Base Properties of Some Inorganic Free Radicals in Water

Solute, S[a]	Method of formation	Radical anion	pK_a[b]	Neutral or monoprotonated radical	pK_a[c]	Diprotonated radical	Ref
H_2O (15.7)	Ionization	e_{aq}^-	9.65	H		H_2^+ (?)	13
H_2O (15.7)	Ionization	O^-	11.9	OH	<0	H_2O^+	16, 18
Oxygen	e_{aq}^- + S	$\cdot O_2^-$	4.8	$\cdot O_2H$			22, 23
Hydroxylamine (6.0)	e_{aq}^- + S	$\cdot NH^-$	≫12	$\cdot NH_2$	6.7	$\cdot NH_2^+$	18
O-Methylhydroxylamine (4.6)	e_{aq}^- + S	$\cdot NH^-$	≫12	$\cdot NH_2$	6.7	$\cdot NH_3^+$	18
N-Chlorodiisopropylamine	e_{aq}^- + S			$(CH_3)_2N\cdot$	6.5–7.5	$(CH_3)_2\dot{N}H^+$	21
Nitrate ion (−1.3)	e_{aq}^- + S	$\cdot NO_3^{2-}$	7.5	$\cdot NO_3H^-$	4.8	$\cdot NO_3H_2$	27
Nitrite ion (3.3)	e_{aq}^- + S	$\cdot NO_2^{2-}$	7.7	$\cdot NO_2H^-$	5.7	$\cdot NO_2H_2$	28
Nitric oxide	e_{aq}^- + S	$\cdot NO^-$	4.7	$\cdot NOH$			29
Nitric oxide	$\cdot NO^-$ + NO	$\cdot N_2O_2^-$	3.5	$\cdot N_2O_2H$			29
Nitric oxide	$\cdot N_2O_2^-$ + NO	$\cdot N_3O_3^-$	3.1	$\cdot N_3O_3H$			29
Tetrathionate	e_{aq}^- + S	$\cdot S_4O_6^{3-}$	6.2	$\cdot S_4O_6H^{2-}$			30
Hydroxylamine (6.0)	OH + S			$\cdot NHOH$	4.2	$\cdot {}^+NH_2OH$	18
O-Methylhydroxylamine (4.6)	OH + S			$\cdot NHOCH_3$	2.9	$\cdot {}^+NH_2OCH_3$	18
Hydrazine (8.1)	OH + S			$\cdot NHNH_2$	7.1	$\cdot N_2H_3^-$	20
Phosphate ions (7.2, 12.3)	OH + S	$\cdot PO_4^{2-}$	~10.7	$\cdot PO_4H^-$	~5.9	$\cdot PO_4H_2$	31

[a] Values in parentheses are pK_a values of the solutes in water; values usually are good to ±0.1 pH unit. [b] For acid dissociation of monoprotonated radical anion. [c] For acid dissociation of diprotonated radical anion.

glet and triplet excited states of the ketone, isc stands for intersystem crossing, and RH_2 is a H-atom donor.

The acidity of the hydroxyl group in these radicals is strongly dependent on the character of R_1 and R_2.

$$R_1R_2\dot{C}—OH \rightleftharpoons R_1R_2\dot{C}—O^- + H^+ \qquad (12)$$

The pK_a values of the $\cdot CH_2OH$, $CH_3\dot{C}HOH$, $(CH_3)_2\dot{C}OH$, and other α-hydroxyalkyl radicals are ~5 pH units lower than those of the corresponding alcohols (see Table II and ref 6, 23, 32, 33). When the OH group is in a β or γ position from the unpaired electron, *e.g.*, in $\cdot CH_2C(CH_3)_2OH$ from *tert*-butyl alcohol, no ionization of the OH group is observed[6] up to pH 14.

The α-hydroxyalkyl radicals are good electron donors, because of their relatively low redox potentials[11a,34,35] (eq 13 and 14), with[36] $k_{14} > k_{13}$. The

$$R_1R_2\dot{C}OH + A \longrightarrow \cdot A^- + R_1R_2CO + H^+ \qquad (13)$$

$$R_1R_2\dot{C}O^- + A \longrightarrow \cdot A^- + R_1R_2CO \qquad (14)$$

redox potentials of $R_1R_2\dot{C}OH$ radicals are all appreciably more positive than those of $R_1R_2\dot{C}O^-$. Thus, the $(CH_3)_2\dot{C}OH$ radical ($E^{\circ\prime}$ = −0.82 V) does not transfer an electron to molecules with a lower redox potential, *e.g.*, benzophenone[36] ($E^{\circ\prime}$ = −1.0 V), whereas $(CH_3)_2\dot{C}O^-$ ($E^{\circ\prime}$ < −1.6 V) transfers with 100% efficiency and $k_{14} = 1.6 \times 10^9\ M^{-1}\ sec^{-1}$ (ref 36). Similarly, the $CH_3\dot{C}HOH$ radical ($E^{\circ\prime}$ = −0.69 V)[34] does not transfer to benzophenone but transfers to *N*-ethylmaleimide[37] ($E^{\circ\prime}$ ~ −0.5 V) and *N*-methylnicotinamide[38] ($E^{\circ\prime}$ = −0.42 V).

