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Review

Vitamin C: Electron Emission, Free Radicals and Biological Versatility

NIKOLA GETOFF

Department for Nutritional Sciences, The University of Vienna, Section of Radiation Biology, Vienna, Austria

Abstract. *The many-sided biological role of vitamin C (ascorbate) is briefly illustrated by specific examples. It is demonstrated that in aqueous solutions, vitamin C emits solvated electrons (e_{aq}^-), when excited in single state. Vitamin C can also react with e_{aq}^- as well as transfer them to other biological systems and thereby acts as efficient electron mediator. Based on its chemical and biological properties, it is clear that vitamin C plays a very important role in various functions in the organism alongside biochemical processes.*

Vitamin C has been designated as ascorbic acid (AH_2) because it prevents and cures scurvy, one of the longest-known diseases in ancient Egypt, Greece and Rome. The isolation of ascorbic acid in crystalline form was first achieved in 1928 by A. Scent-Györgyi. Since then, more active research of vitamin C has ensued, concerning its chemical, many-sided biochemical and nutritional effects. Lately, the study of its free radicals and reaction mechanisms has become a subject of interest (1-5).

Some highlights concerning the ability of vitamin C to emit solvated electrons (e_{aq}^-) and the resulting free radical formation, as well as the biological effects of the latter, are briefly discussed.

The existence of solvated electrons (e_{aq}^-) was first proven by radiation-induced conversion of aqueous CO_2 into simple organic compounds (6) as well as photochemically by using Fe^{2+} ions as electron donor and CO_2 as electron acceptor (7). Subsequently the absorption spectrum of e_{aq}^- (λ_{max}=720 nm) was measured by pulse radiolysis (8). The absorption spectrum of trapped electrons (e_{th}^-; λ_{max}=575 nm) in an aqueous alkaline ice-matrix at 77˚K was determined by electron-spin-resonance (ESR) (9).

Correspondence to: Professor Dr. N. Getoff, Althanstr. 14, A-1090 Vienna, Austria. Tel: +431 427754966, Fax: +431 427754965, e-mail: nikola.getoff@univie.ac.at

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Emission of e_{aq}^- and Ascorbic Free Radicals

Vitamin C belongs to the group of antioxidant vitamins, the action of which is based on the emission of e_{aq}^- in aqueous media (3, 10). In organisms, this process can, for instance, be enzymatically induced. It has been simulated by irradiation with monochromatic UV-light (λ=254 nm, E=4.85 eV/hν) in airfree, aqueous media (pH~7), in which chlorethanol was used as scavenger for the ejected e_{aq}^-, where the quantum yield (Q) of Cl^- equals that of e_{aq}^-.

$$e_{aq}^- + ClC_2H_4OH \rightarrow Cl^- + {}^{\bullet}C_2H_4OH \quad \text{(Eq1)}$$

($k_1=6.4\times10^8$ l mol^{-1} s^{-1}) (11)

Hence: $Q(e_{aq}^-)=Q(Cl^-)$ (Eq2)

The obtained yield of e_{aq}^- as a function of ascorbate concentration determined under these conditions, is shown in Figure 1. The e_{aq}^- represents the basic form of the H atom.

A deeper insight into the reaction mechanisms of free radicals of vitamin C has been obtained by pulse radiolysis (12, 13) and by laser flash photolysis methods (14).

Exhaustive pulse radiolysis studies of vitamin C in aqueous solution delivered a better understanding of the involved free radical's reaction mechanisms (15-17). In aqueous solution, OH-attack on ascorbate (AH^-) results in the formation of an ascorbate radical ($AH^{\bullet}$):

$$AH^- + OH \rightarrow AH^{\bullet} + OH^- \quad \text{(Eq3)}$$

($k_7=1.1\times10^{10}$ l mol^{-1} s^{-1}) (11)

Details of characteristic spectroscopic and kinetic data of AH• transients are given in Table I.

