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Vitamin C Mitigating and Rescuing from Synergistic Toxicity: Sodium Fluoride, Silicofluorides, Aluminum Salts, Electromagnetic Pollution, and SARS-CoV-2

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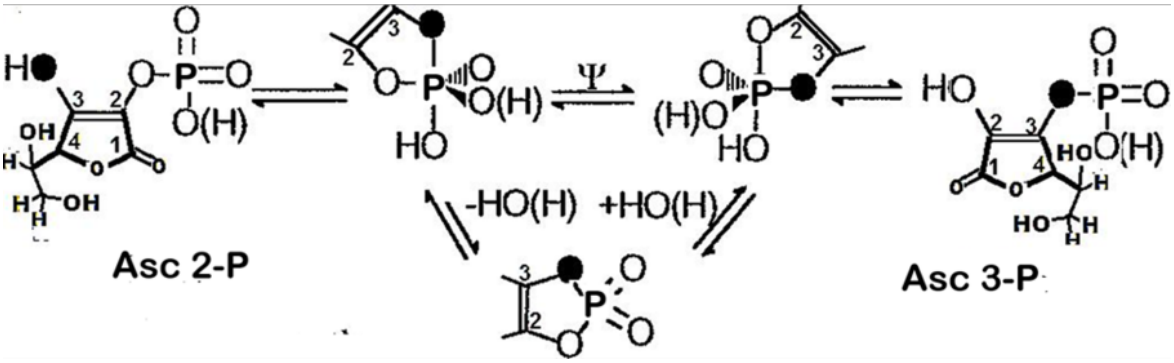
ABSTRACT

A supramolecular paradigm for mitigation and rescue from SARS-COV2 infection is proposed. Similarities between the Sanarelli-Shwartzman phenomenon and biological responses to viral pathogens are considered. Non-enzymatic group transfer catalysis (NGTC) by L-ascorbic acid, the L-ascorbic acid free radical and the 2-O-phosphate substituted L-ascorbic acid derivative are proposed under the ascorbolysis hypothesis to provide a supramolecular basis for mitigating the synergistic toxicity and catalytic mimicry by the environmental toxicants, sodium fluoride, aluminum salts, and silicofluorides in public water supplies. Ascorbolysis is the term we adopt to describe a redox active, hyperconjugated, vinylogous variant of acidolysis. The objective of this paper is to provide a plausible supramolecular basis for mitigation and rescue from well-known environmental toxicity represented by the presence of sodium fluoride, aluminum salts, and silicofluoride species in public water supplies. An overview of the conceptual basis for NGTC by vitamin C during inflammatory states is provided. Controversies concerning the initial oxidation steps and pH-dependent speciation of L-ascorbic acid are addressed. Non-skeletal fluorosis is a serious systemic malady which we propose arises from disruption of hydrogen bond networks and hydrogen bond cooperativity resulting from the marked electronegativity and hydrogen bond accepting ability of fluoride atoms found in NaF and AlF_x species. AlF_x species have been previously shown to arise *in situ* spontaneously from NaF, aluminum salts, and silicofluorides often found in toothpastes and "fluoridated" drinking water. AlF_x species are thought to act as isosteric mimics of biophosphates during group transfers of phosphoryl moieties. We propose that catalytic mimicry by AlF_x species inhibits postulated non-enzymatic kinase-like and RNA polymerase-like function of the AA-2P derivative during inflammatory states. We describe how NGTC by L-ascorbic acid is likely to be disrupted by AlF_x and sodium fluoride of a specific H3-O2 intramolecular hydrogen bond in L-ascorbic acid, the L-ascorbic acid free radical, and their 2-O-substituted derivatives, which are necessary for NGTC in the moderately acidic, mildly oxidative, relatively hydrophobic microenvironment which typify inflammatory states. Suggestions are made to achieve less variation in results of large randomized clinical trials (RCTs) seeking to validate use of high-dose intravenous vitamin C in critical care and cancer settings.

Keywords: *non-enzymatic group transfer catalysis, ascorbolysis, catalytic mimicry, toxic synergy, reproductive biology, electromagnetic pollution, induced intramolecularity, hydrophobic effect, pH-dependent speciation, kinetic solvent effects, intramolecular 1,4 hydrogen atom*

transfer, proton coupled nucleophilic attack, charge reorganization catalysis, oxidative photo-activation, SARS-CcV2, KEAP1 inhibition, NRF2 activation, NFkB-MAPK pathway, MAPK phosphorylation

SUMMARY GRAPHIC



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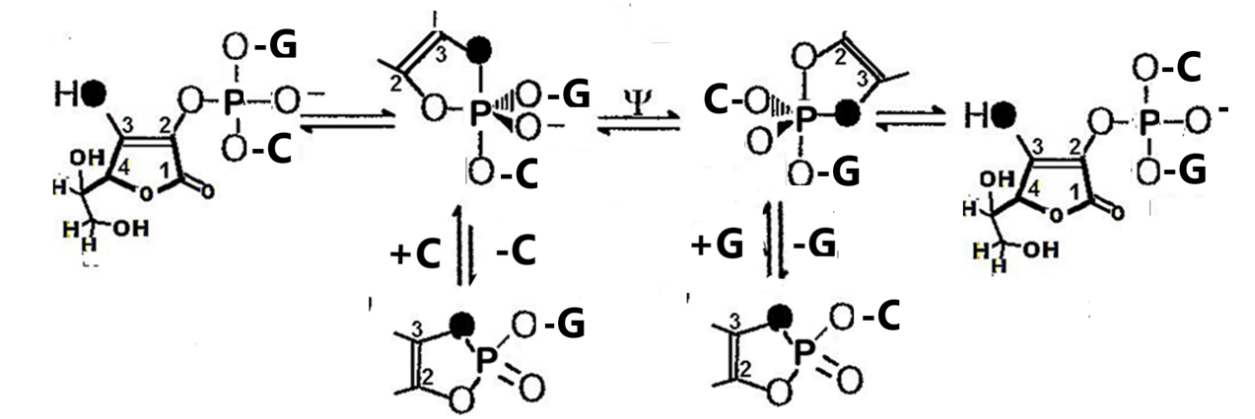


(b)

Figure 1. A supramolecular strategy for combatting the current persistent global SARS-CoV-2 pandemic is urgently needed. If you look under the hood of "vitamin" C, don't be surprised to find ancient molecular motors. (**a**) Generalized depiction of reversible, auto-catalytic prebiotic "kinase-like" function; (**b**) generalized depiction of RNA editing under the non-enzymatic group transfer catalysis (NGTC)/ascorbolysis/universal non-specific mesenchymal reaction (UNMR) framework (as explained in this article).

Introduction

(i) Inferences based on pattern recognition from seemingly unrelated, tangential fact-patterns

The human central nervous system has an absolute requirement for cholesterol, cholesterol sulfate, sphingosine, sphingosine-1-phosphate, and L-ascorbic acid (Strott 2003; Ceccom et al. 2014; Buehrer 1992; Spiegel 2020). Mammalian reproductive biology is strongly dependent on the presence of L-ascorbic acid, including that of fruit bats (Krutzsch cites; Wang 2011), Guinea pigs, and humans, species which can all become scorbutic — showing the symptoms of scurvy — and will die in the absence of exogenous dietary sources of L-ascorbic acid. Bats are known to be

pollinators of plants, and consume mosquitos as a dietary staple. They can also navigate and fly in total darkness. In 2005, a severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats (Lau 2005) was reported. In the midst of the current, persistent, global SARS-CoV2 pandemic, as we "circle the wagons" on a world-wide scale (Davidson et al. 2015a-c), it is also wise to take a more global perspective on human health and our biosignaling systems inside the body and outside in the environment. An additional, seemingly disparate historical observation, is thought by the authors to have considerable implications for the rational design of a supramolecular strategy for coping with the ongoing and promised future scourges of global pandemics (see Shaw's paper in this issue). Specifically, we call the readers' attention to the many literature citations to research examining the non-enzymatic cleavage of bacteriophage polynucleotides by L-ascorbic acid and the essential trace mineral, copper (Richter 1982; Wong 1974; Chiou 1983, 1984). We will return to these observations in both the Results and the Discussion sections to follow.

(ii) Vitamin C in the supramolecular mitigation and rescue from stress and synergism of environmental toxicants

Colostrum and so-called "mother's milk" is known to be very high in levels of L-ascorbic acid (Przybylska 2007). Heffers that calve in freezing weather must nurse their newborns very soon after birth or the calf will not survive. It has been shown that mice, whose reproductive tissues have been damaged by 30 days of sodium fluoride and aluminum chloride in their feed, can be "rescued" from this damage by L-ascorbic acid (Chinoy et al. 2005a-b). None of these observations are mere serendipity in terms of vitamin C. In the 2015 conference proceedings from Atlanta, GA and London, UK, Davidson presented the hypothesis that vitamin C possessed properties far beyond its prodigious anti-oxidant properties, to account for the growing number of its pleiotropic health effects in humans (Davidson et al. 2015a-c). In 2018, Yu et al. showed that genetic reprogramming of porcine oocytes is dependent on L-ascorbic acid. Bovine oocyte maturation is dependent on L-ascorbic acid (Dalvit et al. 2005). Both male and female germ cell lines evidently depend on L-ascorbic acid for maturation. It has been known for at least 3 decades that L-ascorbic acid protects DNA from oxidative damage in human spermatocytes (Fraga et al. 1991).

(iii) Non-enzymatic group transfer catalysis: the proposed biophysical basis for the supramolecular, biophysically-pleiotropic properties of vitamin C

In this paper we will present an overview of what we believe to be the biophysical basis for numerous reports of pleiotropic behaviors of L-ascorbic acid. We have been strongly influenced by the large body of scientific contributions from Linus Pauling and Hans Selye. Cameron and Pauling anticipated the supramolecular properties of vitamin C in relation to cancer (Cameron & Pauling 1973). Hans Selye in the 50's and 60's made compelling arguments for supramolecular biology using small animal histopathology as the basis for this assertion (Selye 1950, 1966, 1967, 1968). In 2016, Kennedy et al. published a paper titled "Environmental Toxicants and IMR…" which should be a wake-up call for toxicologists worldwide (Kennedy et al. 2016). While Davidson was presenting arguments supporting quantum phase-coherence at all biological signaling levels in 2015 conference proceedings in London, UK (Davidson et al. 2015a), Winey was presenting his discovery of activated water at an international conference on water in Varna, Bulgaria (Winey 2015). The present paper represents a brief summary and initial results from the collaboration between Winey and

Davidson, a collaboration whose focus is on supramolecular biology, in a process they describe as non-enzymatic group transfer catalysis ("NGTC"), an over-arching process which spans all levels of biological signaling organization, and subsumes the supramolecular properties of activated water and L-ascorbic acid.

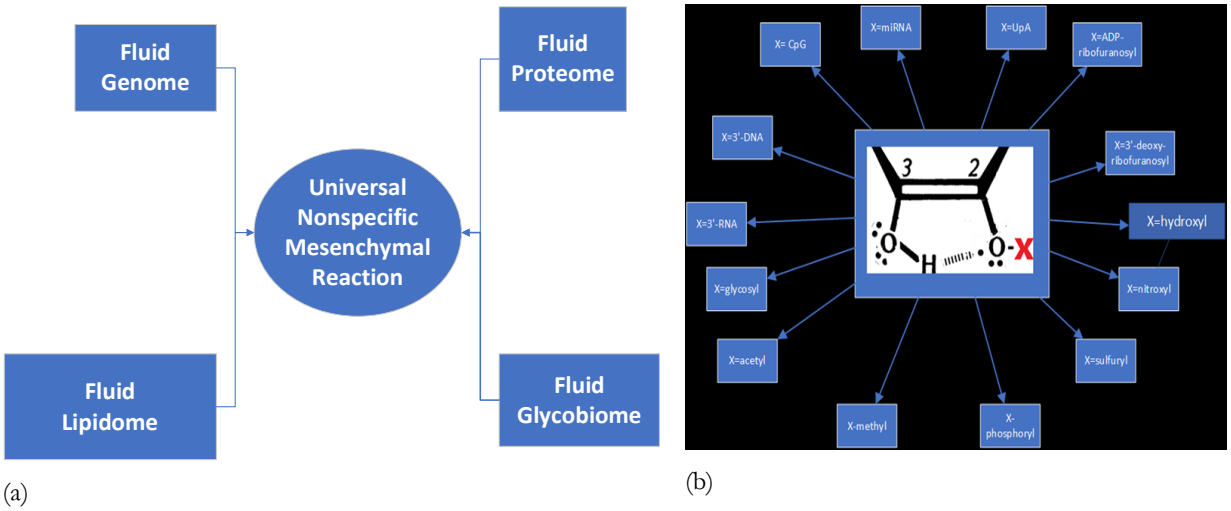


Figure 2. (a) Conceptual depiction of the "universal non-specific mesenchymal reaction" (abbreviated herein as "UNMR") originally described by Hans Selye, and others; (b) conceptual depiction of the "ascorbolysis hypothesis", i.e. the hypothesis that L-ascorbic acid, the L-ascorbic acid free radical, and the 2-O-substituted L-ascorbic acid radical derivatives provide living organisms with non-enzymatic group transfer catalysis (abbreviated herein as "NGTC"). Under this framework, ascorbolysis is a subsystem, i.e. is subsumed by NGTC.

As essential background to this paper, we need to describe the so-called "universal non-specific mesenchymal reaction" (UNMR), originally described by Selye, Hauss, and others (Selye 1950, 1968; Hauss 1962, 1969). Also essential is the "ascorbolysis" hypothesis, initially introduced in 2015, though it has been substantively modified since then. An introduction to the UNMR and ascorbolysis hypotheses are available in the Winey and Davidson conference presentations from 2015, available in the public domain at ResearchGate and YouTube as cited in our reference list. Briefly stated, the UNMR refers to the different causes of accelerated metabolism in connective tissues and in all organs studied (Hauss *et al.* 1962). Selye (1966) described a local or general intravascular coagulation that occurs in response to certain toxins or systemic stress. Figure 3 is a recent depiction of ascorbolysis, wherein the chemical steps and radical chain reactions catalyzed will be presented in the Results and Discussion sections.