Conjugation of the >Ċ–OH group with C=C bonds and aromatic groups further increases[39-46] the acidity of the OH group (see Table II).[47] The effect appears greatest when the >Ċ–OH radical is between two double bonds or aromatic rings, as in $CH_2{=}CH\dot{C}(OH)CH{=}CH_2$[40] and $Ph_2\dot{C}OH$[42] where the pK_a values are 8.9 and 9.2, respectively, compared to pK_a = 12.2 for the $CH_3\dot{C}(OH)CH_3$ radical.

The strongest inductive effect is observed by a carbonyl group in an α position to the >Ċ–OH radical, as in biacetyl,[46] hexenedione,[39] and benzil[42] with pK_a values of 4.4, 5.2, and 5.5, respectively. Strong resonance stabilization of the radical anion no doubt contributes to the strong acidity of the OH group.

Little has been done on free radicals of sulfur compounds[48,49] (Table II). Linear disulfides (*e.g.*, cystine, penicillamine, glutathione) form radical anions ($RSSR\cdot^-$), but their corresponding $R\dot{S}S(H)R$ radicals have not been observed[49] (except for lipoate which is a cyclic disulfide) and are probably very short-lived. The rates of protonation of $RSSR^-$ have been determined[49] and found to be strongly dependent on the configuration of the disulfides (k from 5×10^8 to $5 \times 10^{10}\ M^{-1}\ sec^{-1}$).

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Table II
Acidity of OH and SH Functional Groups in an α Position of >ĊOH, >ĊSH, and >ṠOH Free Radicals in Water

Solute	Neutral radical[a]	pK_a (radical)	Ref
Methyl alcohol	$\cdot CH_2OH$	10.7	23, 32, 33
Ethyl alcohol	$CH_3\dot{C}HOH$	11.6	32, 33
Isopropyl alcohol	$(CH_3)_2\dot{C}OH$	12.2	32, 33
n-Propyl alcohol	$C_2H_5\dot{C}HOH$	11.5	32
Isobutyl alcohol	$(CH_3)_2CH\dot{C}HOH$	11.6	32
Neopentyl alcohol	$(CH_3)_3C\dot{C}HOH$	11.3	6
Penthaerythritol	$(CH_2OH)_3\dot{C}CHOH$	10.4	23
2-Deoxy-*d*-ribose	$\cdot C_5H_9O_4$	9.8	23
Cyclohexyl alcohol	c-$\dot{C}_6H_{10}OH$	12.1	6
tert-Butyl alcohol[b]	$\cdot CH_2(CH_3)_2COH$	>14	6
Acrolein	$CH_2{=}CH\dot{C}HOH$	9.6	39
Crotonaldehyde	$CH_3CH{=}CH\dot{C}HOH$	9.9	39
Vinyl methyl ketone	$CH_3CH{=}CH\dot{C}(OH)CH_3$	10.1	39
Hexenedione	$CH_3COCH{=}CH\dot{C}(OH)CH_3$	5.2	39
1,4-Pentadien-3-ol	$CH_2{=}CH\dot{C}(OH)CH{=}CH_2$	8.9	40
2,4-Hexadien-1-ol	$CH_3CH{=}CHCH{=}CH\dot{C}HOH$	9.6	40
Benzaldehyde	$C_6H_5\dot{C}HOH$	8.4, 10.5	39, 41
Acetophenone	$C_6H_5\dot{C}(OH)CH_3$	9.9, 9.6, 10.9	42–44
Benzophenone	$C_6H_5\dot{C}(OH)C_6H_5$	9.2	42, 43, 45
Fluorenone	$-\dot{C}(OH)-$	6.3	42
2-Benzoylpyridine	$C_6H_5\dot{C}(OH)Py$	12.3[c]	34
3-Benzoylpyridine	$C_6H_5\dot{C}(OH)Py$	9.2[c]	34
4-Benzoylpyridine	$C_6H_5\dot{C}(OH)Py$	12.0[c]	34
Benzil	$C_6H_5CO\dot{C}(OH)C_6H_5$	5.5, 5.9	42, 44
Biacetyl	$CH_3CO\dot{C}(OH)CH_3$	4.4	46
Dimethyl sulfoxide	$CH_3\dot{S}(OH)CH_3$	10.2	48a
Carbon disulfide	$S{=}\dot{C}SH$	1.6	48b
Carbon disulfide	$S{=}C(OH)S\cdot$	4.4	48b
Lipoate (RSSR)	$RS\dot{S}(H)R$	5.8	49

[a] Radicals produced, using the pulse radiolysis technique, from the reaction of OH radicals or e_{aq}^- with the solutes. [b] β radical. [c] See ref 38 for alternate assignment for this radical.