At the absorption maxima obtained, different reaction rate constants for formation and decay of $AH^{\bullet}$ radicals indicate the formation of different ascorbate radicals. This means that

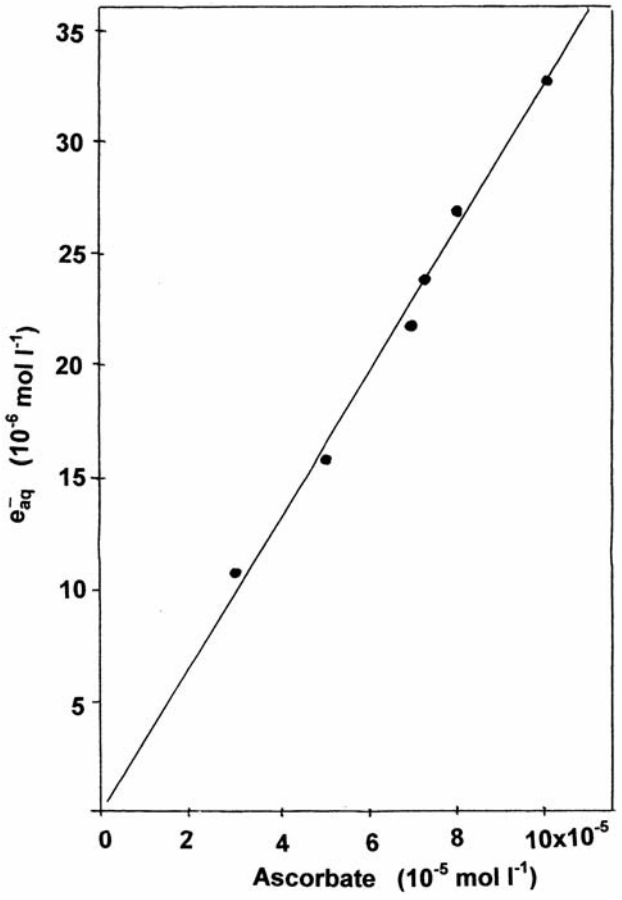

Figure 1. *Yield of ejected e_{aq}^- (mol l^{-1}) as a function of ascorbate concentration (mol l^{-1}) in airfree aqueous solution (pH~7) obtained by absorption of monochromatic UV-light (λ=254 nm, E=4.85 eV hv^{-1}). UV-intensity: I=1×10^{20} hv l^{-1}*

OH-attack takes place on different positions of the ascorbate molecule. Hence, the measured absorption spectrum of $AH^•$ radical is superimposed.

In order to have the ascorbate radical ($AH^•$) exclusively generated by e_{aq}^- emission, azide radicals ($N_3^•$) produced in N_2O-saturated solution were used as a specific reactant. The following reactions take place (3, 10, 18).

$e_{aq}^- + N_2O \rightarrow OH + OH^- + N_2$
($k=0.91\times10^{10}$ l mol^{-1} s^{-1}) (11) (Eq4)
$N_3^- + OH \rightarrow N_3^• + OH^-$
($k=1.1\times10^{10}$ l mol^{-1} s^{-1}) (11) (Eq5)
$AH^- + N_3^- \rightarrow AH• + N3^-$
($k=3.2\times10^{9}$ l mol^{-1} s^{-1}) (11) (Eq6)
$2AH^• \rightarrow AH_2$ + DHA (dihydroascorbate)
($k=1.7\times10^{7}$ l mol^{-1} s^{-1}) (11) (Eq7)

The $AH^•$ radical obtained by this method showed only two absorptions maxima at 300 nm (ε=2360 l mol^{-1} s^{-1}) and at λ=360 nm (ε=3670 l mol^{-1} s^{-1}), with different ε values as compared to those given in Table I.

Table I. *Characteristic data of ascorbate radical ($AH^•$) observed upon OH-attack in aqueous solution at pH~7 (4, 16, 17).*

Absorption (λ_{max}, nm)	ε_{max} (l mol^{-1} cm^{-1})	Reaction rate constant (k, l mol^{-1} s^{-1})	
		Formation	Decay
300	2000	3.1×10^{9}	9.0×10^{5}
360	3240	6.5×10^{9}	7.1×10^{6}
550	100	1.1×10^{8}	6.9×10^{7}

The transient spectrum obtained by this method is assumed to represent the $AH^•$ radical generated by e_{aq}^- emission.

Scavenger for Oxidizing Species

The strong tendency of ascorbate to eject e_{aq}^- under formation of ascorbate free radicals classifies it as a very potent electron donor. By reaction of e_{aq}^- with O_2 in aerated solutions, peroxyl radicals are formed (19), which posses a powerful ability to kill bacteria and inactivate viruses. This property is valid to some extent also for the antioxidant vitamins E and β-carotene.

