Volume 264, number 2, 165–167 FEBS 08410 May 1990

Oxyradical reactions: from bond-dissociation energies to reduction potentials

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Received 20 March 1990

Destructive radical reactions involve alkyl, alkoxyl and alkylperoxyl radicals, as well as alkylhydroperoxides. From bond energies the following reduction potentials vs NHE at neutral pH are derived: $E^{\circ\prime}(RO\cdot/ROH) = 1.6$ V, $E^{\circ\prime}(ROO\cdot/ROOH) = 1.0$ V, $E^{\circ}(ROOH/RO\cdot, H_2O) = 1.9$ V, and the two-electron reduction potential $E^{\circ\prime}(ROOH/ROH, H_2O) = 1.7$ V. Hydrogen abstraction from a *bis*-allylic methylene group by alkoxyl and alkylperoxyl radicals is favourable with Gibbs energies of −23 and −9 kcal/mol, respectively. Similarly, alkoxyl radicals can oxidize alkylhydroperoxides, $\Delta G^{\circ\prime} = -14$ kcal/mol.

Lipid peroxidation; Reduction potential; Alkyl radical; Alkylperoxyl radical; Alkoxyl radical; Bond energy

1. INTRODUCTION

Oxyradicals play an important role in radiation biology [1] and various disorders, such as emphysema, cancer, arthritis [2,3] and reperfusion injury [4,5]. It is generally accepted that the reaction of hydrogen peroxide with a transition metal complex yields an oxidizing species that damages biomolecules. The hydrogen peroxide originates from dismutation of the superoxide anion formed in, for instance, mitochondria [6] or leucocytes [7]. The oxidizing species could be the hydroxyl radical [8] or a higher oxidation state of iron [9,10]. While the thermodynamic properties of hydrogen peroxide, superoxide and the hydroxyl radical are well documented [11], much less is known about subsequent reaction products, such as alkyl and allylic radicals ($R^{\cdot}$), alkoxyl radicals ($RO^{\cdot}$) and alkylperoxyl radicals ($ROO^{\cdot}$). Reduction potentials for these species are derived here. It is shown quantitatively that alkoxyl radicals are more oxidizing than alkylperoxyl radicals, and that both can abstract an allylic hydrogen.

2. THERMODYNAMICS

In a recent paper Sawyer [12] calculated Gibbs bond dissociation energies and enthalpies for a number of O–H bonds in oxygen and hydrogen containing compounds. The method is based on reactions 1–3 and is similar to the approach employed by Bordwell [13].

$$R^{\cdot} + H^{+} + e^{-} \rightarrow RH \quad E^{\circ}(R^{\cdot}/RH) \text{ vs NHE} \tag{1}$$

$$H^{\cdot} \rightarrow H^{+} + e^{-} \quad +2.1 \text{ V} \tag{2}$$

$$R^{\cdot} + H^{\cdot} \rightarrow RH \tag{3}$$

The Gibbs energy of bond dissociation ($\Delta G^{\circ}_{\mathrm{DBE}}$) is $[E^{\circ}(R^{\cdot}/RH) + 2.1 \text{ V}]23.06 \text{ kcal}\cdot\text{V}^{-1}\cdot\text{mol}^{-1}$. Addition of a constant factor, 7.8 kcal ($T\Delta S^{\circ}_{\mathrm{DBE}}$), yields the dissociative bond enthalpy, $\Delta H^{\circ}_{\mathrm{DBE}}$. The agreement with values from the literature is remarkable.

This approach can be extended to carbon-hydrogen bonds with excellent results. For a number of H–C bonds $T\Delta S^{\circ}_{\mathrm{DBE}}$ averages 8.8 kcal/mol, which is used in this paper. Results are given in Table I.

The observation that reduction potentials can be used to calculate reliable H–O and H–C bond energies implies that reduction potentials can be estimated if bond energies are known. As mentioned above, of great interest in the area of free radical biology are reduction potentials for the couples: allylic$^{\cdot}$/allylicH, $RO^{\cdot}/ROH$ and $ROO^{\cdot}/ROOH$. The calculations require a correction if there is a difference in solvation between the radical and parent compound. For a polar H–O bond $\Delta G^{\circ}_{s}(RH) = \Delta G^{\circ}_{s}(R^{\cdot}) - 2$ kcal/mol as discussed in [14], which leads to the following equation: $\Delta H^{\circ}_{\mathrm{DBE}} = [2.1 \text{ V} + E^{\circ}(R^{\cdot}/RH)]23.06 \text{ kcal}\cdot\text{mol}^{-1}\cdot\text{V}^{-1} + 6.8 \text{ kcal}\cdot\text{mol}^{-1}$. Values calculated for the couples allylic$^{\cdot}$/allylicH, $RO^{\cdot}/ROH$ and $ROO^{\cdot}/ROOH$ are listed in Table II.