α-Carboxyalkyl Radicals. The interaction of the unpaired electron on a carbon atom with the COOH group in an α position does not appear to be strong (see Table III and ref 50–62). The pK_a values of these unsubstituted α-carboxyalkyl radicals are close to those of the parent acids, *e.g.*,

$$\dot{C}H_2COOH \rightleftharpoons \dot{C}H_2COO^- + H^+ \qquad pK_a = 4.9 \qquad (15)$$

The inductive effect of some functional groups alters the pK_a's of >ĊCOOH radicals: the pK_a of glycine, glycolic acid, and *N*-acetylglycine are 2.3, 3.8 and 3.7, respectively, while those of the corresponding radicals are significantly *higher*.

$$H_2N\dot{C}HCOOH \rightleftharpoons H_2N\dot{C}HCOO^- + H^+ \qquad pK_a = 6.6 \qquad (16)$$

$$HO\dot{C}HCOOH \rightleftharpoons HO\dot{C}HCOO^- + H^+ \qquad pK_a = 4.6 \qquad (17)$$

$$CH_3CONH\dot{C}HCOOH \rightleftharpoons CH_3CONH\dot{C}HCOO^- + H^+ \qquad pK_a = 4.6 \qquad (18)$$

The carboxy radical $\cdot CO_2^-$ also undergoes protonation, but disagreement exists concerning the exact pK_a value.[50,51] The $\cdot CO_2^-$ has a low redox potential,[11a] $E^{\circ\prime} \sim -1.0$ V, and is a convenient reducing agent for many substrates.

Polyfunctional Radicals

In polyfunctional radicals (see Table III), strong electron-withdrawing or electron-donating groups coupled closely with the unpaired electron and the CO_2H group considerably affect their acid-base properties. Replacement of the CO_2H group by $CONH_2$ or CO_2R (R = alkyl) decreases the acidity of the OH group by 3–5 pH units, *e.g.*, the glycolamide $\dot{C}H(OH)CONH_2$[56] and the ethyl lactate[55] $CH_3\dot{C}(OH)CO_2C_2H_5$ radicals have pK_a's of 5.5 and ~6.0. The CO_2H and $CONH_2$ groups also affect ionization of the $^+NH_3$ group (eq 19 and 20). When the

$$H_3\overset{+}{N}\dot{C}HCO_2H \rightleftharpoons H_2N\dot{C}HCO_2H + H^+ \qquad pK_a \leq 1.0 \qquad (19)$$

$$H_3\overset{+}{N}\dot{C}HCONH_2 \rightleftharpoons H_2N\dot{C}HCONH_2 + H^+ \qquad pK_a = 4.3 \qquad (20)$$

unpaired electron is localized further away from the $^+NH_3$ group, as in various oligopeptides,[59,60] the acidity of this group approaches that of the parent compound.

The peptide group, -CONH-, has been estimated[63] to have p$K_a \sim$ 15–18. Peptide radicals, -CONHĊH-, ionize at much lower pH values (eq 21). The acidity of the peptide group is lowest in the

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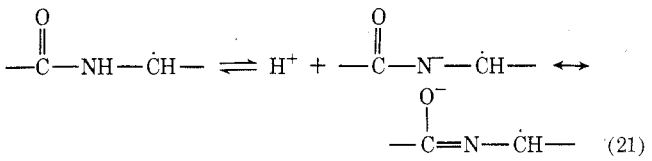
Table III
Acidity of COOH, OH, NH_3^+, and NH Functional Groups in an α Position of Various Free Radicals in Water

