

Relationship of Organic Acids to Reactive Oxygen Species and Oxidative Stress in Biochemistry and Drug Action

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Abstract

This report deals with involvement of organic acids, such as acetic, citric and lactic, in biochemistry and drug actions. In certain cases, there is participation in physiological action of electron transfer, reactive oxygen species and oxidative stress. Electron transfer agents include quinones, metals, ArNO_2 and imines. Acids play important roles in transamination, electron transfer processes and antibiotic action. Much attention has been devoted to vinegar (acetic acid) as a condiment with health benefits.

Keywords: Organic acids; Reactive oxygen; Bioaction

Abbreviations: ET: Electron Transfer; ROS: Reactive Oxygen Species; OS: Oxidative Stress; FAD: Flavin Adenine Dinucleotide

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Mini Review

There are reports on involvement of organic acids in the action of drugs and biochemistry. However, there is rare discussion concerning the mode of action. This commentary provides evidence for the mechanistic role involving electron transfer (ET), reactive oxygen species (ROS), and oxidative stress (OS). Common ET agents are quinones, metal compounds, aromatic nitro compounds, and imines. Superoxide, generated via ET as illustrated in **Figure 1**, then serves as a precursor of other ROS.

One example of imine-iminium ET agents involves protonation by acid of physiologically active conjugated imine species [1] (**Figure 2**).

There is increasing support for involvement of ET-ROS-OS in the mode of action entailing ET by iminium which is more active [1]. pK values are favorable for a number of bioacids, namely, citric (3.13), succinic (4.21) and acetic (4.76) [2]. The pK value involves the extent of dissociation from the required proton. The higher the dissociation, the greater the acidity. Participation of ET-ROS-OS imines represents a novel application for organic acids.

Acids are known to play important roles in various chemical processes, some of which may involve ET-ROS, whereas others may not. Transamination comprises conversion of the amine group in an amino acid to the corresponding keto acid [2]. The

protonated imine (Schiff base) represents the first case of ET-ROS involvement in transamination (**Figure 3**).

Glutathione reductase incorporates an ET prosthetic group Flavin adenine dinucleotide (FAD) which is a conjugated diminium type protonation of FAD, followed by electron uptake, yields FADH radical. The overall process comprises addition of the H (**Figure 4**).

Involvement of acids with other ET agents is illustrated for quinones in **Figure 5** and for aromatic nitro compounds in **Figure 6**.

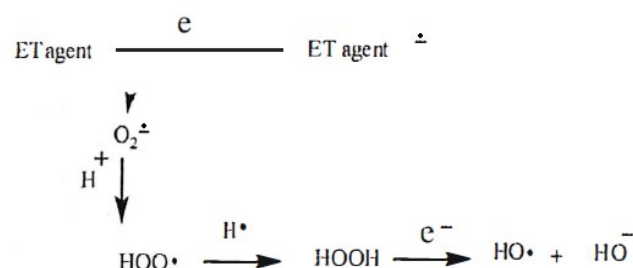


Figure 1 Superoxide via ET.

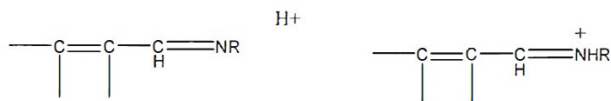


Figure 2 Imine protonation to iminium.

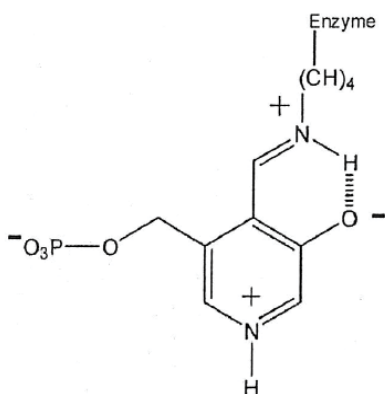


Figure 3 Protonated imine.

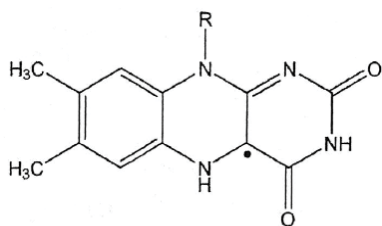


Figure 4 FADH.

A highly relevant article deals with organic acids as antibiotics [3]. The acids most involved are acetic (vinegar), citric, propionic, succinic, tartaric, malic and lactic. There is detailed discussion of mechanistic aspects. The acids are believed to function as

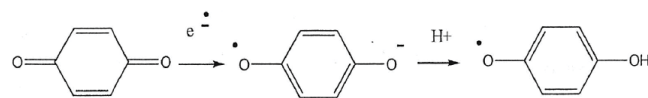


Figure 5 Quinone reduction and protonation.

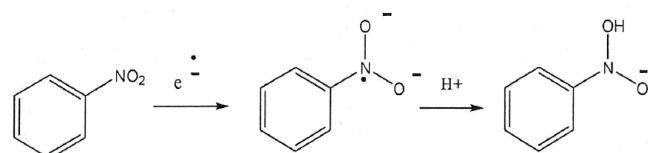


Figure 6 Reduction and protonation of ArNO_2 .

antimicrobials by two modes of action. There is cytoplasmic acidification followed by uncoupling of energy generation and regulation, and build-up of the acid arises with resultant toxicity.

The cells of the bacteria react by attempting to expel the protons. An alternate to the theoretical aspects was advanced proposing uncoupling of electron transport involving oxidative respiration. Both theories provide satisfactory rationale for mode of action. The one involving electron transfer is somewhat similar to the ET-ROS-OS approach, which has previously been broadly applied as a mode of action for anti-infective agents. In addition, ET-OS mechanisms may contribute to the biological effects of various antibiotic classes, including the inhibition of enzymes and metabolic processes [4]. The respiration aspect and energy uncoupling are related to mitochondria.

There is discussion of means of bacterial resistance to acids involving different signals to induce the synthesis of acid shock proteins among internal and external pH [5]. A number of related articles are available [6,7]. The role of acids and ET-ROS-OS in antibiotics represents a new finding.

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