$e_{aq}^- + O_2 \rightarrow O_2^{•-}$ (Eq8)
($k=2\times10^{10}$ l mol^{-1} s^{-1}) (11)
$HO_2^• \rightleftharpoons H^+ + O_2^{•-}$ (pK=4.8) (Eq9)

Ozone also reacts with e_{aq}^-, generating strong oxidizing transients:
$O_3 + e_{aq}^- \rightarrow O_3^{•-}$ (Eq10)
($k_5=3.7\times10^{10}$ l mol^{-1} s^{-1}) (11)
$O_3^{•-} \rightleftharpoons O^{•-} + O_2$ (Eq11)

As a consequence of e_{aq}^- emission, vitamin C becomes a neutral free radical ($AH^•$), whereas vitamin E (α-tocopherol) and β-carotene (β-car) in such case are converted into the corresponding radical cations, namely into $E^{•+}$ and β-$car^{•+}$, respectively. All antioxidant vitamins react with reducing and oxidizing species, generating very active secondary transients. Some kinetic data for vitamin C are given in Table II for illustration.

The most reactive oxidizing species are the OH radicals. Their preferred reaction sites are double bonds of biological molecules, mostly at *ortho*- and *para*-positions, but to some extent also at *meta*- and ipso-positions of the molecules. The OH radicals can also split off a H atom or electron from substrate molecules. Vitamin C and related compounds are

Table II. *Reaction rate constants (k) of ascorbate and ascorbic acid with reducing (e_{aq}^-, H) and oxidizing radicals (OH, ROO$^\bullet$), as well as with singlet oxygen ($^1O_2$). Reactions of such type can be induced by reductase and oxidase enzymes in the organism.*

Substrate	k (l mol^{-1} s^{-1})				
	e_{aq}^-	H	OH	ROO$^\bullet$	$^1O_2$
Ascorbate (AH^-), pH~7	3.5×10^8 (11)	3×10^8 (11)	1.10×10^{10} (11)	2×10^8 (19)	2×10^7 (19)
Ascorbic acid (AH2), pH 1	-	1.3×10^8 (11)	1.0×10^{10} (11)	-	-

very efficient scavengers of the attacking species, as indicated by the data shown in Table II. This subject matter is discussed in more detail elsewhere (19).

Protection of Cell Membranes

Ascorbate plays an important role in the protection of cell membranes. Cell membranes (7-10 nm thickness) consist of 20-25% proteins and lipids as well as of 2-5% vitamins (C, E and β-carotene) and water. The structure of the membrane depends on its origin, and on the specific function of the cell. The cell membranes in organisms are constantly being attacked by oxidizing free radicals (OH, $O_2^{\bullet-}$, ROO$^\bullet$ *etc*.), which are generated also in the human organism by enzymes. It was established by pulse radiolysis that membrane degradation is efficiently avoided by an electron cascade transfer within the above mentioned antioxidant vitamins (3). The following reactions proceed *e.g.*:

$$OH + \beta\text{-car} \rightarrow OH^- + \beta\text{-car}^{\bullet+} \quad \text{(Eq12)}$$
$$\beta\text{-car}^{\bullet+} + \text{Vit.E} \rightarrow \beta\text{-car} + \text{Vit.E}^{\bullet+} \quad \text{(Eq13)}$$
$$\text{Vit.E}^{\bullet+} + AH^- \rightarrow \text{Vit.E} + AH^\bullet \quad \text{(Eq14)}$$
$$AH^\bullet + AH^\bullet \rightarrow AH_2 + \text{DHA} \quad \text{(Eq7)}$$

These reactions are very fast, having rate constants of $k>2\times10^9$ l mol^{-1} s^{-1} (**3**).

The resulting main product, DHA is found to be an even better electron donor than to AH^- (see later).

DHA is not stable in aqueous solution and decomposes into about 50 products (20, 21).

Radiation Protection by Vitamin C

Using *Escherichia coli* (AB1157), as well as cultured cells (SCCVII), as a model for *in vitro* experiments, it was established that vitamin C acts as a radiation-protecting agent (22). The obtained ΔD37 (Gy)-values derived from survival curves, representing the N/N_0 ratio as a function of absorbed radiation dose (Gy), serves as a measure of the protecting effect, where, N_0=number of bacteria colonies before and N=number after the exposure to vitamin C. The D_{37} (Gy) value represents the reaction dose (Gy) corresponding to N/N_0=0.37 and ΔD_{37} (Gy)=D37 (sampe) – D37 (buffer). The radiation-protecting effect is predicated on the primarily acting radicals of water radiolysis, under the given conditions. The experimental results for *E. coli* are summarized in Table III.