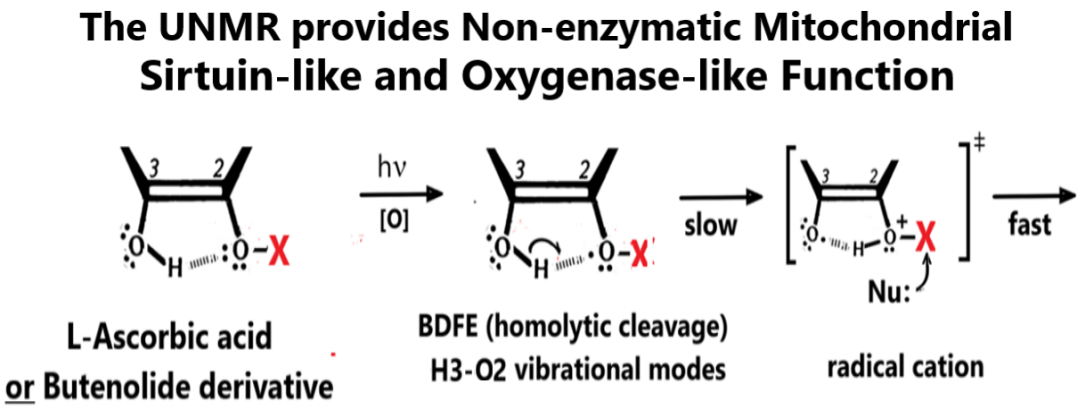
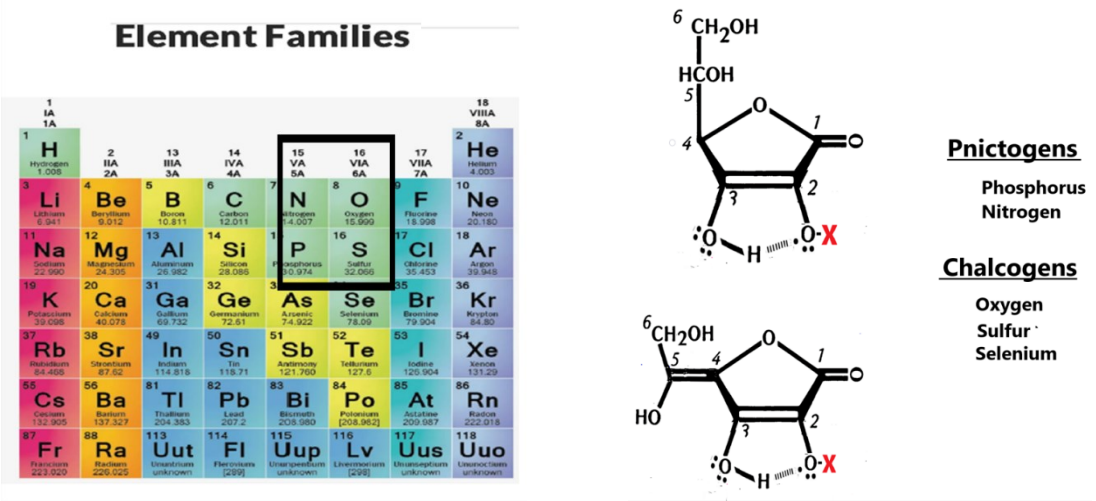


Figure 3. Proposed scheme by which photo-oxidatively super-activated derivatives of L-ascorbic acid are thought to provide reversible non-enzymatic trans-acetylation function and non-enzymatic hydroxylation function throughout the entirety of chemical evolution, within a moderately acidic, mildly oxidative, relatively hydrophobic aqueous microenvironment. Importantly, reversible, non-enzymatic kinase-like, methyl-transferase-like, sulfuryl transferase-like, acetyl transferase-like, hydroxylase-like, glycosyl transferase-like, and nitrosyl-nitroxyl-transferase-like function are examples of pnictogen- and chalcogen-based functional groups whose transfers are contemplated by the NGTC and ascorbolysis hypotheses. Ascorbolysis is postulated to provide the biophysical basis for the regio-, stereo-, and chemio-specificity of reversible post-translational modifications (PTMs) of proteins, including PTMs of genetic transcription factors, e.g. reversible PTMs of the NRF2-KEAP1 pathway (Mukhopadhyay 2015; Suzuki 2015; Song 2017).



(**a**) (**b**)

Figure 4. Relationship of chalcogen- and pnictogen-based functional groups to the periodic table of elements: (a) group 15 elements (denoted pnictogens) and group 16 elements (denoted chalcogens); (b) the chiral redox active hyperconjugated L-ascorbic acid free radical and its early planar (achiral) oxidation products (butenolides) are both postulated to non-enzymatically catalyze biological group transfers of chalcogen- and pnictogen-based functional groups, in quantum phase-coherent manner within activated "spin water" during inflammatory states, within moderately acidic, mildly oxidative, relatively hydrophobic aqueous microenvironments.

(iv) Proposal for mitigation and rescue from environmental toxicants by means of NGTC, ascorbolysis, and the UNMR

It has long been known that fluorides impair collagen structure and function (Gupta 2013; Lee 2018; McGarvey 1996). Collagen structure and PTMs of collagen proteins form the vast majority of the "mesenchyme" throughout our bodies for our entire lifetime. PTMs of cytoskeletal proteins are thought to be dynamical and reversible, demonstrating both mechanical and conductive properties (Mittal and Saluja 2015). The tensile properties of both fibrillar and globular proteins play a structural role in many tissues throughout our bodies. From an architectural perspective, Buckminster Fuller coined the term "tensegrity" to describe such structural properties (Ingber 2003; Bywater 2017). In the folding of milk proteins, the "molten globular state" is thought to be an intermediate (Qi 2001). Hydrogen bonding networks are thought to provide for much of the tensile strength and structural determinants during protein folding (Bywater 2017) in proteins such as collagen, actin, and milk proteins, including prions and amyloid proteins. Misfolded proteins are distinct from unfolded proteins.

Vitamin C has long been known to play an essential role in the synthesis, modelling, *and remodelling* the structure of various collagen biopolymers (Robertson 1953; Murad 1981; Franceschi 1994; Park 2010; Robertson 2014; Gomez Ruiz 2018) as well as playing a role in the regulation of collagen gene expression (Chojkier et al. 1989). A very provocative observation was made by Kumano et al. in 1998, when they reported that the 2-O-alpha-D-glucopyranosyl derivative of L-ascorbic acid has an "enhancing effect" on collagen synthesis (Kumano 1998). When these facts are considered in combination, our proposed mechanisms for "rescue" of various fluoride-intoxicated tissues, becomes much easier to appreciate. One need not postulate the necessity of innumerable intermediate enzymatic steps in the chain of causation under the NGTC/ascorbolysis framework.

(v) Ascorbolysis endows vitamin C with a supramolecular means of "stimulating" intracellular antioxidant activity, cytoprotective activity, and anti-ageing activity

In 2016, Katsuyama et al. reported that a novel derivative of L-ascorbic acid demonstrated not only antioxidant effects and direct ROS radical scavenging activity, but also stimulated intracellular antioxidants (Katsuyama 2016). They said it

> … up-regulates the expression of mRNAs encoding peroxisome proliferator activated receptor-γ (PPAR-γ) and nuclear factor E2-related factor 2 (Nrf2), which in turn up-regulate the levels of mRNAs encoding γ-glutamyl cysteine synthase (γ-GCS), heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase-1 (NQO1).

We will present in the Results and Discussion sections, our proposal for how ascorbolysis endows vitamin C with supramolecular characteristics that enable it to stimulate intracellular antioxidants at all biological signalling levels, in a quantum phase-coherent manner, including but not limited to regulating the reversible expression of genes, e.g. antioxidant genes whose expression is stimulated or inhibited by the interaction of transcription factors, e.g. NRF2 and KEAP1. The "ascorbyl phosphate" derivative of L-ascorbic acid has been identified intracellularly. We propose, herein, that the 2-O-phosphate-L-ascorbic acid radical acts as a non-enzymatic kinase in the reversible PTMs of proteins such as KEAP1 (Abed et al. 2015) and MAPK of the NFkB-MAPK pathway (Eguchi 2003).

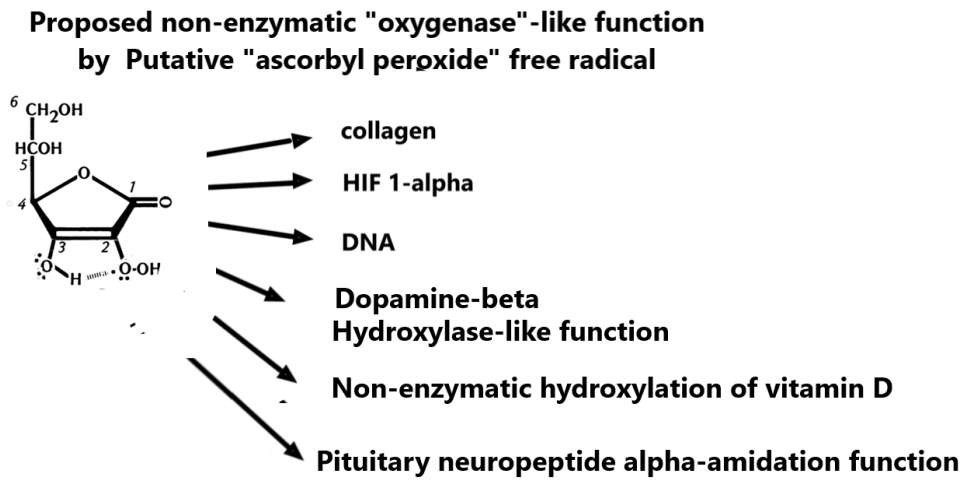
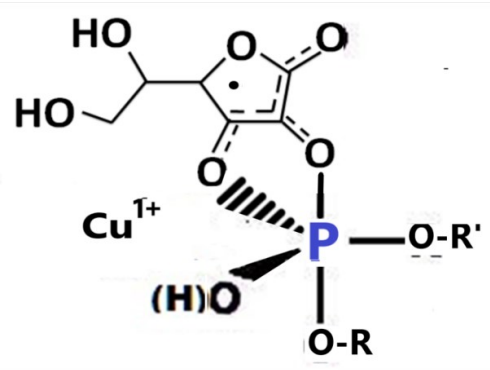


Figure 5. Postulated role of ascorbyl peroxide free radical in hydroxylation of collagen, HIF-1-alpha, vitamin D (Sergeev 1990), DNA, dopamine-beta hydroxylase (Weinshilboum 1978), and alpha-amidation of pituitary neuropeptides (Simpson 2015). Scheme depicts postulated reversible non-enzymatic "oxygenase" and "dioxygenase" functions of putative "ascorbyl peroxide" free radical in inflammatory states, such as that induced by fluoride and aluminum environmental neurotoxicants. L-ascorbic acid, the L-ascorbic acid free radical, and their 2-O-substituted derivatives may provide a chemical biological means of reversal and rescue from fluoride- and aluminum-based neurotoxicity, reproductive toxicity, immune toxicity, and the multi-faceted toxicity associated with viral pathogens, such as for example, Dengue, Ebola, and SARS-CoV-2. Fluoride-related mitochondrial dysfunction and oxidative stress can be mitigated by L-ascorbic acid (Chinoy et al. 2005a, 2005b) wherein its function as a "cofactor" for mitochondrial oxygenases and dioxygenases is likely to actually represent NGTC via ascorbolysis. See Figures 3, 6(e), and 23. Under the current embodiment of the NGTC/ascorbolysis/UNMR hypotheses, all "kinases", including protein kinases, generally, are likely to be rendered superfluous during inflammatory states, wherein the pH does not match the pH optimum of the kinase or the stability of the endogenous phosphorylation factor, typically ATP. ATP is well known to be highly labile to hydrolysis in the acidic pH range (Stecher 1968).



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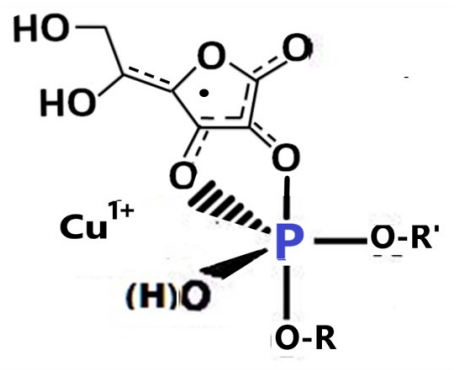

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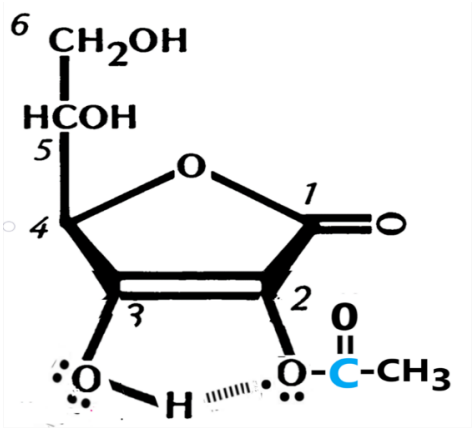

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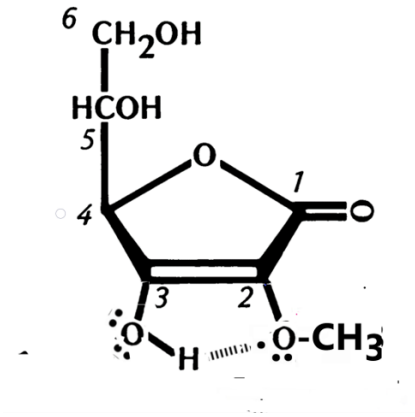

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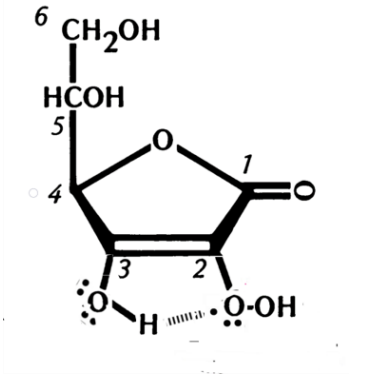