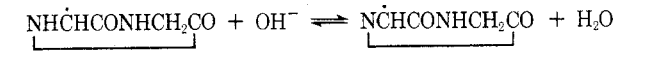
Solute[a]	Neutral Radical	pK_a (radical) COOH	OH	NH_3^+ or NH	Ref
Formic acid (3.8)	$\cdot CO_2H$	3.9, 1.4			50, 51
Acetic acid (4.8)	$\cdot CH_2CO_2H$	4.5, 4.9			52, 61
Propionic acid (4.9)	$CH_3\dot{C}HCO_2H$	4.9			52
n-Butyric acid (4.8)	$CH_3CH_2\dot{C}HCO_2H$	4.8			52
Isobutyric acid (4.9)	$(CH_3)_2\dot{C}CO_2H$	5.8			52
Trimethylacetic acid (5.0)	$\cdot CH_2(CH_3)CO_2H$	4.8			52
Phenylacetic acid (4.3)	$C_6H_5\dot{C}HCO_2H$	5.5			53
Malonic acid (2.9, 5.7)	$HO_2C\dot{C}HCO_2H$	5.7			54
Glycolic acid (3.8)	$\cdot CH(OH)CO_2H$	4.6	8.8		54
Lactic acid (3.9)	$CH_3\dot{C}(OH)CO_2H$	5.3	9.8		54
Ethyl lactate	$CH_3\dot{C}(OH)CO_2C_2H_5$		~6.0		55
Tartaric acid (3.0, 4.3)	$HO_2CCH(OH)\dot{C}(OH)CO_2H$	4.5	12.4		54
Oxalacetic acid	$HO_2C\dot{C}(OH)CH_2CO_2H$		9.2		36
Glycolamide	$\dot{C}H(OH)CONH_2$		5.5		56
Lactamide	$CH_3\dot{C}(OH)CONH_2$		6.5		56
Glycine (2.3, 9.6)	$^+NH_2\dot{C}HCO_2H$	6.6		<1.0	9b, 57, 58
Glycylglycine (3.1, 8.1)	$^+NH_3CH_2CONH\dot{C}HCO_2H$	~5.0			59
Triglycine (3.3, 7.9)	$^+H_2(Gly)_2NH\dot{C}HCO_2H$	~5.0			59
Glycinamide (8.0)	$^+NH_2\dot{C}HCONH_2$			4.3	60
N-Acetylglycine (3.7)	$CH_3CONH\dot{C}HCO_2H$	4.6		≥13.0	59
N-Acetylglycylglycine	$AcGlyNH\dot{C}HCO_2H$	4.5		~12.0	59
N-Acetyldiglycinamide	$AcGlyNH\dot{C}HCONH_2$			~11.8	60
Glycylsarcosine (3.0, 8.6)	$^+NH_3CH_2CON(CH_3)\dot{C}HCO_2H$	~3.4		~8.0, ~13.0	60
Glycine anhydride	$-CONH\dot{C}H-$			9.6	62
Alanine anhydride	$-CONH\dot{C}(CH_3)-$			9.6	62
Sarcosine anhydride	$-CON(CH_3)\dot{C}H-$			None	62

[a] Values given in parentheses are pK_a of the solutes.

$CH_3CONH\dot{C}HCO_2^-$ and $AcGlyNH\dot{C}HCO_2^-$ radicals[59,60] (≥13.0 and ~12), but increases in the cyclic dipeptides[62] (pK_a = 9.6). Sarcosine anhydride -CO-N(CH_3)CH- does not ionize,[62] indicating unequivocally that the -NH- group is the proton donor (eq 22).



(21)



$$k = 8.0 \times 10^9\ M^{-1}\ \text{sec}^{-1} \qquad (22)$$

Radical Anions (Electron Adducts)

Radical anions have been generated electrochemically in various aprotic polar and nonpolar solvents. In these solvents, many of them are stable and have been studied by esr and absorption spectroscopy. In protic solvents, they protonate and become relatively unstable. The hydrated and solvated electrons generated in pulse radiolysis have provided a most convenient way to study the physicochemical properties of radical anions.

The electrophilic character of various functional groups greatly affects the acid–base properties of the radicals (see Table IV, ref 13 and 64–86). Alkyl groups are the least electrophilic ($k < 10^5\ M^{-1}\ \text{sec}^{-1}$), and the OH, NH_2, CO_2^- and >C=C< groups have low reactivity with electrons. A combination of these, however, greatly increases their reactivity toward e_{aq}^- through resonance stabilization of the radical anion electron adduct, leading to considerable effect on the ionization constants of these functional groups. Further increases in acidity result through the introduction of strongly electrophilic groups such as >CO, NO_2, CO_2H, CO_2R, $CONH_2$, -CONH-, SH, -SS-, etc.