Table III. *ΔD37 (Gy) values as a measure of the radiation-protection ability of vitamin C in different media were [AH^-]=1×10^{-3} mol l^{-1} in media saturated with different gases, at pH=7.4. Positive ΔD37 (Gy) values reflect radiation protection, whereas the negative ones demonstrate a cytostatic effect. Biological model: E coli AB1157 (22).*

Series	Acting primary radicals (%)	D_{37} (Gy)		ΔD_{37} (Gy)
		Buffer	AH^-	
Airfree	46 OH, 44 e_{aq}^-,10 H	560	570	10
Air	46 OH, 54 $O_2^{\bullet-}$	185	265	80
N_2O	90 OH, 10 H	180	275	95

Obviously, the highest radiation-protecting effect was observed in N_2O, in which OH radicals were predominant since AH^- acts as a very strong OH-scavenger (see Table I). Similar results were also obtained using SCCVII cells as an alternate *in vitro* model (22).

Synergistic Effect of Vitamin C on Mitomycin C

It has been experimentally found that vitamin C, as a potent e_{aq}^- donor, can significantly affect the activity of cytostatics. This effect is demonstrated on mitomycin C (MMC) and on sanazole.

MMC, based on its peculiar chemical structure (aziridine, carbamate and quinone cytotoxic groups on the same pyrrole nucleus, 1.2 α-indolic), belongs to the drugs having preferential toxicity towards hypoxic cells. MMC can be activated enzymatically (NADPH-cytochrome *P-450* reductase) (23), chemically or by ionizing radiation (3, 24, 25) to yield MMC-quinone or hydroquinone. Both forms of MMC lead to the formation of a covalent cross-link adduct with DNA, which stops the proliferation of tumor cells. The same effect is observed by the action of MMC metabolites, generated by attacks of OH, $O_2^{\bullet-}$ or other oxidizing species (26).

Table IV. *Synergistic effects of vitamin C on cytostatic efficiency of MMC, derived by in vitro experiments, dose range: 0-300 Gy (3, 18).*

Substrate *	Acting radicals: 46% OH, 54% $O_2^{\bullet-}$	
	D_{37} (Gy)	ΔD_{37} (Gy)
Buffer	200	0
Vitamin C	285	85
MMC	110	–90
MMC + Vit.C	70	–130

*[Vit.C]=1×10^{-4} mol l^{-1}; [MMC]=1×10^{-5} mol l^{-1}.

Table V. *ΔD_{37} (Gy)-values of (MMC), (DHA) and a mixture of both, derived from survival curves (E. coli AB1157), and expressing the N/N_0 ratio as a function of γ-irradiation dose of the corresponding systems (27).*

Substrate *	ΔD_{37} (Gy)
Buffer	0
DHA	–8
MMC	–93
MMC-DHA	–141

*[DHA]=1×10^{-4} mol l^{-1}; [MMC]=1×10^{-5} mol l^{-1}.

Table VI. *Synergistic effect of vitamin C on the activity of sanazole (Sz). D_{37} (Gy) and ΔD_{37} (Gy) where derived from in vitro experiments (E. coli AB1157) under γ-irradiation (dose up to 300 Gy) in different aqueous media at pH 7.4 (29).*

Substrate*	Airfee-acting radicals: 46% OH, 44% e_{aq}^-, 10% H		Aerated 46% OH, 54% $O_2^{\bullet-}$		N_2O-saturated 90% OH, 10% H	
	D_{37} (Gy)	ΔD_{37} (Gy)	D_{37} (Gy)	ΔD_{37} (Gy)	D_{37} (Gy)	ΔD_{37} (Gy)
Buffer	310	0	166	0	305	0
Sz	235	–75	111	–55	225	–80
Sz + MMC	130	–180	56	–110	187	–118

*[Sz]=5×10^{-5} mol l^{-1}; [Vit. C]=1×10^{-4} mol l^{-1}.

It has been demonstrated by *in vitro* experiments (model: E coli AB1157) that under γ-irradiation of aerated, aqueous solution (pH~7.4), vitamin C acts as a powerful provider of e_{aq}^-, forming also $MMC^{\bullet-}$ transients (Table IV). As expected, vitamin C used solely, demonstrates its ability to protect against oxidation (see Table IV: ΔD_{37} (Gy)=85). However, in combination with MMC, it causes a very strong increase of MMC cytostatic properties by the formation of MMC-quinones.