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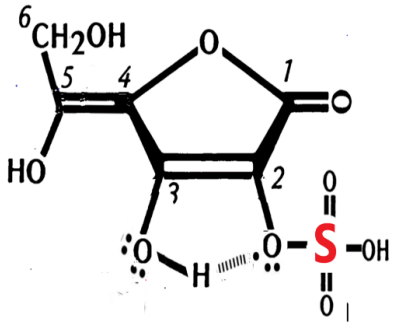


(f)

Figure 6. Putative prebiotic photo-oxidatively super-activated "molecular motor" catalysts/reactants for radical chain reactions: (a) putative primordial ascorbyl phosphate "kinase-like" reactive transient; (b) putative "pro-chiral" butenolide early oxidation product of "ascorbyl phosphate"; (c) putative primordial "sirtuin" (non-enzymatic trans-acetylase; (d) putative primordial methylation "factor" (reactive transient); (e) putative primordial hydroxylation factor (dioxygenase-like reactive transient); and (f) putative primordial "sulfotransferase". In the acidic pH range, ca. pH 4-6, (a)-(f) would be "free radicals" (uncharged) and butenolide derivatives would be "pro-chiral" reactive transients. In a moderately acidic, mildly oxidative, relatively hydrophobic micro-environment, (c)-(f) are postulated to be intramolecularly hydrogen bonded, i.e. they would all demonstrate "induced intramolecularity" and increased "effective molarity" at the H3-O2 hydrogen bond, the path postulated to be taken for "intra 1,4 HAT" (hydrogen atom transfer) (see both our Results and Discussion sections to follow, for explanation). Within so-called activated "spin water", homo-chiral "bias" or "filtering" of (a)-(f) is postulated to occur. Generally, chiral induced spin selectivity (CISS) is a central tenet to the NGTC/ascorbolysis/UNMR framework. CISS is today a very active field, as is the field of nano-biology, generally (Naaman 2015, 2019, 2020). In total, the processes are proposed to comply with the Second Law of thermodynamics and Jeremy England's dissipative-adaptation theory of biological complexity (J. England 2015). Inflammatory states are postulated to favor the anabolic direction to the reversible reactions proposed under the NGTC/ascorbolysis/UNMR framework.

Before embarking on an overview of our work, we posit that the increasing US infant mortality rate (IMR) represents a reality (Kennedy et al. 2016) that should concern us all, including non-US countries, especially in the midst of a global pandemic. Both man-made chemical and electromagnetic toxicants are rapidly increasing in numbers and quantity, in parallel with rising IMR. Here we focus on the known effects of certain environmental toxicants and micro-trauma from radiant energy: fluoride, aluminium, and EM radiation. Scorbutism, especially the sub-clinical variety

of scurvy (Booth 1972), is rarely diagnosed, yet readily treatable. Certain mammalian species have lost their ability to synthesize their own L-ascorbic acid. While the explanation for the loss of this capacity is uncertain, we suggest that the greater complexity of the central nervous systems in these species, calls for a greater need in the "input function" provided by environmental sunlight, for trapping and transduction, by interfacial water, and in a non-adiabatic environment, leads to greater complexity in the form of homo-chirality, anisotropy, and quantum phase-coherence on all scales of time and space. Fractals based upon "the fractal dimension" will one day, we firmly believe, be shown to be the rule, not the exception due to the quantum phase-coherence of living organisms, including humans (Davidson et al. 2015a). What price, if any, might be paid for this increase in complexity? Dissipation of heat is the price which might be paid, under Jeremy England's dissipative adaptation theory (2015). What price, if any, might be paid for ever increasing amounts of environmental toxicants, including fluoride, aluminum, and EM pollution? Extinction of the species is a distinct possibility, for which many examples exist in nature, over time (Liu et al. 2012). Computer modeling of populations for risk of extinction should arguably include the concept of toxic synergy discussed in the Kennedy et al. 2016 review article.

To manage the scope of the requisite global internal and external perspective of this paper, we direct attention to the seminal earlier work by Chinoy, et al. (2005a; 2005b), and the review articles by Barbier et al. (2010) and Kennedy et al. (2016), to provide essential background. With that in mind, to make our arguments fully intelligible, we must briefly describe the relevant findings from those works, before moving on to our own Results and Discussion sections. We will conclude this paper with the assertion that in the future AI techniques are almost certain to be employed to reverse engineer, with clinical translational potential, the "initial common pathway" to life on Earth. We suppose that time is running short on maintaining our own genomic resilience, stability, and the long term survival of our species as discussed recently by Robert F. Kennedy, Jr. and Zach Bush: (see *'Truth' with RFK, Jr. and Dr. Zach Bush* at https://vimeo.com/490903719). Their discussion is entirely consistent, incidentally, with the thesis one of us, along with Stephanie Seneff, put forward some years ago concerning the critical role of inflammation in disorders, diseases, and the catastrophic systems failure that we call death (Davidson and Seneff 2012). We can liken the status quo to being at sea in a rudder-less ship with icebergs on the horizon — witness the alarming rise in IMR in the US, and in other so-called "developed" nations (Kennedy et al. 2016), along with exponential increases in a vast and growing list of chronic non-communicable diseases (Calitz et al. 2015), not to mention pandemics of infectious pathogens such as SARS-CoV-2.

Chinoy's studies of fluoride toxicology in a mice model of human disease is prescient (Chinoy et al. 2005a; 2005b). The review article by Barbier (2010) links fluoride toxicology to that of aluminum toxicology. The Kennedy et al. review article (2016) describes how NaF and the silicofluorides in public water supplies are likely to impair biological signalling by G-proteins. We will describe in the Results and Discussion sections, how according to the NGTC hypothesis, vitamin C and activated water may serve as a means of reversing and rescuing living species, including ourselves, from aluminum and fluoride toxicity. The ever increasing presence of EM pollution, e.g. from the advent of 5G technology globally, remains an evolutionary "wild card" for which there are many uncertainties. In any case, the long term safety of ramped up EM exposure has not been established. Because EM fields from sunlight, e.g. environmental torsion fields, play a central role in NGTC, ascorbolysis, and the UNMR, and given that manufactured environmental EM pollution is on the rise, an irreversible state might soon be reached which is unsustainable, in terms of inflammation, disease, and deaths.

Chinoy's Work Summarized

Male mice were orally fed sodium fluoride 10 mg/kg body weight) and $AlCl_3$, 200 mg/kg body weight for 30 days. Alterations in structure of the testis with formation of giant cells and decreased protein levels were observed. Alterations in steroidogenesis, spermatogenesis, and decreased activities of 3β- and 17β-hydroxysteroid dehydrogenases were observed with concomitant accumulation of cholesterol (Chinoy et al. 2005a). Also in 2005, Chinoy showed that epididymis cell damage and damage to the testes in mice induced by fluoride and aluminum were reversed by vitamin C (Chinoy et al. 2005b).

Barbier's Review Article Summarized

Aluminum is a ubiquitous environmental toxicant which is exposed to humans by multiple routes, including orally, topically, and parenterally. Considerable published data provides several likely bases upon which the pathophysiology is based (Barbier 2010).

The Kennedy et al. Review Article Summarized

Just as lead in terra cota pipes for public water supplies may have posed serious unexpected health risks in ancient Rome, so too does lead, Al, F, and HFSA (hexafluorosilicic acid) in public water supplies, e.g. that found in Flint, MI (Flint, MI link). Bio-sequestration of heavy metals by living tissue has been postulated. Importantly, pH dependent speciation and reactivity of NaF and silicofluorides in public water supplies may disrupt hydrogen bonds and hydrogen bond cooperativity and impair G-protein signaling by providing catalytic mimickry of biological phosphorylation reactions, wherein AlF_x species act as transition-state analogues of phosphoryl moieties in biological transphosphorylation reactions (Kennedy et al. 2016).

Of particular note, especially for policy-makers (see the second paper, "Plan B..." by James Lyons-Weiler in this issue of the *IJVTPR*), is the undeniable association between neurotoxicity and neurobehavioral pathology, for which the events in Flint, MI are a microcosm (Masters 1998, 2003; Masters et al. 2016). The "generally recognized as safe" (GRAS) mantra fails because of the concept of synergistic toxicity and non-linearity of the typical dose-response (Kennedy et al. 2016). The human central nervous system has a strong tendency to "sequester" heavy metal environmental toxicants, including aluminum salts and gadolinium salts, both of which have been identified in human brain tissue on MRI and histopathological evaluation (Iadecola 2015; Mold & Exley 2019; Alkhunizi 2020). Also, of note, the undeniable neurotoxicity is associated with neuro-immune toxicity, and has been described as Shoenfeld's syndrome, also referred to as the "Autoimmune-inflammatory syndromes induced by adjuvants" (ASIA; see Shoenfeld and Agmon-Levin 2012). We propose that human tissues of ectodermal embryological origin are biophysically predisposed to bio-sequestration of heavy metal environmental toxicants. Cells of ectodermal origin include pluripotent stem cells, brain cells, reproductive cells, and immune cells. Fortunately, cells of ectodermal origin appear to be high in their level of L-ascorbic acid (Ang 2018), unless of course, the subjects were rendered scorbutic by one or more environmental toxicants, with associated oxidative stress, poor dietary intake of vitamin C, such as was likely to be the case in Flint, MI (Flint, MI). The embryological envelopment of ectoderm by mesoderm and endoderm is biophysically-driven (Brodland 2002).

Results

In this section, we present our proposal as to how environmental toxicants pose distinct risks of disrupting biological group transfers of the non-enzymatic type, i.e. the type of group transfers which logically had to occur long before the advent of biomacromolecules on Earth, i.e. the prebiotic/primordial planet Earth. We present herein a conceptual framework for chemical evolution, biological complexity, and biological diversity, that is biophysically based on homo-chiral molecular morphology in the sequence: water → carbohydrates → nucleic acids → proteins → lipids → glycosaminlglycans → glycosphingolipids → etc. We propose further, that of the earliest carbohydrates, L-ascorbic acid, an oft-studied "vitamin", played a central role based in catalyzing non-enzymatic group transfers.

In agreement with Baccolini's theory of life (2015), it is logical to infer that in the beginning "small and fast" took precedence over "big and slow" and in a "carbohydrates first" sequence to chemical evolution, L-ascorbic acid was likely to be one of the earlier molecular entities to emerge. Under the NGTC and ascorbolysis framework, L-ascorbic acid is postulated to undergo reversible photo-oxidative "super-activation" in the presence of activated ortho/para spin states of water and photo-sensitization by the redox active transition metal, specifically certain oxidation states of highly polarizable essential ultra-trace mineral, copper. We propose herein that in a moderately acidic, mildly oxidative, relatively hydrophobic microenvironment, L-ascorbic acid, its 2-O-substituted derivatives, and its butenolide oxidation products, undergo photo-oxidative super-activation to form radical species that initiate, propagate, and terminate radical chain reactions, in quantum phase-coherent manner, wherein homo-chirality, stereo-, regio-, and chemio-specificity is externally-driven by the handedness of external torsion fields, in a non-adiabatic, open, dissipative environment. Under this hypothetical framework, water plays a central role. Water, itself, is capable of oxidation catalysis in presence of certain redox active transition metals (Rudshteyn 2018). In combination, activated "spin water" is postulated to lower the free energy barriers via quantum nuclear tunneling, effectively flattening the free energy landscape for chemical biology. In this scenario, ever increasing complexity is gained at a cost of dissipation of heat to the environment, in an open dissipative system which exists far from thermodynamic equilibrium.

We will focus on our proposed mechanism for the toxicity of human exposure to various species of fluoride, aluminium, and EM radiation. A large body of published research provides the scientific basis for the assertion that fluoride species, in vivo, have a pleiotropic supramolecular basis for their toxicity which arises largely by disrupting hydrogen bond coopertivity in vivo, in many microenvironments (Froede 1985; Murphy 1992; Kentsis 2004; Strunecka 2012). The magnitude and kinetics of this disruption is thought to be strongly pH- and solvent dependent. A corollary assertion is that the biological activity of L-ascorbic acid is strongly influenced by hydrogen bond cooperativity, both intra- and inter-molecular (Berg 2015; Ebrahimi 2016). The systematic detail underlying the ascorbolysis hypothesis is beyond the scope of this paper, but we can briefly give the reader an overview of the concept and its underlying theoretical basis.

(i) Assignment of nucleophilic "radical philicity" to the L-ascorbic acid free radical

(a) (b)

Figure 7. (a) Calculated incremental spin density map from DFT study of O'Malley (2001) showing the most favorable hydrogen bond acceptor sites for the radical (-150.0 kcal/mol electrostatic potential contour) for the R-hydroxytetronic acid radical (reproduced here from O'Malley (2001) with permission of the publisher); (b) our proposed "intra H-bonded" mono dehydro ascorbic acid free radical depicting the mesomer with the greatest nucleophilic radical philicity.

(ii) Ascorbolysis – what is it?

Ascorbolysis may be thought of as a possible mechanism by which chemical biology "evolved" so as to provide the UNMR with a means of responding in a reversible generalized adaptive response to environmental stress. The adaptive response takes the form of branching cascades of phase-coherent radical chain reactions within an open, dissipative, non-adiabatic system which complies with the second law of thermodynamics. The system is proposed to be externally-driven by EM energy and information from sunlight which has been transduced by activated ortho/para populations of "spin-water" (Glemza 2000; Tikhonov 2006; Horke 2014; Kilaj 2018; Chaplin 2020). Quantum mechanical tunnelling "flattens" the free-energy landscape for genomics, proteomics, lipidomics, and glycomics. Circadian rhythms are imparted to the system by the redox active, photo-sensitizer and time-keeper, the essential ultra-trace mineral, copper. The radical chain reactions are initiated by the unimolecular dismutation of L-ascorbic acid which generates the L-ascorbic acid free radical and DHA without net oxidation or reduction (Deutsch 1997). The first of two serial propagation steps is proposed to occur by means of the L-ascorbic acid free radical reacting in an S_N2 mechanism with any of the myriad endogenous electrophiles, providing 2-O-substituted derivatives of the L-ascorbic acid free radical. The products of the first chain propagation step represent photo-oxidatively super-activated mixed anhydrides which are postulated to possess electrophilic radical philicity. In the secpmd of two propagation steps, the super-activated reactive transients (radical cations) react chemio-, regio-, and stereo-specifically, with any of a myriad of endogenous biological nucleophiles, in a reversible acid-catalyzed proton-coupled nucleophilic attack (PCNA) S_N2 reaction, with the L-ascorbic acid free radical, acting as a resonance-stabilized (mesomerically-delocalized) leaving group.