3. DISCUSSION

The positions of doubly allylic hydrogens in polyunsaturated fatty acids (PUFAs) are comparable to those

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Published by Elsevier Science Publishers B.V. (Biomedical Division)

Table I

ΔH_{DBE} of carbon-hydrogen bonds

Bond	Couple	E°, V vs NHE[a]	$\Delta H^{\circ}_{\mathrm{DBE}}$ (kcal)	$\Delta H^{\circ}_{\mathrm{DBE}}$ (kcal) (lit.)
$H\text{-}CH_3$	$^{\cdot}CH_3/CH_4$	2.0	105	104 ± 1[b]
$H\text{-}CH_2CH_3$	$^{\cdot}CH_2CH_3/C_2H_6$	1.9[c]	101	98 ± 1[b]
$H\text{-}CH_2OH$	$^{\cdot}CH_2OH/CH_3OH$	1.6	95	94 ± 2[b]
$H\text{-}CHO$	$^{\cdot}CHO/H_2CO$	1.4	89	87 ± 1[b]
$H\text{-}CO_2^-$	$CO_2^{-\cdot}/HCO_2^-$	1.5	92	94.8[d]
$H\text{-}CO_3^-$	$CO_3^{-\cdot}/HCO_3^-$	2.1	106	–[e]

[a] From [19] after correcting for pH, 1 molal reference state

[b] From [20]

[c] Calculated as in [19], with the assumption that $^{\cdot}C_2H_5$ has the same solvation energy as C_2H_6, +3.8 kcal/mol [21]

[d] From [22]

[e] No literature value was found

Table II

Reduction potentials of the couples $R^{\cdot}/RH$, $RO^{\cdot}/ROH$ adn $ROO^{\cdot}/ROOH$

Bond	$\Delta H^{\circ}_{\mathrm{DBE}}$ (kcal)[a]	$E^{\circ\prime}$(pH 7)[b], V vs NHE
		$R^{\cdot}/RH$
H-allyl (in propene)	89 ± 1	0.96
H-cyclopentenyl-3	82.3 ± 1	0.70
H-cyclopentadien-1,3-yl-5	81.2 ± 1.2	0.65
H-pentadien-1,4-yl-3	80 ± 1	0.60
		$RO^{\cdot}/ROH$
$H\text{-}OC_6H_5$	86.8 ± 2.2[c]	0.93 ± 0.10[d]
$H\text{-}OC_2H_5$	104.2 ± 1	1.65
$H\text{-}OC(CH_3)_3$	105.1 ± 1	1.70
$H\text{-}OCH_2C(CH_3)_3$	102.5 ± 1.5	1.55 ± 0.08
		$ROO^{\cdot}/ROOH$
H-OOR	≈ 90[e]	1.0

[a] From [20]

[b] The error in $E^{\circ\prime}$ is estimated at 0.06 V as a result from a 1 kcal error in the bond strength and an estimated 1 kcal error in the $T\Delta S_{\mathrm{DBE}}$ term

[c] From [23]

[d] As a control the reduction potential of the couple $PhO^{\cdot}/PhOH$ at pH 7 was calculated. The value found is in excellent agreement with the literature, 0.90 V [24]

[e] From [18]

in 1,4-pentadiene. It seems likely that the reduction potential of the PUFA radical/PUFA couple is as low as that of the pentadiene-1,4-yl-3 radical/1,4-pentadiene couple. The calculated standard reduction potential of only 1.0 V (0.60 V at neutral pH) suggests that this species can be oxidized by the hydrodioxyl radical ($HO_2^{\cdot}$) [15], $E^{\circ}(HO_2/H_2O_2) = 1.48$ V, and several transition metal complexes. Thermodynamically, the hydrodioxyl radical should also be able to oxidize the singly allylic hydrogen in oleic acid, but no evidence for this reaction has been found [15]. Aliphatic alkoxyl radicals are stronger oxidizing agents than alkylperoxyl radicals by approx. 0.6 V. Gibbs energy changes at pH 7 for the following hydrogen abstraction reactions are calculated via the relation $\Delta G^{\circ\prime} = -23.06\Delta E^{\circ\prime}$, used above.

$$RO^{\cdot} + bis\text{-allylicH} \rightarrow ROH + bis\text{-allylic}^{\cdot} \quad \Delta G^{\circ\prime} = -23 \text{ kcal/mol} \tag{4}$$

$$ROO^{\cdot} + bis\text{-allylicH} \rightarrow ROOH + bis\text{-allylic}^{\cdot} \quad \Delta G^{\circ\prime} = -9 \text{ kcal/mol} \tag{5}$$

$$RO^{\cdot} + ROOH \rightarrow ROH + ROO^{\cdot} \quad \Delta G^{\circ\prime} = -14 \text{ kcal/mol} \tag{6}$$