Synergistic Effect of DHA on MMC

The survival curves (N/N0 ratio as a function of γ-radiation dose) observed in *in vitro* experiments (E coli AB1157) demonstrated a very strong effect on the cytostatic property of MMC in mixtures with DHA. Obviously DHA, as well as its numerous degradation products, are efficient e_{aq}^- donors, which leads to increased $MMC^{\bullet-}$ formation. Some typical results are given in Table V.

Vitamin C Synergism with Sanazole

Sanazole (AK-2123) acts as sensitizer for various cytostaticas, *e.g.* MMC (28). It possesses the property to enhance the chemical sensitivity of tumors and has a rather low toxicity.

Table VII. *Regeneration (%) of some hormones by electron transfer from vitamin C in airfree water/ethanol=40/60 under monochromatic UV-irradiation (λ=254 nm; E=4.85 eV/hv) at pH~7.4 at 37°C (34-36).*

Substrate	Concentration (mol l^{-1})	Hormone regeneration (%)
17β-Estradiol	1×10^{-4}	35.7
Vitamin C	1×10^{-4}	
17β-Estradiol	1×10^{-4}	63.2
Vitamin C	1×10^{-3}	
Progesterone	1×10^{-4}	52.7
Vitamin C	1.04×10^{-4}	
Testosterone	0.95×10^{-4}	58.6
Vitamin C	2.5×10^{-4}	
Corticosterone	5×10^{-5}	80.7
Vitamin C	1×10^{-4}	

The effect of vitamin C on sanazole efficiency has been investigated in the frame of *in vitro* experiments (*E. coli* AB1157) under irradiation with γ-ray in three test media: airfree, aerated and saturated with N_2O at pH~7.4 (29). Under these conditions, information was obtained about the specific action of the primary radicals generated by water radiolysis. The obtained results, expressed ΔD_{37} (Gy) values which were derived from the corresponding survival curves and are presented in Table VI.

The ΔD_{37} (Gy) values given in Table VI clearly demonstrate that independent of the nature of the free radicals, vitamin C very strongly affects the efficiency of sanazole. This is based on its capability to act as efficient radical scavenger (Table II) as well as a potent electron donor. These features are, so far, also valid for vitamin C degradation products including DHA, however, the reaction mechanism in this case is not yet completely understood.

Regeneration of Hormones

It has been experimentally shown that hormones and phytohormones can emit e_{aq}^- when excited into singlet state in aqueous or in water-alcohol solution (30, 31). The emitted e_{aq}^- retains the specific frequency of the corresponding mother molecule (32). By electron transfer from a given hormone, *via* the brain, to other hormones or to a biological system, communication is established (32, 33). The transients generated as a sequence of e_{aq}^- emission from a hormone under given conditions can induce the formation of cancerons cells, undergo degradation, or in the presence of a potent electron donor, such as vitamin C, they can be regenerated (33, 36).

The regeneration process of hormones by electron transfer from vitamin C to a hormone transient can be realized only within the life-time (*status nascendi* state) of the given transient (33-36). Since the hormones emit, as well as react with, e_{aq}^- (rate constants, $k \sim 10^9$-10^{10} l mol^{-1} s^{-1}) (11) and can transfer electrons to other systems, they can also be classified as electron mediators in the organism (37). The regeneration process of hormones, for instance by vitamin C, and hormone degradation (*e.g.* caused by free radicals in the organism) are in permanent competition. Therefore, an adequate consumption of vitamin C is very recommendable.

The regeneration of hormone transients depends on several factors, including hormone molecular structure, concentration, rate constant of reaction with e_{aq}^- and with ascorbate (Table II) and pH of the medium (33-37). The regeneration process of some hormones by electron transfer from vitamin C are given as examples in Table VII.

It should be mentioned that the hormones at $>10^{-7}$ mol l^{-1} tend to form associates (36), similar to vitamin C. This fact favorizes electron transfer, even in the presence of air.

Conclusion

The many-sided biological effects of vitamin C as well as those of its degradation products (*e.g.* DHA) are mainly founded on their ability to emit e_{aq}^- at a relatively high yield (Figure 1). Although vitamin C also consumes e_{aq}^-, it also acts as a radical scavenger (Table II). Hence, it can be postulated that in humans, a number of competitive reactions, initiated by enzymes, proceed under the involvement of vitamin C as a potent electron donor.

The briefly discussed biological effects of vitamin C represent just some abilities of its many-sided involvement in important physiological processes.

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