The L-ascorbic acid free radical can then dismutate to terminate the radical chain reaction. Each step in the radical chain reaction is postulated to proceed via intramolecular 1,4 hydrogen atom transfer ("intra 1,4 HAT") mechanism. Added hydrophobes and amphiphiles are proposed to "induce intramolecularity" for inner sphere hydrogen atom transfer, wherein moderate acidity effectively "labilizes" hydrogen atoms at the 2-, 3-, and 4-positions of the gamma-lactone ring system according to the GCMS studies of John Deutsch (see Deutsch et al. 1994; and Deutsch 1997, 1998a-d). The

rate-limiting step for the radical chain reactions is thought to be homolytic cleavage of the O-H bond at the 3-position of the gamma-lactone ring system. Electronegativity of the various pnictogen-based and chalcogen-based functional groups being transferred is thought to influence the kinetics. The "intra 1,4 HAT" mechanism suggests nuclear quantum mechanical tunneling (McKenzie 2014) along the path of the pre-equilibrium H3-O2 hydrogen bond whose vibrational modes are likely to have been activated cooperatively with the four additional intramolecular hydrogen bonds identified in the global minimum structure for L-ascorbic acid reported by Rolf Berg in a UV/IR Raman and DFT study (2015). Figure 8 depicts one of the many radical chain reactions proposed to be catalyzed by the L-ascorbic acid free radical.

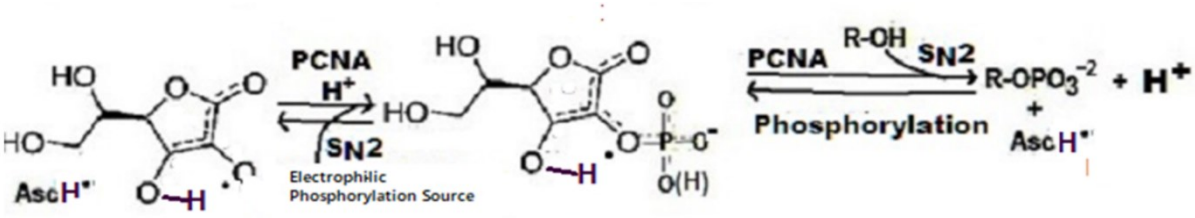


Figure 8. Proposed radical chain propagation steps in phosphoryl group transfer via ascorbolysis (non-enzymatic group transfer catalysis by L-ascorbic acid), i.e. the proposed basis for the "fluid genome" (Maewan Ho 2013). Reversible, auto-catalytic cascades of radical chain reactions provide non-enzymatic kinase-like and DNA/RNA polymerase-like function. The scheme is generalizable to group transfer catalysis of many chalcogen- and pnictogen-based functional groups, thereby occupying a central role in the UNMR. We postulate that ascorbolysis provides a means for non-enzymatic oxidative phosphorylation in eukaryotes, including humans during inflammatory states. The proposed mechanism would enable non-enzymatic ATP production and post-translational modification of proteins during inflammatory states, e.g. within cancer tissues many of which are characterized by a Warburg shift to anaerobic glycolytic energy metabolism and inflammatory states characteristic of non-skeletal fluorosis, oxidative stress, and endothelial dysfunction, e.g. cancer, ischemia, and sepsis (Oudermans-Van Stratton et al. 2014).

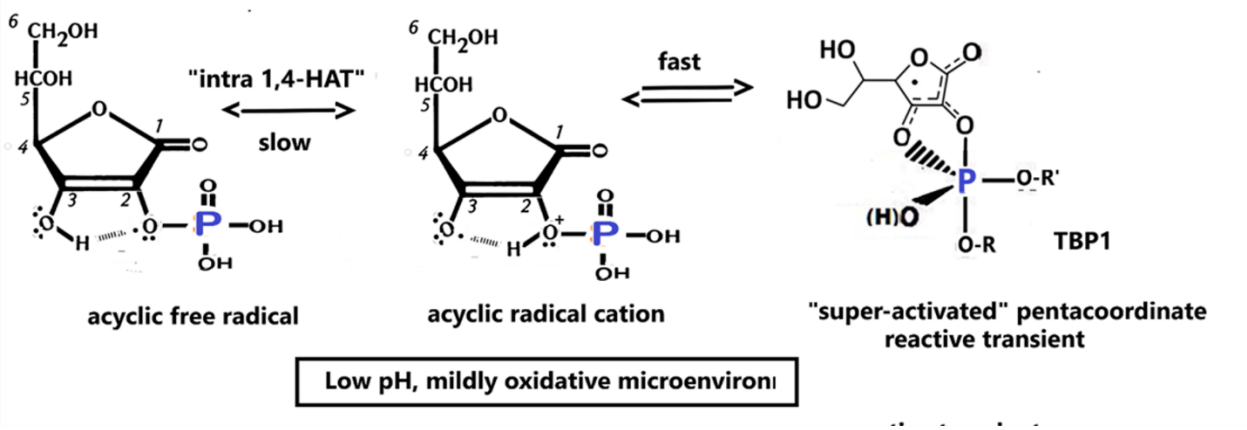


Figure 9. Pre-equilibrium intramolecular H-bonding precedes oxidative photo-activation, followed by (a) rate-limiting homolytic cleavage of the O-H bond at the 3-position accompanied by intramolecular 1,4 hydrogen atom transfer with formation of a radical-cation during charge reorganization ("umpolung" catalysis; Schmittel 1990, 1994) and orbital steering towards the "sigma hole", quantum tunneling; and (b) subsequent fast cyclization to form a cyclic pentacoordinate phosphorus free radical. The trigonal bipyramidal cyclic pentacoordinate free radical reactive transient is then able to pseudorotate following Westheimer's rules (1968), with "flattening" of the free energy landscape. In the low pH, mildly oxidative, relatively hydrophobic aqueous microenvironment the super-activated cyclic pentacoordinate phosphorus reactive transient is able to stereo-specifically, regio-specifically, and chemio-specifically phosphorylate endogenous nucleophiles, including RNA, DNA, and proteins, behaving much like a primordial molecular motor, e.g. a non-enzymatic RNA polymerase, or nuclease in the reverse direction.

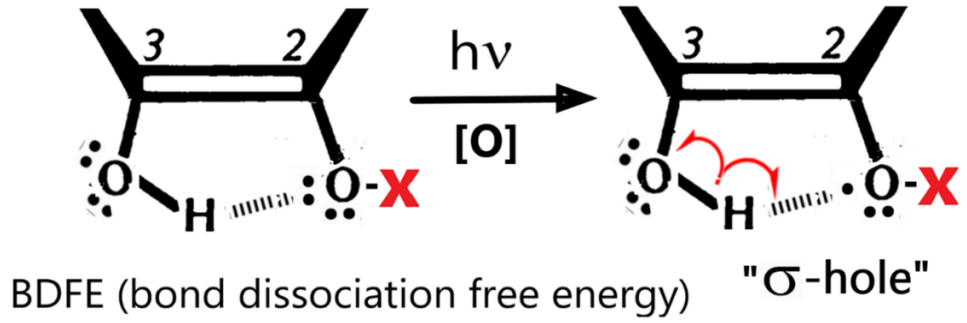


Figure 10. Proposed oxidative photo-activation of AA during uni-molecular first-order dismutation and Group Transfer Catalysis

Ascorbolysis is our proposal for a redox active vinylogous, hyperconjugated variant of acidolysis by L-ascorbic acid (vitamin C), its derivatives, and its butenolide oxidation product (Merriam-Webster; Penczek 2008; Deutsch et al. 1994). An understanding of the distinction between acidolysis and ascorbolysis is crucial. Acidolysis is reversible, general acid catalyzed, and solvent dependent. Whereas, ascorbolysis is reversible, general acid catalyzed, solvent dependent, and redox active (redox potential dependent). In the 1970s, Davidson demonstrated several examples of auto-catalytic acidolysis in the study of various analogues of phosphoenol pyruvate (PEP; this was done in his dissertation work in 1976; also see Davidson & Kenyon 1980). In 1961, Lichtenthaler wrote an excellent review article on the chemistry of enol phosphates (Lichtenthaler 1961). See IUPAC Glossary (Penczek 2008) for acidolysis. The Merriam-Webster definition of acidolysis is useful (Webster Definition). Early proof of concept was provided by the seminal work of Ralph Mumma (1968), who made the remarkable discovery that the 2-O-sulfate derivative of L-ascorbic acid can act as an efficient sulfurylating agent, both in vitro, and subsequently, in vivo (Verlangieri & Mumma 1973). Non-enzymatic sulfurylation of cholesterol forms the ubiquitous, and biophysically-pleiotropic, amphiphilic natural product, cholesterol sulfate (Strott 2003). Further proof of concept was provided when Egami & Hatanaka employed the 2-O-sulfate-L-ascorbic acid derivative in the non-enzymatic sulfurylation of chondroitin (Hatanaka 1976). Of particular note, Frederic Mercier's group, in their study of human stem cell "niches" in the subventricular zone of the hippocampus, referred to as CNS "fractones", made the remarkable discovery that heparin sulfate proteoglycans (HSPGs) of CNS fractones are deficient in sulfur, when the brains of autism subjects were studied histopathologically (Mercier 2012).

(iii) The necessity to challenge conventional wisdom

In several conference proceedings, Davidson and colleagues (2015a-c) inferred the need for a universal sulfurylation factor, in vivo, and proposed a radical-anion structure for such an agent. The original proposal in 2015, however, was critically-flawed by failure to consider the moderately acidic pH range, mildly oxidative, relatively hydrophobic microenvironment in which ascorbolysis, charge reorganization (umpolung) catalysis (Schmittel 1990, 1994), and proton-coupled nucleophilic attack (Hamer et al. 2015), upon photo-oxidative super-activation and intra 1,4 HAT, are most likely to occur. The lipophilicity and physicochemical properties of small molecules are known to be affected by the presence of intramolecular hydrogen bonds (IMHBs; Chen et al. 2019, 2020; Abraham et al. 2020). NMR methods offer convenient alternatives to use of partition coefficients (logP methods) for analysis of IMHBs (Abraham et al. 2020). Chen et al. have recently developed a full *in silico* (computational) linear free energy approach to accurately "predict the effects of organic compounds

on environments and the physicochemical properties of organic compounds", *including neutral organic compounds* (Chen et al. 2020). We assert that the physicochemical properties of the neutral organic compounds, L-ascorbic acid, the L-ascorbic acid free radical, and their neutral lipophilic derivatives affect inflammatory tissue microenvironments in such ways as to substantially affect human health. The global minimum DFT structure obtained by Berg (2015) for L-ascorbic acid had no less than *5 intramolecular hydrogen bonds*, which we assert imparts increased lipophilicity to the molecule. Of particular note, was a 2.751 Å H3-O2 hydrogen bond, which was notably lacking in several calculateed DFT structures for the *L-ascorbate mono-anion*.

The original embodiment of the ascorbolysis hypothesis was critically-flawed by reason of falling into a "rabbit hole" of conventional wisdom, the widely-held longstanding view that the redox biology of vitamin C is dominated by that of the L-ascorbate mono-anion at physiological pH. For readers wishing to consider this topic in greater detail, a large body of published data is recommended, whose scope is beyond that of the present paper (Warren & Mayer 2008; Warren & Mayer 2010a-b; Mayer 2011; Du & Buettner 2012; Saouma & Mayer 2013; Tu & Njus 2017; Njus et al 2020; Sajenko et al 2010; Karković Marković 2020; Handayani 2020). A single-minded focus on the ascorbate mono-anion and the ascorbate anion-radical effectively (a) marginalize studies of the vitamin in the moderately acidic pH range, (b) confounds the conclusions reached in large randomized clinical trials (RCTs), and (c) "starves" NGTC, ascorbolysis, and the UNMR from a source of protons.

Whereas, ascorbolysis postulates that intra 1,4 HAT, i.e. the diagonal cross relation (CR) path on a "box diagram" for HAT under Marcus' theory of proton-coupled electron transfer (PCET), is the favored reaction path within moderately acidic, mildly oxidative, relatively hydrophobic microenvironments. Intra 1,4 HAT is postulated to represent an "inner sphere", first-order process, with a "tight" transition state, and large negative activation entropy in the moderately acidic pH 4-6 range. According to Mayer, "HAT reactions typically have $\Delta S^\circ \cong 0$ because there is no change in the charges of the species involved and little change in their sizes" (Warren & Mayer 2008, 2010a-b; Mayer 2011). We suggest, however, that large negative activation entropies during ascorbolysis are likely to be associated with *intramolecular* 1,4 hydrogen atom transfers and substantial charge reorganization ("umpolung") catalysis which we propose occurs in the anabolic direction of reversible ascorbolysis (see Figures 3, 9, 14, 18b, and 23). The mechanism we propose for ascorbolysis is substantially based on entropic charge reorganization. The effective molarity of the postulated path for hydrogen atom transfer is predicted to be very high, and the likelihood of nuclear quantum mechanical tunneling along this path is likewise predicted to be very high. Neutral uncharged free radicals and radical anion species lead via charge reorganization to radical-cation intermediates and transition states in the anabolic direction of the proposed reaction coordinate for ascorbolysis and the UNMR. In the catabolic direction of reversible ascorbolysis/UNMR, the opposite sequence of charge reorganization would be likely to prevail, within inflammatory microenvironments, which are typically low in pH and high in oxidative stress. Thus, in this theoretical framework, inflammatory states are likely to favor the anabolic direction over the catabolic direction of non-enzymatic group transfers, as long as adequate L-ascorbic acid is provided, and environmental intoxicants (e.g. NaF, silicofluorides, aluminum salts) and EM pollution are avoided.