Acids. An interesting example is the electron adduct to benzoic acid. Protonation takes place at the carboxyl group and not at the benzene ring[64] (eq 23).

$$C_6H_5\dot{C}(OH)_2 \underset{pK_a = 5.3}{\rightleftharpoons} (C_6H_5CO_2H)^- \underset{pK_a = 12.0}{\rightleftharpoons} (C_6H_5CO_2)^{2-} \qquad (23)$$

This interpretation has been confirmed[12] by esr. The

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Table IV
Acid–Base Properties of Radical Anions Produced from the Reaction of e_{aq}^- with Solutes in Water

Solutes[a]	Radical	pK_a (radical)	Ref
Acids			
Benzoic (4.2)	$C_6H_5\dot{C}(OH)_2$	5.3	64
	$(C_6H_5CO_2H)^-$	12.0	64
Phthalic, PH_2 (3.0), 5.4)	$\cdot PH^{2-}$	>12.0	12
Terephthalic, TH_2 (3.5, 4.8)	$\cdot TH^{2-}$	10.1	12
Fumaric, FH_2 (3.0, 4.4)	$\cdot FH_3$	~3.0	65
	$\cdot FH_2^-$	⩽4.0	65
	$\cdot FH^{2-}$	10.9, 10.4	65, 12
Maleic, MH_2 (1.9, 6.2)	$\cdot MH_3$	~4.0	65
	$\cdot MH_2^-$	5–6	65
	$\cdot MH^{2-}$	>13, >12	65, 12
Acrylic, AH (4.3)	$\cdot AH_2$	5.0 and 7.0	66, 67
Methacrylic, MAH (~4.3)	$\cdot MAH_2$	5.3	67
Crotonic, CH (~4.7)	$\cdot CH_2$	7.5	67
Sorbic, SH (~4.8)	$\cdot SH_2$	6.4	67
Esters			
Methyl fumarate	$-\dot{C}(OH)OCH_3$	11.5	65
Dimethyl fumarate	$-\dot{C}(OH)OCH_3$	2.8	65
Dimethyl maleate	$-\dot{C}(OH)OCH_3$	4.8	65
Methyl glycinate	$-\dot{C}(OH)OCH_3$	11.1	68
Methyl benzoate	$-\dot{C}(OH)OCH_3$	5.5	64
Amino acids			
N-Acetyltriglycine	$-CH_2\dot{C}(OH)NH-$	⩾13.0	69
N-Acetylsarcosine	$-CH_2\dot{C}(OH)N(CH_3)-$	⩾13.0	69
Imidazole (7.1, 14.5)	e_{aq}^- adduct	8.1	70
N-Methylimidazole (6.95)	e_{aq}^- adduct	9.3	70
Amides and imides			
Acetamide	$-\dot{C}(OH)NH_2$	⩾13.5	71
Malonamide	$-\dot{C}(OH)NH_2$	9.8	71
Succinamide	$-\dot{C}(OH)NH_2$	11.3	71
Biuret	$-\dot{C}(OH)NH_2$	7.3	71
Oxamide	$-\dot{C}(OH)NH_2$	⩽3.7	71
Oxamic acid	$NH_2\dot{C}(OH)CO_2^-$	⩾12.5	
	$NH_2\dot{C}(OH)CO_2H$	5.2	71
Acrylamide	$CH_2{=}CH\dot{C}(OH)NH_2$	7.9	72
Methacrylamide	$CH_2{=}C(CH_3)\dot{C}(OH)NH_2$	8.0	72
Benzamide	$C_6H_5\dot{C}(OH)NH_2$	7.7	42
Succinimide	$-\dot{C}(OH)NHCO-$	8.4	71
N-Ethylmaleimide	$-\dot{C}(OH)N(Et)CO-$	2.9	37
Pyrimidines			
Uracil (9.5, 13)	$-\dot{C}(OH)-$	7.3	73
Thymine (9.9, 13)	$-\dot{C}(OH)-$	7.2	73
1,3-Dimethyluracil	$-\dot{C}(OH)-$	7.0	73
Orotic acid (2.8, 9.5, 13)	$-\dot{C}(OH)-$	3.3–4.0	74
Nitro compounds			
Nitromethane	$-\dot{N}O_2H$	4.4	75
Nitrobenzene	$-\dot{N}O_2H$	3.2	76
o-Dinitrobenzene	$-\dot{N}O_2H$	2.2	77
m-Dinitrobenzene	$-\dot{N}O_2H$	2.6	77
p-Dinitrobenzene	$-\dot{N}O_2H$	1.6	78
o-Hydroxynitrobenzene	$-\dot{N}O_2H$	2.0	79
m-Hydroxynitrobenzene	$-\dot{N}O_2H$	3.1	79
p-Hydroxynitrobenzene	$-\dot{N}O_2H$	3.6	79
p-Nitroacetophenone	$-\dot{N}O_2H$	2.6	80
OH adduct to $CH_2{=}NO_2^-$	$HOCH_2\dot{N}O_2^-$	12.8	82
p-Nitrobenzyl chloride	$-\dot{N}O_2H$	3.1	83
p-Nitrobenzoic acid	$-\dot{N}O_2H$	2.8	77
Pentaammine-*p*-nitrobenzoato-cobalt(III)	$-\dot{N}O_2H$	2.8	84
Nitrosobenzene	$-\dot{N}OH$	11.7	85
Benzonitrile		7.2	86

[a] Values in parentheses are the pK_a values of the solutes.

pK_a for ionization of the e_{aq}^- adducts[12] to phthalate and terephthalate (to give the trianions) are >12 and 10.1, respectively. The higher negative charge density in the *o*-dicarboxy structure of phthalate agrees with the results obtained[65] for maleic and fumaric acids.