The energetics of reactions 4 and 5 provide a quantitative basis for the empirical observation that alkoxyl radicals are more reactive than alkylperoxyl radicals in hydrogen abstraction reactions [16]. The enthalpy of the reaction of an alkyl radical with oxygen, reaction 7, has been estimated at −28 kcal/ mol [17]. With an estimated $-T\Delta S^{\circ}$ of +8 kcal/mol ΔG° is −20 kcal/mol:

$$R^{\cdot} + O_2 \rightarrow ROO^{\cdot} \quad \Delta G^{\circ} = -20 \text{ kcal/mol} \tag{7}$$

Reactions 5 and 7 constitute the chain propagating reactions during lipid peroxidation with a combined Gibbs energy change of −29 kcal. The data in Tables

I and II indicate that an alkylperoxyl radical cannot abstract a non-allylic hydrogen from a hydrocarbon, $\Delta G^{\circ\prime} = +12$ kcal. Aside from the reaction of $R^{\cdot}$ with O_2, alkylperoxyl radicals can be formed, at least thermodynamically, from the oxidation of an alkylhydroperoxide by an alkoxide, as shown in reaction 6.

An important pathway to alkoxides is the one-electron reduction of an alkylhydroperoxide. For the evaluation of the energetics of this reduction two reduction potentials are needed: $E^{\circ}(RO^{\cdot}/ROH)$ and $E^{\circ}(ROOH/ROH, H_2O)$. The first reduction potential has been calculated above. The two-electron reduction potential $E^{\circ}(ROOH/ROH, H_2)$ may be estimated from reactions 8–12 below. The bond enthalpy of RO–OH is approximately 44 kcal/mol [18]. If the standard entropy change of the reaction $RO^{\cdot}_g + {}^{\cdot}OH_g \rightarrow ROOH_g$ is taken to be equal to that of $O^{\cdot}_g + {}^{\cdot}OH_g \rightarrow HO_{2g}$, then the standard Gibbs energy of bond formation, ΔG°_{BF}, equals -36 kcal/mol. For the calculation of the difference in solvation between $RO^{\cdot}$ and ROOH it is important to recognize that ROOH can form three more hydrogen bonds, which makes solvation more favourable by approximately 6 kcal [14].

$$RO^{\cdot}_g + {}^{\cdot}OH_g \rightarrow ROOH_g \quad \Delta G^{\circ}_{BF} = -36 \text{ kcal} \tag{8}$$

$$ROH_{aq} \rightarrow RO^{\cdot}_{aq} + H^+ + e^- \quad -1.7 \text{ V (Table II)} \tag{9}$$

$$H_2O \rightarrow {}^{\cdot}OH_g + H^+ + e^- \quad -2.3 \text{ V [11]} \tag{10}$$

$$RO^{\cdot}_{aq} \rightarrow RO^{\cdot}_g \quad -\Delta G^{\circ}_s (RO^{\cdot}) \tag{11}$$

$$ROOH_g \rightarrow ROOH_{aq} \quad \Delta G^{\circ}_s (ROOH) = \Delta G^{\circ}_s (RO^{\cdot}) - 6 \text{ kcal} \tag{12}$$

The sum of these reactions is:

$$ROH_{aq} + H_2O \rightarrow ROOH_{aq} + 2H^+ + 2\,e^- \quad E^{\circ} = -2.2 \text{ V} \tag{13}$$

Converting to a reduction potential and adjusting to pH 7, $E^{\circ\prime}(ROOH/ROH, H_2O) = 1.8$ V. Finally, $2E^{\circ\prime}(ROOH/ROH, H_2O) - E^{\circ\prime}(RO^{\cdot}/ROH) = E^{\circ\prime}(ROOH/RO^{\cdot}, H_2O) = 2.0$ V at pH 7. This result indicates that, thermodynamically, an alkylhydroperoxide can oxidize any metal complex to its highest oxidation state while forming reactive alkoxyl radicals. Interestingly, the one-electron reduction of an alkylhydroperoxide is far more exothermic than the equivalent reduction of hydrogen peroxide where $E^{\circ\prime}(H_2O_2/{}^{\cdot}OH, H_2O) = 0.32$ V [11].

Acknowledgements: Supported by The Council for Tobacco Research-USA, Inc. I would like to thank Professor W.A. Pryor, Dr P.L. Bounds and Dr J.D. Rush for helpful discussions.

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