Warren and Mayer obtained a better fit of their model with experimentally obtained rate constants when Michael Abraham's parameters accounted for kinetic solvent effects which enabled the

prediction of a wide range of rate constants for HAT under the cross relation path of the Marcus theory of PCET (Warren & Mayer 2008, 2010a-b; Mayer 2011). The ascorbolysis hypothesis fails unless all three microenvironmental parameters (pH, redox potential, and hydrophobicity) are considered. Additional multi-component cyclic voltammetry studies of the type recently reported by Handayani (2020) can in principle be designed to prospectively control for all three environmental parameters (pH, redox potential, hydrophobicity) as well as comparisons of kinetics within activated ortho/para spin water (see Figure 11). Multi-component Pourbaix diagrams (plots of pH or pKa versus redox potential) might yield unexpected results, perhaps confirming existing theories, validate new ones, or suggest alternate avenues to explore.

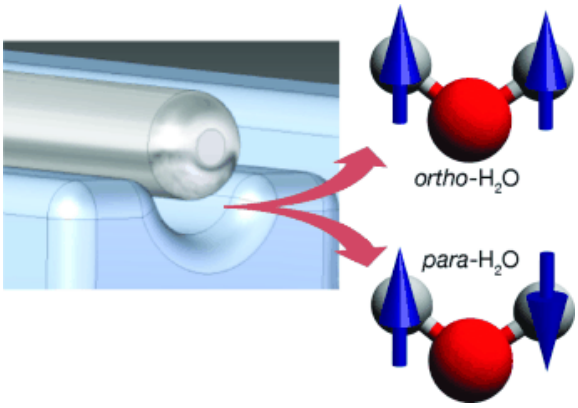
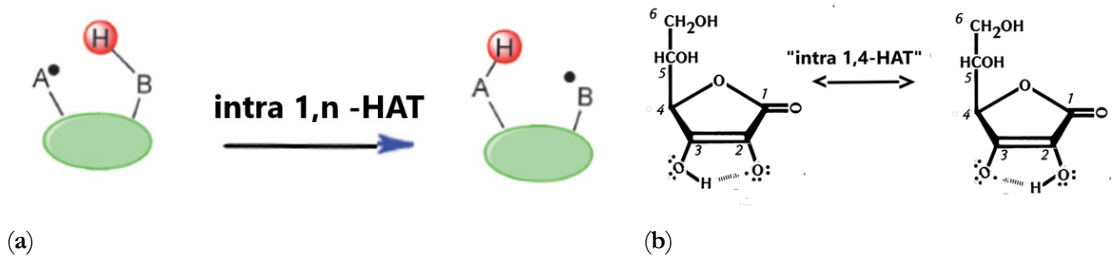


Figure 11. Depiction of ortho and para nuclear spin states of "spin water" reproduced here from Horke et al. (2014) with permission of the publisher.

We argue herein that use of the term "physiological pH" should be abandoned because of its vagueness. Physiological pH is now known to be dynamical and heterogeneous in both time and space (Gebicki 2018; Tsai 2014). Lipid/water extraction coefficients are greater for hydrophobic derivatives of L-ascorbic acid than for their conjugate bases. Truly "free" radicals are neutral, uncharged species which would favor relatively hydrophobic microenvironments to a greater extent than radical-anions. The L-ascorbic acid free radical in the moderately acidic pH 4-6 range has also been inappropriately marginalized by conventional dogma in favor of the L-ascorbate radical anion. Even today, the term "ascorb(ate)" is often conflated with that of vitamin C (L-ascorb(ic) acid). In our view, this practice must be abandoned. The distinction has considerable significance, both retrospective and prospective. The suffix "*-ate*" connotes the conjugate base of the free acid. It is simply misguided to conflate the terms ascorb*ate* and ascorb*ic*. Inflammatory states are moderately acidic states (Tsai 2014).

We propose herein that the moderately acidic, mildly oxidative, relatively hydrophobic inflammatory microenvironment induces "intramolecularity" of L-ascorbic acid (vitamin C), i.e. induces intramolecularity of pre-equilibrium (precursor) hydrogen bonding and intramolecularity of hydrogen atom transfers, and charge reorganization, followed by fast bimolecular (S_N2) proton-coupled nucleophilic attack. Whereas, the stable isotope labeled GCMS studies of John Deutsch (1998a-d) and the recent multi-component cyclic voltammetry study by Handayani (2020) suggest that the oxidative degradation of vitamin C is actually *promoted* within a neutral to alkaline pH range. To wit, the gamma lactone ring of dehydroascorbic acid (DHA) has been shown by Deutsch's work to be more susceptible to ring-opening and subsequent oxidative degradation than the gamma lactone ring of L-ascorbic acid and that of the L-ascorbic acid free radical. We, therefore, ppropose that the in vivo biological activity of vitamin C is dominated by that of the L-ascorbic acid free

radical due to its central role in NGTC, ascorbolysis, and the UNMR, as a supramolecular (biophysically pleiotropic) generalized adaptive response to environmental stress. Testing of these hypotheses, of course, is called for.



(**a**) (**b**)

Figure 12. The "intra 1,4 HAT" depictions: (a) Adapted from Nechab (2014) with permission of the publisher; (b) Proposed "intra 1,4 HAT": stabilizing the "dismutation" of AA and DHA. Proposed stabilization of the ascorbic acid free radical in the dismutation and non-enzymatic intermolecular group transfers via mesomerism and entropically-advantaged (Page & Jencks 1971) intramolecular-1,4-hydrogen atom transfer ("intra-1,4-HAT") in low pH, mildly oxidative aqueous micro-environment.

In our current conception of these processes, we assert that the in vivo redox properties and chemical reactivity of vitamin C is dominated by that of its free acid, i.e. that of L-ascorbic acid and the L-ascorbic acid free radical in the moderately acidic pH range (ca. 4-6). An inflammatory microenvironment is thought to be typically mildly oxidative, relatively hydrophobic, and moderately acidic. We propose that inflammatory states are likely to promote (a) intramolecularity of precursor pre-equilibrium hydrogen bonding, and (b) intramolecular 1,4 hydrogen atom transfer, denoted "intra 1,4 HAT" following Nechab's nomenclature for intramolecular 1,n hydrogen atom transfers (Nechab 2014) upon photo-oxidative super-activation of L-ascorbic acid and its 2-O-substituted derivatives. Upon oxidative super-activation, the vibrational modes of the O-H bond at the 3-position are postulated to predispose to rate-limiting (slow) homolytic cleavage of the O-H bond at the 3-position and nuclear quantum tunneling along the path of the pre-equilibrium H3-O2 hydrogen bond (McKenzie 2014; Berg 2015), in the direction of a "sigma hole", i.e. a singly occupied sp3 hybridized oxygen orbital at the 2-position, formed upon photo-oxidative super-activation. We suggest that the large solvent- and pH- dependent kinetic isotope effects (KIEs) observed by Stanko Uršić's group (Karković Marković 2020) might be better explained by the mechanism and *pH-dependent speciation* proposed herein for nuclear quantum mechanical tunneling by intra1,4 HAT of the L-ascorbic acid free radical during the initiation, propagation, and termination steps of the radical chain reactions we describe as ascorbolysis.

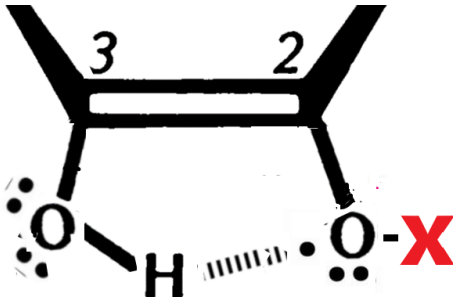


Figure 13. Proposed structure of "intra H-bonded" oxidized AA derivatives provide a novel putative class of reactive transients (AA radical derivatives). This class of AA radical derivatives is proposed to provide the biophysical basis for

branching cascades of radical chain reactions described historically as the UNMR, initially described by Selye as the "general adaptation syndrome" (1950). This class of radical derivatives of L-AA is thought to possess electrophilic radical philicity and their presence, in vivo, is likely to represent an electrophilic reserve capacity for responding to environmental stress, e.g. environmental sources of exogenous interfacial water stress (EIWS) described by Davidson and Seneff (2012), and by Davidson, Lauritzen, and Seneff (2013). Today, many sources of environmental EM pollution pose potentially-detrimental effects to the biological water dynamics represented by the recently discovered ortho/para spin states of water, described loosely as "spin water" (Mamrashev 2018).

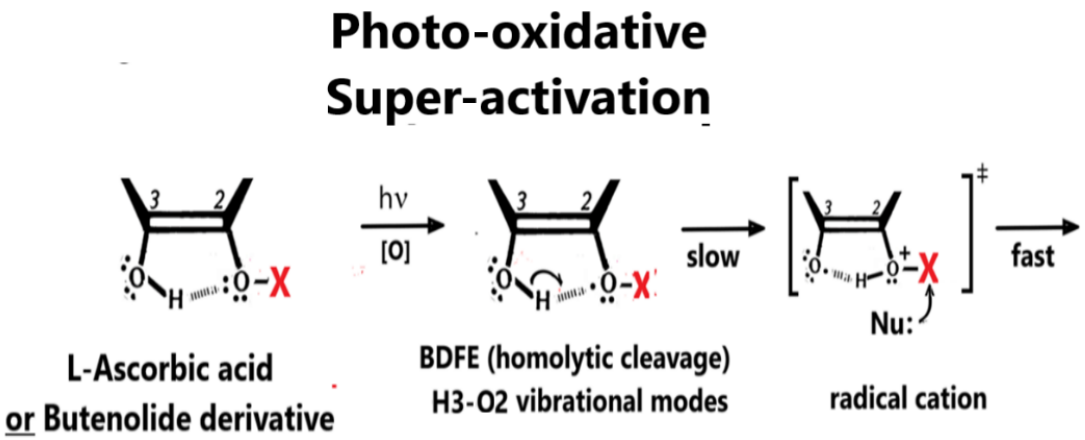


Figure 14. Generalized reaction scheme for the photo-oxidative super-activation of L-ascorbic acid derivatives and butenolide derivatives under moderately-acidic, mildly oxidative, relatively hydrophobic conditions, The hydrophobic effect is postulated to induce intramolecularity of the five precursor pre-equilibrium intramolecular hydrogen bonds in the global minimum DFT structure of L-ascorbic acid predicted by Berg's UV/IR Raman and DFT study (Berg 2015). It is likely that the vibrational modes of L-ascorbic acid interact cooperatively in the relatively hydrophobic, moderately acidic pH 4-6 range. It should be mentioned that Ebrahimi's quantum theory of atoms in molecules ("QTAIM") study (Ebrahimi 2016) predicted hydrogen bond cooperativity of L-ascorbic acid and also predicted the presence of an H3-O2 hydrogen bond which plays a central role in the ascorbolysis hypothesis. In the moderately acidic pH 4-6 range, (a) hydrogen atoms are labilized at the 2-, 3-, and 4-positions (Deutsch et al. 1994); (b) charge reorganization ("umpolung") catalysis (Schmittel 1990; Schmittel 1994); and (c) proton coupled nucleophilic attack ("PCNA"; see Hamer et al. 2015) are postulated to represent central mechanistic tenets, herein.

Pioneering work by Takebayashi et al. (2007) led us to propose that sluggish, "slow and continuous" radical scavenging by 2-O-substituted L-ascorbic acid derivatives, generate reactive transients, short-lived radical species (Takebayashi 2007), for subsequent propagation steps in radical chain reactions of non-enzymatic group transfers during inflammatory states. Branching cascades of non-enzymatic group transfer during inflammatory states are proposed, herein, to provide a plausible physical chemical basis for the so-called UNMR, a process studied by Selye in 1950's and 60's (Selye 1950, 1966, 1967, 1968) employing histopathological characterization of inflammatory states in small animal models of human disease. Hauss also studied (Hauss 1962, 1969) inflammatory changes in the extracellular matrix in response to inflammatory states, which were ultimately described as the Sanarelli-Shwartzman Phenomenon (SSP), subsets of Selye's thrombohemorrhagic phenomena (THP), which of note, include the hemorrhagic fever viral pathophysiology, e.g. that of Dengue and Ebola outbreaks. It remains to be determined whether the current global COVID-19 pandemic represents a consumptive coagulopathy of the microvasculature which typify the SSP (Davidson et al. 2015b).

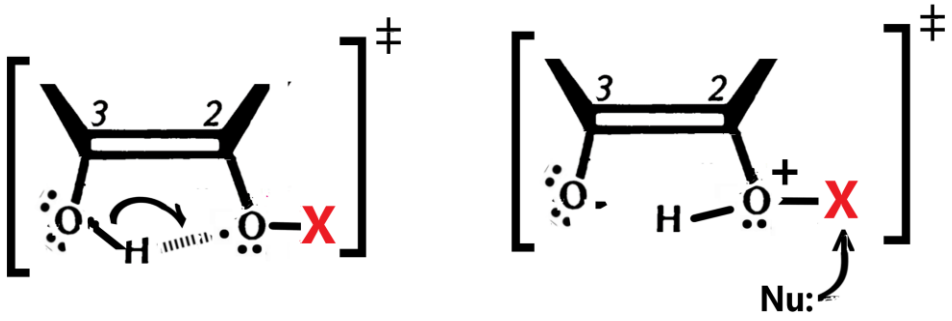
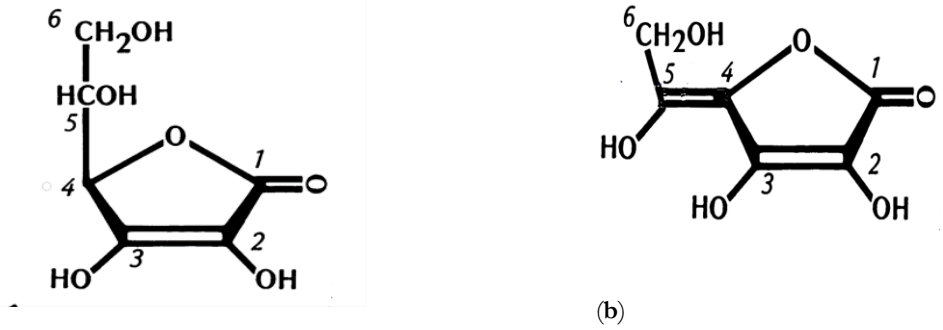


Figure 15. Proposal for "intra 1,4 HAT": Putative rate-limiting (slow) step in ascorbolysis

Central to the ascorbolysis hypothesis is the acidity, oxidative potential, and hydrophobicity of the inflammatory tissue microenvironment. These conditions are postulated to favor the anabolic direction over the catabolic direction of biological group transfers. For example, inflammatory states are thought to promote the anabolic direction to post-translational modifications (PTMs) of proteins, and pre-transcriptional/pre-translational modification of polynucleotides, chromatin, and histone proteins, e.g. cytoproliferative events necessary for assembly and function of the meiotic spindle during human germ cell maturation.