Esters. Replacement of the weakly electrophilic CO_2^- group by the strongly electrophilic CO_2R group increases considerably the acidity of the electron adduct. These species have p$K_a \leq 7.0$, in most cases. For methyl benzoate,[64] the pK_a of $Ph\dot{C}(OH)OCH_3$ is 5.5.

The acid–base properties of the radical anions of dimethyl fumarate (DMF) and dimethyl maleate (DMM) are of particular importance, since this is the first case where the effect of the cis and trans forms on the acidity of the electron adducts was clearly demonstrated:[65] $\cdot DMF^-$ trans, $pK_a = 2.8$; $\cdot DMM^-$ cis, $pK_a = 4.8$. Protonation takes place at the CO_2R group and not at the double bond. When only one of the carboxyl groups is esterified, increase in the negative charge and greater localization of the added electron on the CO_2R group lead to a higher pK_a; the pK_a is 11.5 for monomethyl fumarate, which is comparable to that of simple saturated esters.

Amides and Imides. The amide group is not a strong electrophile (much less than CO_2H and CO_2R). Hence the pK_a values of the electron adducts to simple amides[71] are rather high ($pK_a \geq 13.5$ for $CH_3\dot{C}(OH)NH_2$). The introduction of a second amide group increases the acidity through delocalization of the excess electron. The pK_a depends strongly on the coupling of the amide groups. This is evident if one compares[71] the pK_a values of 3.7, 9.8, and 11.3 for the e_{aq}^- adducts of oxamide, malonamide, and succinamide, respectively. It follows that resonance through carbon atoms is greatly reduced if 2 or more $-CH_2-$ groups are interpolated between the two amide groups (see Table IV).

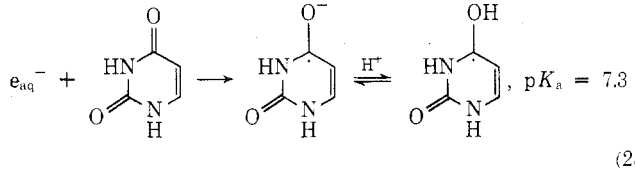
Conjugation of the amide group with aromatic rings leads to increased acidity, *e.g.*, $pK_a = 7.7$ for $C_6H_5\dot{C}(OH)NH_2$.[64] Conjugation to C=C bonds[72] also has a large effect.

$$CH_2{=}CH\dot{C}(OH)NH_2 \rightleftharpoons CH_2{\cdots}CHCNH_2^{\,O^-} \qquad pK_a = 7.9 \quad (24)$$

The radical anions of imides behave similarly to the amides: the pK_a of the radical anion of *N*-ethylmaleimide[37] is 2.9 while that for saturated succinimide[71] is 8.4.

Amino Acids and Peptides. The addition of an electron to the peptide linkage produces the $-CH_2-\dot{C}(OH)NH-$ radicals. These have relatively high pK_a values,[69] *e.g.*, ≥13.0 for *N*-acetyltriglycine and *N*-acetyltrisarcosine. With aromatic and heterocyclic amino acids, the electron adds primarily to the ring structure followed by rapid protonation.[53,87,88]

Pyrimidines. The primary site for addition of e_{aq}^- to uracil, thymine, and other pyrimidines, has been postulated[73] to be the carbonyl groups at the 2 and 4 positions, *e.g.*,



(25)

Delocalization of the unpaired electron throughout the ring probably takes place. Both forms of the radical have been found[89] to have very low redox potentials, $E^{\circ\prime} \sim -1.5$ V, and are powerful reducing agents.

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Nitro Compounds. Due to the extremely high resonance stabilization present in $-\dot{N}O_2^-$, these radicals[75,79] are very acidic ($pK_a \leq 4.4$; Table IV) and have rather low reactivity and relatively long lifetimes. When protonated, the resonance is diminished and these radicals disappear ($k \sim 10^8\ M^{-1}\ sec^{-1}$) through disproportionation and other reactions. The acidity of $-\dot{N}O_2H$ is further increased by introduction of other electron-withdrawing groups (*e.g.*, NO_2). The interaction of e_{aq}^- with molecules containing nitro and other electrophilic groups, *e.g.*, *p*-nitroacetophenone and *p*-nitrobenzyl chloride,[83] produce $-\dot{N}O_2^-$ rather than ketyl or benzyl (*via* dechlorination) radicals.