In 2019, Zhou et al. demonstrated that vitamin C can protect against human meiotic failure in human oocyte maturation. Under the ascorbolysis hypothesis, L-ascorbic acid provides a source of hydrogen atoms for the first-order, uni-molecular dismutation and non-enzymatic intermolecular group transfer to endogenous nucleophiles in the acidic pH range. Branching cascades of auto-catalytic, general acid catalyzed radical chain reactions of regio-, stereo-, and chemio-specific quantum phase-coherent functional group transfers in response to inflammation, effectively provides a plausible potential basis for a unified theory of human health, disease, evolutionary resilience, and genomic stability.



(**a**) (**b**)

Figure 16. (a) L-ascorbic acid with numbering convention, structure is used as template in this paper with permission of the American Chemical Society (Crawford 1982); (b) Butenolide early oxidation product of L-ascorbic acid, in acidic aqueous media with $Cu2^{+}$ oxidant, identified by John Deutsch and colleagues GCMS study (1994).

We further propose that the toxicology of NaF and the silicofluorides in public drinking water is highly-likely to disrupt the 5 intramolecular hydrogen bonds identified by Rolf Berg's UV/IR Raman and DFT study (Berg 2015). Of note, a particular intramolecular hydrogen bond identified in Berg's global minimum calculated DFT study, i.e. the H3-O2 hydrogen bond between the hydrogen atom

at the 3-position and the oxygen atom at the 2-position of the gamma lactone ring system, is called to the readers' attention. *This particular intramolecular hydrogen bond was not found in the calculated DFT studies of the L-ascorbate mono-anion.* This is a non-trivial point, because according to the evolving ascorbolysis hypothesis, the pre-equilibrium hydrogen bonding of L-ascorbic acid is thought to predispose, in the presence of activated water, sunlight, added hydrophobes, and trace quantities of the essential ultra-trace mineral copper, to photo-oxidative super activation of L-ascorbic acid, forming the L-ascorbic acid free radical, which is proposed to be resonance stabilized by mesomerism (Neta 1972; Went 1988; Kerber 2006) of the hydrogen atom at the 3-position, upon homolytic cleavage of the O-H bond at the 3-position. Such mesomerism (resonance delocalization) follows the path of the pre-equilibrium intramolecular H3-O2 hydrogen bond. Cooperative vibrational modes of the O-H bond at the 3-position, upon photo-oxidative "super activation" results in a reactive transient, i.e. the entity referred to historically as the "semidehydroascorbic acid free radical" (Deutsch 1998a).

Chinoy's prior work establishing the reversibility and rescue of fluoride toxicity with vitamin C, gives us the opportunity to propose, herein, how environmental pollution might impair ascorbolysis and human chemical evolution. We propose that non-enzymatic group transfers are disrupted by NaF and silicofluorides in the water supply and fluoride in toothpaste, at a cost of inducing both skeletal *and non-skeletal* fluorosis in humans which we propose entails the disruption of hydrogen bond cooperativity necessary for non-enzymatic biological group transfers, necessary for the UNMR, hence necessary for biological complexity, diversity, and morphogenic determinants.

Initial hypothesis testing is underway and promising early results have been found. When unpasteurized, fresh dairy cow milk, is exposed to NaF containing emulsions found in toothpaste, visible differences in protein layering by high resolution still frame and time lapse photography have been observed when activated "spin water" is compared with ordinary water as a control. It is suggested that the unfolded protein response (UPR) is induced by fluoride species. Whether these observations are direct effects of the fluoride species upon protein folding, perhaps associated with a decrease in carrying capacity of water manifested by the zeta potential, or indirect effects of fluoride species upon interfacial water dynamics previously stabilized by L-ascorbic acid and the L-ascorbic acid free radical, are yet to be determined. Further experiments are underway comparing the replicative life span (RLS) of yeast in the presence of NaF and silicofluorides, comparing visible changes by high resolution still frame and time lapse photography in activated to ordinary water control. Subsequent experiments will examine the reversal and rescue by vitamin C from the effects of NaF and the silicofluorides.

A parallel set of experiments comparing the results with and without the presence of 5G radiation might demonstrate differences in folding of milk proteins associated with PTMs, catalyzed non-enzymatically via ascorbolysis, associated with differences in carrying capacity of water observable on the macro scale, hence discernible by microscale microscopy and macroscale photography. Nanoscale experiments might also be conducted employing newer technologies such as atomic force microscopy (AFM).

Discussion and Conclusions

(i) The rationale for proposing a mechanistic change at the inflection point of the biphasic pH-potential diagram for vitamin C: acidity promotes inner-sphere dismutation, whereas neutral to alkaline pH promotes outer-spere disproportionation

Seminal work by John Deutsch in the 1990s clearly established that L-ascorbic acid behaves very differently in the acidic pH range of ca. 4-6 than it does at neutral to alkaline pH (Deutsch 1994, 1997, 1998a-d) which motivated us to propose that a mechanistic change is likely to occur in the acidic pH range, at the inflection point of Bielski's classically-shaped sigmoidal pH-potential diagram (Bielski 1981). In 1997, in acidic aqueous media, Deutsch reported very compelling stable isotope labeled GCMS studies of an interconversion between L-ascorbic acid and L-dehydroascorbic acid (DHA) catalyzed by Cu2+ (cupric) ions. Importantly, the non-exchangeable site deuteriums of Deutsch's deuterium-labeled L-ascorbic acid became distributed at equilibrium under acidic conditions between L-DHA and L-AA, without net loss of label at the non-exchangeable deuterium-labeled 6-position of the gamma-lactone ring system and the kinetics were observed to be first-order.

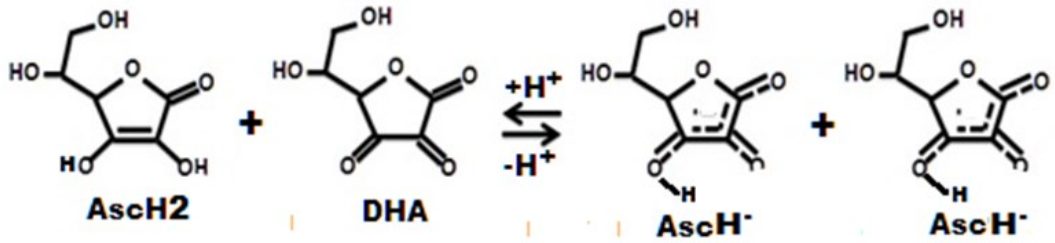
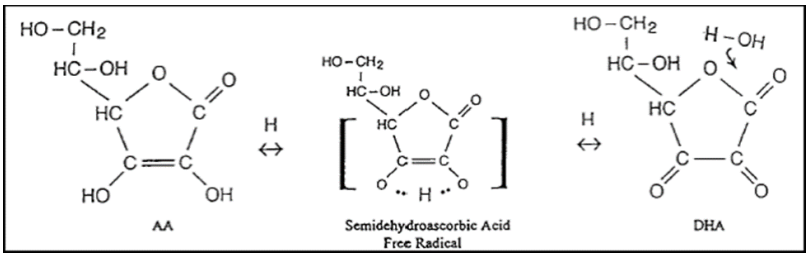
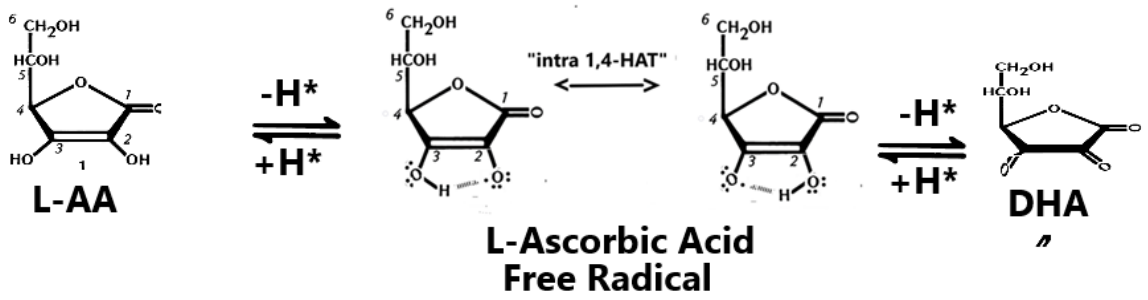


Figure 17. Putative bimolecular "disproportionation" reaction for the L-ascorbic acid free radical. While such a mechanism would follow second-order kinetics, this mechanism is not compatible with Deutsch's stable isotope-labeled GCMS study (Deutsch 1997), wherein his kinetic data were clearly first-order without net loss of label at the non-exchangeable deuterium-labeled 6-position.



(a)



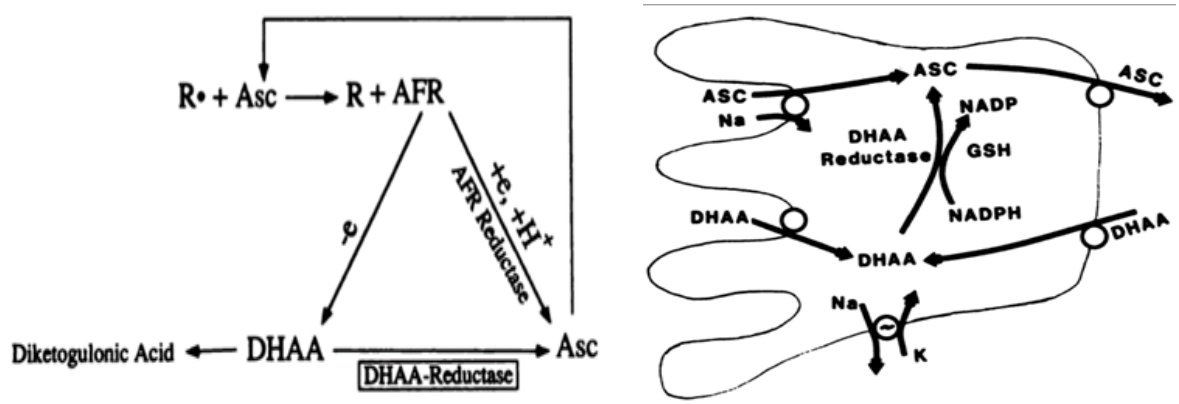
(b)

Figure 18. Mechanistic depictions of the proposed "dismutation" of L-ascorbic acid in the moderately acidic pH 4-6 range. (a) John Deutsch's depiction of proposed "dismutation" (our terminology) of AA and DHA in acidic aqueous media via an L-AA free radical intermediate, referred to historically as "semi-dehydroascorbic acid free radical", reproduced here with permission of publisher (Deutsch 1998a); (b) Our rendering of the proposed dismutation of L-ascorbic acid via "intra 1,4 HAT" upon "labilization" of hydrogen atoms at the 2-, 3-, and 4-positions of the gamma lactone ring system reported by Deutsch's stable isotope labeled GCMS studies in 1994, 1997, and 1998.

> Certain experimental data imply there is more to the antioxidant effect s of AA than simply the reversible AA:DHA reaction. For instances, it has been reported (32) that solutions of DHA better prevented cupric ion-induced low-density lipoprotein oxidation than AA. The mechanism of this effect is unclear since AA is readily oxidized to DHA and *both AA and DHA should provide a source of DHA. However, the formation of AA to DHA generates the semi-DHA-free radical (25) which wouldn't be present if DHA were the starting material*. The situation is further obscured by rapid hydrolysis of DHA to DKG or other degradative products (26). After a short time, a DHA-containing solution will con- tain other species which could contribute importantly to the overall antioxidant capacity. (Deutsch 1998a; italics added by Davidson and Winey)

(ii) The L-ascorbic acid free radical is the key to understanding the oxidation of vitamin C

An important clue to solving this long-standing mystery may be found in the literature (Rose 1993). See Figure 19.



(**a**) (**b**)

Figure 19. Excerpted figures and captions from Rose (1993) are reproduced here with permission of publisher. (a) "A possible scheme by which a free radical species (R 0 is neutralized by single-electron transfer with a scavenger, in this example, ascorbate (Ase). This results in a detoxified product, R, and the ascorbyl free radical, AFR. Pairs of AFR

disproportionate to form one molecule of dchydro-L-ascorbic acid (DHAA) and one Ase. DHAA can undergo a biologically irreversible opening of the lactone ring to form the inert product, diketo-L-gulonic acid; alter- natively, it can be reduced to the useful Asc"; (b) "A working model that describes intestinal absorption of ascorbic acid (Ase) and dehydro-L-ascorbic acid (DHAA) in animal species that require it in the diet (primates and guinea pigs). At the luminal border, Asc is transported against a gradient by a Na•-dependent mechanism and DHAA is transported down a gradient by an Na•-independent process. Cellular DHAA is maintained low by GSH/NADPH-dependent enzymatic reduction. At the basolateral membrane, transport of each form of the vitamin is down an electrochemical gradient. Note that ascorbate is a mono- valent anion and DHAA is uncharged. The cell interior is 30-60 mV negative with respect to the extracellular fluid. The model also accounts for renal handling of ascorbate in mammalian species that synthesize the compound from glucose as well as those that absorb it from dietary sources as a vitamin." (Original caption from Rose 1993.)