Due to lack of resonance stabilization, the $-\dot{N}OH$ radicals are much weaker acids then $-\dot{N}O_2H$ (see Table IV).

Biochemical Radicals

Electron-transport phenomena in the mitochondria and the chloroplast provoked an early interest in free-radical mechanisms of some biochemical systems. Some of the free radicals expected to play a role in biochemical redox reactions have been produced by flash photolysis or pulse radiolysis (Table V, ref 38 and 90–101).

Table V
Acid–Base Properties of Some Free Radicals of Biological Interest in Water

Substrate[a]	pK_a (radical)	Ref	Method of formation[b]
Nicotinamide	1.1, 13.4	38	pr
N-Methylnicotinamide	1.3	38	pr
Riboflavine (10.0)	8.3, 8.36, 8.27	90–92	pr, fp, pt
Lumiflavine	8.36	91	fp
FMN	8.5	91	fp
FAD	8.8	91	fp
Pterin (2.3, 7.9)	6.6, 10.3	93	pr
Folic acid (8.3)	6.7, 10.2	93	pr
Glucose oxidase	7.5	94	pc
p-Benzoquinone	4.0, 4.1	95, 96	pr, pr
2,5-Dimethyl-*p*-benzoquinone	4.6	96	pr
Duroquinone	5.1, 4.9, 5.9	96–98	pr, pr, fp
Ubiquinone	5.9, 6.4[c]	97, 99	pr
Adrenalone	3.6	96	pr
Epinephrine	3.7	96	pr
Diphenoquinone	3.2	96	pr
1,4-Naphthoquinone	4.1, 4.1	96, 97	pr, pr
1,2-Naphthoquinone	4.8	96	pr
Menaquinone (Vit. K_3)	4.5, 4.4	100, 97	pr, pr
Vitamin K	5.5	97	pr
Anthraquinone	5.3	96	pr
Anthraquinone-1-sulfonate	5.4	101	pr

[a] Values in parentheses are pK_a values of substrate. [b] pr = pulse radiolysis, fp = flash photolysis, pt = potentiometric titration, pc = photochemistry. [c] In pure methanol.

(90) E. J. Land and A. J. Swallow, *Biochemistry*, 8, 2117 (1969).
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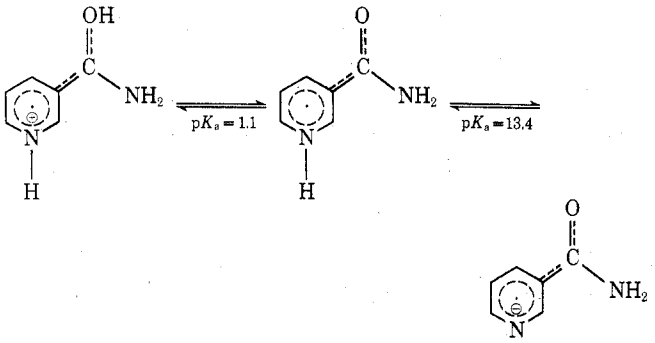
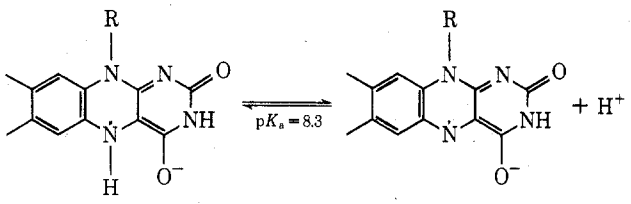
The addition of e_{aq}^- to nicotinamide and nicotinic acid[38,102] takes place on the ring nitrogen followed by rapid protonation. These radicals do not undergo measurable acid dissociation in the biological pH range.



The flavine semiquinones have been implicated as intermediates in electron-transfer reactions to oxygen, cytochromes, and quinones. These give radicals with the unpaired electron localized on the pyrazine ring nitrogens.[103] For riboflavin[90-92,103] (other resonance forms are not shown)



Relatively little is known about the acid–base properties of heterocyclic -NH⁺- and -Ṅ H- radicals. The pterin semiquinone radical is present[93] in neutral solutions as the dihydro cation and ionizes (pK_a = 6.6) before enolization of the C-4 carbonyl. At higher pH, the pterin semiquinone radical -Ṅ H- is ionized, with pK_a = 10.4.

Quinones[3,104] play an important role in biochemical electron-transport processes. The pK_a values of semiquinone radicals vary from about 3.0 to 5.5 (see Table V). A linear correlation was shown[96] to exist between the pK_a of the semiquinone radical and the redox potential of the quinones (see also Figure 1), with the pK_a decreasing with increase in the $E^{\circ\prime}$ value of the quinones.