(iii) Enzymatic "mimicry" of NGTC?

It should have come as no surprise to us that the answer to fathoming the prodigious supramolecular biological activity might be found on considering how ancient NGTC might be mimicked by enzymatic catalysis. Arriving at the conclusion that the L-ascorbic acid free radical provides the key to solving a long-standing mystery and source of confusion in the published literature, was tricky, complicated by the fact that Deutsch's stable isotope labeled GCMS studies in acidic aqueous media in the presence of different oxidants was spread out over several papers between 1994 and 1998. His data are *very important chemically and clinically*, however, and it is well-worth the effort to try to explain them. Upon reconsideration of Deutsch's data, we propose that the reaction is aptly described as a uni-molecular dismutation reaction and, importantly, we further propose that the mechanism likely proceeds by means of an intramolecular 1,4 hydrogen atom transfer, denoted "intra 1,4 HAT". We have adopted Nechab's nomenclature, for the general case, intra 1,n HAT (Nechab 2014). The intra 1,4 HAT mechanism proposed herein (see Figure 18b) is very distinct kinetically and mechanistically from that of the oft-cited historical bimolecular (second-order) mechanism proposed by Bielski for the "disproportionation" of vitamin C (Deutsch et al. 1994; Deutsch 1997; Bielski 1981).

> Cupric ion, on the other hand, formed only trace amounts of the *m/ z* 607 product. Over time, cupric ion (but not hydrogen peroxide) formed relatively large amounts of a six carbon species with four derivatizable sights, a single retention time, *and no disturbance of the hydrogens on the carbon at position 6*. (Deutsch 1994; italics added by Davidson and Winey).

When viewed in total, these many seemingly disparate historical experimental, theoretical, and clinical observations, call for a unified theory. Such a theory has been proposed in the paper about "the initial common pathway to inflammation, disease, and death" (Davidson et al. 2012). Its corrolaries account for health, anti-ageing, and longevity. In any case, it is understood that the meiotic spindle apparatus during mammalian germ cell maturation and replication places greater demands upon biosignaling systems than are required for mitosis (Ahmad 2016; Yu 2018; Zhou 2019). Under the NGTC/ascorbolysis/UNMR framework, it is very reasonable to expect that L-ascorbic acid would play a central role in mammalian reproductive biology, including that of fruit bats, Guinea pigs, and humans.

(iv) Are we inadvertently "starving" ascorbolysis from a proton source?

It warrants mention that widespread dietary supplementation with L-ascorbate anions, various conjugate base salt forms of vitamin C, might actually be deleterious to health, by effectively

overloading our bodies with salt, e.g. sodium or calcium and "starving" the body for an adequate source of protons needed for ascorbolysis. Importantly, several endogenous and exogenous 2-O-substituted derivatives of vitamin C have been identified intracellularly (Eguchi 2003; Saitoh 2004), e.g. the 2-O-glucopyranosyl- and the 2-O-phosphate-substituted derivatives. If as we propose in the present study, that one of the primary, heretofore undescribed, roles of vitamin C in human physiology is actually to provide for non-enzymatic group transfer catalysis, dietary supplementation with naturally-occuring polyphenolic anti-oxidants, flavonoids, and anthocyanins, may provide the great benefit of effectively sparing vitamin C from the comparably menial role of being a "sacrificial" antioxidant. Under the NGTC framework, weak organic acids and hydrophobes, such as anionic amphiphilic surfactants, e.g. lauric acid, capric acid, etc. may play an important role of retarding the formation of DHA, whose ring-opening and downstream degradation is promoted at neutral to alkaline pH (Handayani 2020; Deutsch 1998a-d).

(v) Inconsistent results of intravenous vitamin C (IVC) randomized clinical trials (RCTs)

It is generally accepted that NaF, aluminum salts, and silicofluorides increase oxidative stress in biological microenvironments (Zhang 2007; Chouhan 2008; Agalakova 2012). Thus, many of the inconsistent results from RCTs may be due to failure to control for the presence of NaF, aluminum salts, and silicofluorides in the drinking water of the study subjects enrolled. Failure to control for baseline blood levels of L-ascorbic acid may be an additional source of inconsistent results. The incidence of subclinical and marginal scurvy is thought to be high, and is rarely if ever diagnosed (Dalldorf 1933; Rinehart 1942). Smoking-related oxidative stress would predictably confound RCT, although this is usually controlled for, by their exclusion from enrollment.

Perhaps the largest source of variation and inconsistencies between RCTs is related to inadequate control, both within study and between study, of the dose, osmolality, pH, and buffer of the IVC solution infused. Standards for the infusate in high dose IVC RCTs are urgently needed. In our opinion, there are many valid reasons why ascorbate salts should not be employed for the infusions. The L-ascorbate anion is not bio-equivalent to the free diacid, i.e. L-ascorbic acid. From a pharmacological perspective it is very wrong to conflate ascorbate salts with vitamin C (L-ascorbic acid). Their biodistribution and pharmacokinetics differ substantially. From a chemist's perspective, it's an oxymoron.

To summarize, the wide variation in RCTs of IVC are likely multi-factorial, and fall into two main categories: (a) lack of infusate/infusion standardization, and (b) lack of study subject inclusion/exclusion criteria uniformity. The lack of standardization and uniformity between RCTs, results in a worst-case scenario, faulty conclusions, attributable to failure to adequately control for (a) pH- and solvent-dependent speciation of vitamin C, (b) pre-existing subclinical scurvy at baseline, (c) adventitious contamination of infusate buffers by redox active metals, e.g. Cu^{2+} and Fe^{3+} contaminated buffers (Buettner 1988; Buettner 1990; Buettner 1996), and (d) NaF, silicofluoride, aluminum salts, and AlF_x species at baseline and during study. Importantly, use of ascorbate salts would predictably confound RCT results due to their inability to provide NGTC, in addition to increasing the total body burden of sodium, e.g. with use of sodium ascorbate, instead of L-ascorbic acid. Care should be given to the choice of buffer for the intravenous infusion of IVC. Ideally, a pH of between 4 to 6 would be obtained. Buffers and water purification should be standardized between studies in RCTs, so as to avoid the contamination with redox active metals (Buettner 1988; Buettner 1990; Buettner 1996). A lactate or citrate buffer might be considered.

(*vi) In the midst of a persistent global COVID-19 pandemic, what can we lose by hypothesis generation and testing?*

If one were to propose that structural topological motifs in RNA sequences of RNA viruses such as the SARS-CoV-2 pathogen exist which are at all similar to topological motifs, i.e. RNA sequences, found in bacteriophages and RNA viruses, would it be worthwhile to see if Cu2+ and the L-ascorbic acid free radical cleave the polynucleotide at sites dependent on the structural motifs, e.g. CpG or UpA or other sequence? A supramolecular experimental strategy could logically target SARS-CoV-2 either (a) directly, at the RNA level, catalyzing RNA cleavage of specific phospho-diester bonds, or (b) alternatively, targeting one or more of the SARS-CoV-2 translation/transcription factors (Peng 2008) at the protein kinase and sirtuin levels, exploiting potential "vulnerabilities" of the pathogen's replicative life cycle. Under the experimental strategy proposed, the reversibility, supramolecularity, intramolecularity, pH- and solvent-dependent speciation, and reactivity of L-ascorbic acid, the L-ascorbic acid free radical, the 2-O-phosphate-L-ascorbic acid derivative, its radical, and its lipophilic derivatives, in a moderately acidic pH range (ca. 4-6), mildly oxidative, and relatively hydrophobic microenvironments, can be systematically explored.

Precedent for the existence of intracellular AA-2P was amply provided in the prior studies by Eguchi (2003) and Saitoh (2004). The ascorbolysis hypothesis provides a potentially provable supramolecular (biophysically-pleiotropic) means of non-enzymatically regulating gene expression, including perhaps expression of the SARS-CoV-2 genome, and that of similar viral pathogens. Such proof would have considerable clinical translational potential for all medical disciplines. We strongly maintain that AA-2P and many of the 2-O-substituted derivatives of L-AA are not merely pro-drugs for intracellular L-AA as is commonly believed. Instead, a central tenet of the ascorbolysis hypothesis is that the 2-O-substituted derivatives of L-AA provide a distinct class of "slow and continuous" non-enzymatic i*ntermolecular* group transfer factors, in addition to impressive radical scavenging properties (Takebayashi 2007). Of note, several of the 2-O-substituted-L-AA derivatives have shown marked anti-neoplastic and anti-metastatic properties, which are being tested in RCTs. Therapeutic synergies with existing anti-inflammatory agents are anticipated. Difficulties with drug delivery (bioavailability) and pH-stability of such agents may likely be overcome by use of liposomal formulations (Shao 2017) and/or various lipophilic analogues of such L-AA derivatives to provide adequate intracellular, blood, lymphatic, and CSF levels, potentially providing new therapies in oncology and infectious disease.

In the formulation of "Westheimer's rules" in 1968 governing the ring-opening and hydrolytic preferences of cyclic pentacoordinate phosphate esters, Frank Westheimer made the experiential and prophetic declaration: "Five-membered esters of phosphoric acid are strained. They hydrolyze millions of times faster than their acyclic analogs, with ring opening and with retention of the ring" (Westheimer 1968). For this reason, our proposal for NGTC via ascorbolysis by photo-oxidatively super-activated AA-2P radical posits that the super-activation step is relatively slow or sluggish by comparison to the subsequent fast cyclization and ring-opening or hydrolysis steps. See Figure 9 presented earlier.

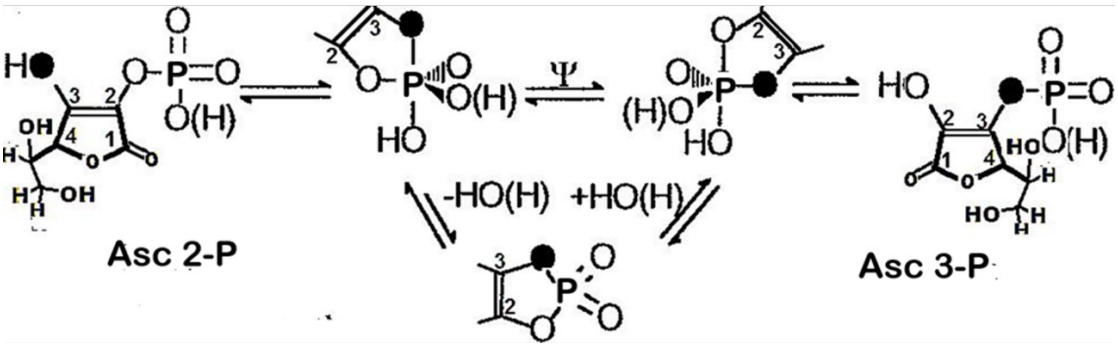
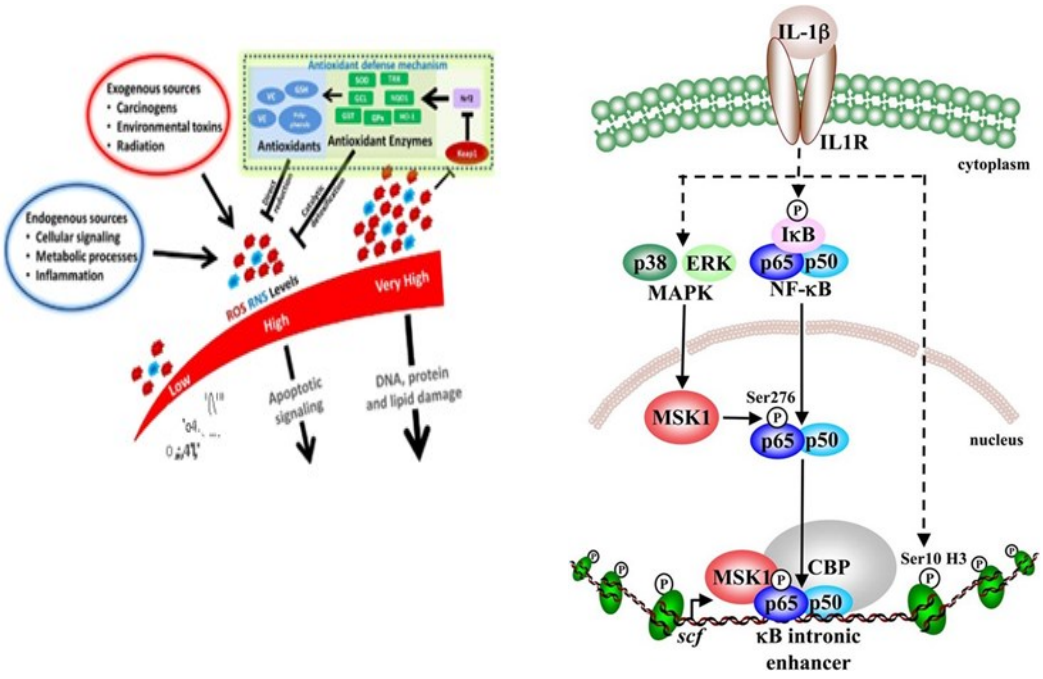


Figure 20. In a scheme adapted from Cameron & Thatcher (1996) for *Berry* pseudorotation (fluxional isomerization, i.e. pairwise exchange of equatorial and axial ligands) of cyclic penta-coordinate sulfates (Cameron 1996; Westheimer 1968; Ugi et al 1971; Davidson & Kenyon 1980; Cabral & Haake 1988; Cass 2006), we propose the following mechanism for intramolecular trans-phosphorylation by the 2-O-phosphate substituted L-ascorbic acid derivative, which subsequently undergoes photo-oxidative super-activation to generate the 2-O-phosphate-L-ascorbic acid radical (see Figure 9 above) which we denote as the "ascorbyl phosphate radical" for brevity. In such a scheme, the cyclic penta-coordinate phosphate derivative and cyclic penta-coordinate phosphate radical derivative lower the activation energy barriers for reversible non-enzymatic transfer of phosphoryl moieties to endogenous biological nucleophiles in the pH range 4-6 (Westheimer 1968; Baccolini 2010). Of particular note, there is a recently published multi-component cyclic voltammetry study (Handayani 2020) to support the addition of hydrophobes and/or amphiphilic anionic surfactants in order to promote and induce intramolecularity of the pre-equilibrium H3-O2 hydrogen bond in a moderately acidic, mildly oxidative, relatively hydrophobic microenvironment. The intramolecular rearrangement of 3-O-acyl derivatives of L-AA to the thermodynamically-favored 2-O-acyl derivatives was demonstrated by Cabral and Haake in 1988. Structure proofs for the derivatives were made by NMR techniques. The intramolecular trans-phosphorylation (rearrangement) was acid-catalyzed and is thought to predict the capacity for reversible, auto-catalytic intermolecular group transfer of acyl moieties, in vivo, as was subsequently demonstrated by Verlangieri and Mumma for the non-enzymatic sulfurylation of cholesterol (Verlangieri and Mumma 1973).

Activation of our endogenous antioxidant defense system, which occurs largely via NRF2 activation and/or KEAP1 inactivation, is highly relevant to developing potentially useful therapeutic approaches to the current COVID-19 pathophysiology, which has been associated with severe inflammatory and oxidative stress in infected victims.

The anti-inflammatory properties of oral, inhaled, and parenteral corticosteroids have shown efficacy. Under the NGTC/ascorbolysis framework, the corticosteroids (hydrophobes) are likely to be of synergistic benefit when administered with lipophilic derivatives of L-ascorbic acid in the pH range of 4-6 (Ohba 1994; Capuzzi 1996; Fan 2004; Miura 2017; Kato 2011; Xiao et al. 2014). Liposomal preparations of L-ascorbic acid and curcumin are likely to also be synergistically efficacious under the NGTC/ascorbolysis framework (Shao 2017). It is conceivable that intracellular ascorbyl phosphate is able to non-enzymatically phosphorylate both serine-40 of KEAP1 (Abed 2015) and serine-276 of NF-kB (Reber 2009), thereby regulating two major transcription pathways, in response to the COVID-19 related oxidative stress, which is likely to be especially profound in patients who might already be suffering from subclinical or marginal scurvy, and often intoxicated with NaF, aluminum salts, and silicofluorides, in an environment which is also replete with EM pollution.



(**a**)

(**b**)

Figure 21. Graphical depictions of potential protein targets for PTMs via reversible ascorbolysis: (**a**) Graphical depiction of NRF2-KEAP1 pathway with NRF2 activation and KEAP1 inhibition reproduced here from Abed 2015 with permission of publisher; (**b**) graphical depiction of the phosphorylation cascade shown to be involved in regulation of the NFκB-MAPK pathway reproduced here from Reber 2009 with permission of publisher. It should be noted that the NGTC/ascorbolysis/UNMR framework, proposes concomitant supramolecular regulation of sirtuin and methylation function, i.e. reversible acetylation and methylation of chromatin proteins via the intermediacy of L-ascorbic acid, the L-ascorbic acid free radical, the 2-O-acetyl-substituted derivative, the 2-O-methyl-substituted derivative, and their photo-oxidatively super-activated radicals, i.e. the2-O-acetyl-L-ascorbic acid free radical and 2-O-methyl-L--ascorbic acid free radical, respectively. See Figures 6c and 6d for proposed structures of the putative free radicals.

According to Abed et al (2015), Keap1-mediated ubiquitination is avoided by phosphorylation of a highly-conserved serine residue (Ser40) in the Keap1 binding domain of Nrf2 (Abed 2015). Thus, at least one kinase is likely required for Nrf2 to dissociate from Keap1. Whereas for the phosphorylation cascade of the NFκB-MAPK pathway multiple kinases are required, whose enzyme pH optima and ATP substrate instability (acid lability), during inflammatory states, suggest the need for intracellular AA-2P. We propose that intracellular AA-2P acts supramolecularly providing the function of many, if not all, "kinases" *non-enzymatically*. AA-2P is proposed to act concomitantly and phase-coherently with putative 2-O-acetyl-L-ascorbic acid and 2-O-methyl-L-ascorbic acid derivatives providing *non-enzymatic* kinase, sirtuin, and methylation functions, respectively (see Figures 6c and 6d presented earlier). Acting in concert, intracellular L-AA, the L-AA free radical, the AA-2P derivative, the putative 2-O-acetyl substituted and 2-O-methyl substituted L-AA derivatives, and their free radicals are proposed to restore genomic stability and rescue from meiotic failure during inflammatory states. In this scenario, endogenous functional group donors, e.g.,ATP, S-adenosyl methionine, and acetyl-coenzyme A would potentially be spared a hydrolytic or oxidative degradative fate during inflammatory and cytoproliferative states. In Figure 8 presented earlier, the first of two propagation steps involves the proposed S_N2 reaction between the L-AA free radical and any of several possible endogenous electrophilic phosphoryl donors, including phosphate monoesters, phosphodiesters, and ATP. NGTC and ascorbolysis provide a plausible biophysical basis for spatio-temporal phase-coherence of PTMs and "cross-talk" between chromatin and histone

proteins (Fischle 2003). Activated spin water (Morré 2011) and Cu^{2+} might provide the rhythm and tempo for the intricately choreographed, ancient molecular "dance", upon which all life depends.

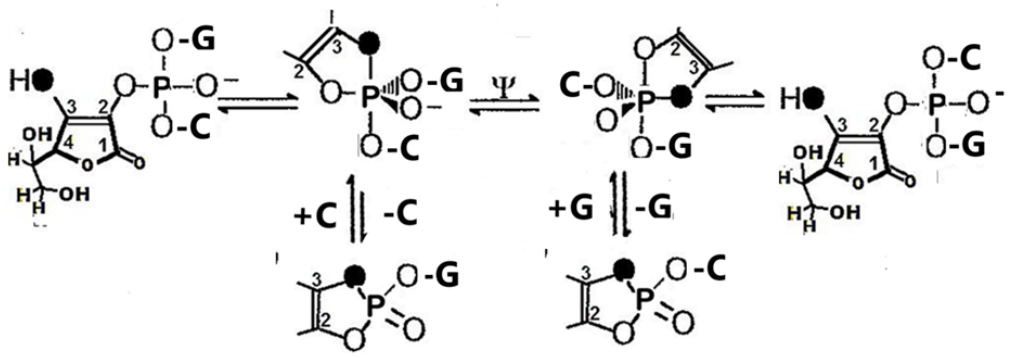


Figure 22. With respect to the current SARS-CoV-2 pandemic, and potential future viral pandemics, we propose that the L-ascorbic acid and Cu2+ in the moderately acidic pH 4-6 range, with added hydrophobes and/or amphiphilic anionic surfactants, may be studied for concomitant supramolecular cleavage of the protein "cloak" (a.k.a. the "corona" or nucleocapsid and spike proteins) and certain motifs in the RNA sequence of the viral pathogen(s), thereby supramolecularly attacking potential vulnerabilities of the protein-"cloaked" moving target represented by the SARS-CoV-2 viral pathogen(s).

To more readily grasp the concepts presented (herein), the proposed reaction schemes (Figures 20 and 22, above) ask the question whether a reversible putative primordial/prebiotic reaction might have existed during early chemical evolution, which is evidenced by the published reports of L-ascorbic acid and Cu^{2+} non-enzymatically cleaving bacteriophage, viral RNA, and viral DNA, *including cleavage of proteins* (Wong 1974; Richter 1982; Chiou 1983, 1984). The proposed mechanistic scheme (above) asks the question whether structural topological motifs (Bon 2008; Gan 2003; Koirala 2019), based either on nucleotide and amino acid sequence, or alternatively based on hydrogen bond cooperativity, might expose viral pathogens to vulnerabilities. Fluctuations in protein folding and polynucleotide folding might expose vulnerabilities of viral pathogens to nucleophilic attack by a the L-ascorbic acid free radical. Experiments can be designed to explore the possibility of L-ascorbic acid promoting health, longevity, and anti-ageing (Furumoto 1998; Zglinicki 2000, 2002; Sebastián et al. 2009), while fluoridesaluminum salts, silicofluorides, and EM pollution, synergistically promote oxidative stress, inflammation, disease, immune scenescence, replicative scenescence, ageing, and death.

It should be noted that chiral intermediates, including the formation of chiral centers at the phosphorus atom of 3'-5'-phosphodiesters of RNA are proposed intermediates in Figure 22 above. In 1980, Jeremy Knowles reviewed the biological phosphates, their enzyme-catalyzed phosphoryl transfer reactions, including the synthesis of phosphate mono-esters and diesters with chirality *at the phosphorus atom* (Knowles 1980). Under the ascorbolysis hypothesis, *Berry* pseudorotation of RNA and DNA polynucleotides is intrinsically "chimeric pseudorotation" (Cass 2006), i.e. pro-chiral at the phosphorus atom of the 3'-5' phosphodiester sites. In ortho/para "spin water", chirality-induced spin selectivity ("CISS" discussed earlier) may be operative in the regiospecificity of postulated RNA cleavage, as well as regulating the chirality and stereo-selectivity of the bio-phosphate intermediates and transition states postulated for editing and error-correcting the genome during inflammatory and cytoproliferative states.

Potential Benefits and Applications of the Ascorbolysis Hypothesis

The ascorbolysis hypothesis provides the basis for (a) a novel "radical theory" of oxidative phosphorylation (Schole 1994), and (b) reversible polynucleotide synthesis (Lichtenthaler 1961). The AA-2P derivative of L-AA, acts as a "slow and continuous" intracellular radical scavenger which generate super-activated high-energy mixed anhydride radicals capable of catalyzing reversible non-enzymatic polynucleotide and protein synthesis within a microenvironment conducive to "intra 1,4 HAT", general acid catalysis, and PCNA. Auto-catalytic radical chain reactions that reversibly generate polynucleotides and regulation of gene expression, are predicted consequences of super-activation of vitamin C. Lipophilic derivatives of AA-2P have been reported. It should be possible to rigorously test this hypothesis, e.g. with the mouse macrophage model of ageing developed by Sebastián et al.(2009). According to their results, the STAT5a phosphorylation defect was secondary to the prior oxidation (hydroxylation) defect, i.e. an "oxygenase defect", *both* of which can, in principle, be corrected concomitantly by increasing intracellular L-AA and L-AA-2P levels. Potential therapeutic synergy with vitamins D3, E, and folic acid should be explored..

The elderly and those suffering from chronic inflammatory and degenerative diseases are especially vulnerable to infections with SARS-CoV2. Generally, the elderly typically experience age-related decline in their natural immune function and antioxidant defense system. In principle, they might be effectively "rescued" by means of increasing their intracellular L-AA and L-AA-2P levels. In aged mice, macrophage-related immune function and telomere length were shown to be impaired by oxidative stress, defective oxidation and phosphorylation of the signaling protein STAT5a (Sebastián et al. 2009).

Telomere length has been shown to be a biomarker for ageing and chronic oxidative stress (Houben 2007; Zglinicki 2000; Zglinicki 2002). Intracellular L-ascorbic acid has been demonstrated to slow telomere-shortening (Furumoto 1998). Under the ascorbolysis framework, telomere length is proposed to likely be regulated by intracellular L-ascorbic acid and its 2-O-phosphate substituted derivatives in a manner that might well involve a mechanism similar to those depicted in Figures 20 and 22 (above), wherein Westheimer's rules (preferences) and the quality of the microenvironment influence where the equilibrium lies, with respect to discrimination between "healthy" genes, e.g. long, properly shaped, functional telomeres, as opposed to "unhealthy" genes, such as that of viral pathogens, e.g. Dengue, Ebola, SARS-CoV-2 sequence-based topologies. Just as proteins are thought to fluctuate between folded and unfolded morphologies, so too are DNA and RNA polynucleotides likely to fluctuate between folded and unfolded morphologies. Assembly of the meiotic spindle apparatus must occur in a tightly choreographed sequence of events which must arguably be coherent withmodeling and remodeling of chromatin and histone proteins. Application of a supramolecular therapeutic approach against the SARS-CoV-2 pathogen is an approach which is diametrically distinct from the linear "magic bullet" approaches adopted by most vaccine strategies, at least that was the historical pproach by vaccines against infectious pathogens.

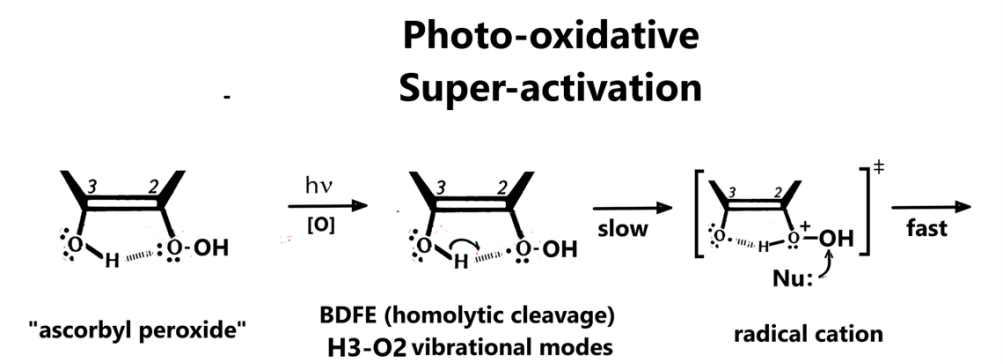


Figure 23. Proposed "Ascorbyl Peroxide" hydroxylation Factor, for provision of non-enzymatic mono-oxygenase function within inflammatory tissue microenvironments.

In any event, the global SARS-CoV-2 pandemic provides the impetus to be pro-active. At such a time, the NGTC and ascorbolysis hypotheses may suggest ways to develop the much needed re-direct for a unified theory of synergistic environmental toxicology in general, and for the known experimental effects of aluminum, fluoride, and EM pollution. It is time for serious and intensive hypothesis generation, testing, and for critical re-evaluation of much of the longstanding conventional wisdom about disease conditions, their causes, and effective treatments.

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