Redox Potentials and Acid–Base Properties of Free Radicals

The ionization constants of the α-hydroxyalkyl radicals given in Tables II and V have been plotted as a function of the redox potentials of the parent compounds, and a linear correlation[105] was obtained (Figure 1[106]). This correlation, which stretches from

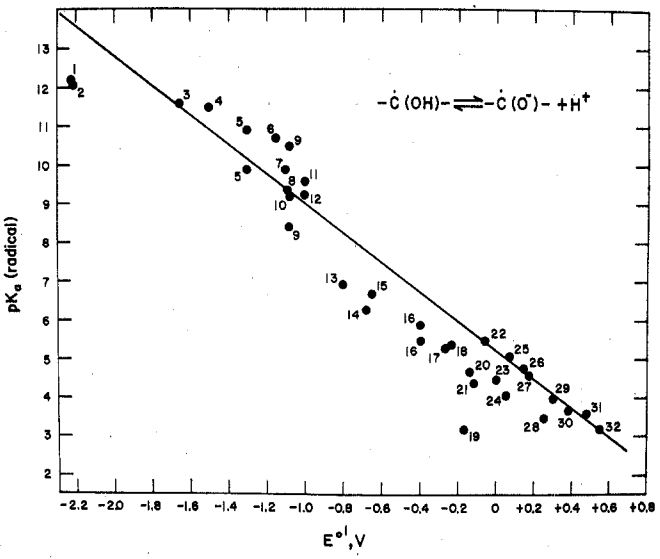


Figure 1. Dependence of the pK_a of >ĊOH radicals upon the redox potential, $E^{\circ\prime}$ (at pH 7.0, ~25°), of the parent molecules. **1**, acetone;[32] **2**, cyclohexanone;[6] **3**, acetaldehyde;[32] **4**, propionaldehyde;[32] **5**, acetophenone;[42] **6**, formaldehyde;[32] **7**, crotonaldehyde;[39] **8**, *p*-chloroacetophenone;[80] **9**, benzaldehyde;[39,44] **10**, *p*-bromoacetophenone;[80] **11**, acrolein;[39] **12**, benzophenone;[42] **13**, *p*-cyanoacetophenone;[80] **14**, fluorenone;[42] **15**, benzalacetophenone;[106] **16**, benzil;[42] **17**, 9,10-anthraquinone;[96] **18**, 9,10-anthraquinone-1-sulfonate;[101] **19**, 9,10-anthraquinone-2,6-disulfonate; **20**, 2-hydroxy-1,4-naphthoquinone;[96] **21**, biacetyl;[46] **22**, vitamin K;[97] **23**, menaquinone;[97,100] **24**, 1,4-naphthoquinone;[96,97] **25**, duroquinone;[96-98] **26**, 1,2-naphthoquinone;[96] **27**, 2,5-dimethyl-*p*-benzoquinone;[96] **28**, 2-methyl-*p*-benzoquinone;[96] **29**, *p*-benzoquinone;[95,96] **30**, epinephrine;[96] **31**, adrenalone;[96] **32**, diphenoquinone.[96]

$E^{\circ\prime}$ values of −2.2 to +0.60 V and pK_a 3.0–12.0, establishes and emphasizes the role and importance which the acid–base properties of free radicals play in electron-transfer processes. LCAO calculations[39] also gave a good linear correlation between the pK_a values of some radicals and ΔH_{Res}.

The electron-transfer properties of a wide range of organic free radicals (RH·) to dyes[107] and a number of other acceptors[25,35,88,89] have been studied. One finds that the efficiency (expressed as percentage) and rate of electron-transfer processes, *e.g.*, reactions 13 and 14, are dependent on $\Delta E^{\circ\prime} = E^{\circ}_{A}{}' - E^{\circ}_{D}{}'$, where $E^{\circ}_{A}{}'$ = redox potential of acceptor and $E^{\circ}_{D}{}'$ = potential of donor radical.

Organic peroxy radicals, ·OORH, formed by addition of O_2 to organic free radicals have usually lower pK_a values for groups in the α position to the peroxy group (see ref 6, 23, and 108). Their role in biochemistry is not yet clearly established.

Conclusions

The patterns of the various reaction mechanisms, based on the energetics and kinetics of the acid and base forms of free radicals, have emerged during the last few years. An expansion of research along those lines is expected. It is hoped that these studies will be applied to oxidative processes and to biological systems in which free-radical reactions may play a considerable role. The study of the chemical dynamics of free radicals in solution is truly an interdisciplinary field, and the development of new techniques and new approaches can be predicted.

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(105) This correlation can be used (and has been used in our laboratory) to predict the pK_a of such radicals if the $E^{\circ\prime}$ value is known or, *vice versa*, to estimate $E^{\circ\prime}$ if the pK_a value is known.
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