CHAPTER 5

Redox Potential

INTRODUCTION

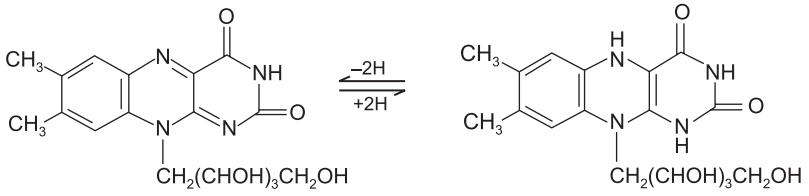
Redox potential may be defined as a quantitative expression of the tendency of a compound that has to give or receive electrons. It may be compared with an acid–base reaction. In the case of acid–base reaction, there is transfer of a proton from an atom in one molecule to the atom in another molecule, while in the case of oxidation–reduction reaction, there is an electron transfer. Since living organisms function at an optimum redox potential range, which varies with the organism, it might be assumed that the redox potential of the compounds of a certain type would correlate with the observed biological effect. This correlation is applicable for all compounds of similar structure and physical properties.

The redox potential of a system may be calculated from the following equation: $E_h = E_1^0 - 0.06/n$ (concentration of reductant/concentration of oxidant), where

E_h = Redox potential of the system being studied
E_1^0 = Standard potential at given pH
n = Number of electrons transferred

However, there are a number of reasons why only a few satisfactory correlations have been observed:

- The redox potential applies to a single reversible ionic equilibrium, which does not exist in a living system.
- A living cell carries on many reactions simultaneously involving oxidation of ionic and non-ionic character, some of which are reversible and others are irreversible.
- The access of a drug to the sites of oxidation–reduction reactions in the intact animal is hindered by the complex competing events occur during absorption, distribution, metabolism, and excretion.

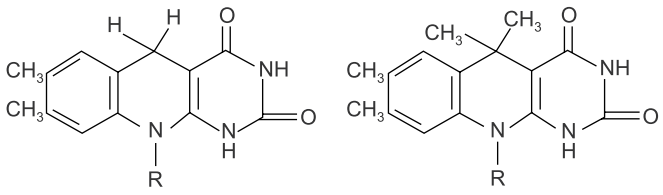


Riboflavin (**I**) Dihydroriboflavin (**II**)

- Therefore, it is to be expected that correlations between redox potential and biological activity, generally, hold only for compounds of very similar structure and physical properties. In such series, variations in the route of distribution and in steric factors, which might modify the redox system interaction, would be minimized.

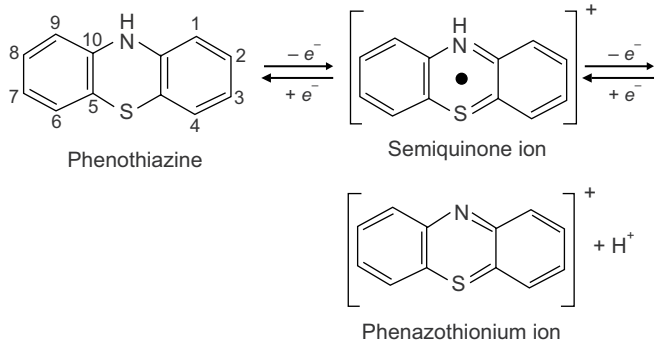
When riboflavin (I) accepts electrons, it is converted into its dihydro (II) form. This reaction has a redox potential E_0 = –0.185 volt. Kuhn (1943) prepared the analogue in which the two methyl groups of riboflavin were replaced by chlorine. The resulting compound had a potential of E_0 = –0.095 volt, and its antagonistic properties were suggested as being due to the dichloro-dihydro form being a weaker reducing agent than the dihydro form of riboflavin. It may be absorbed at the specific receptor site, but may not have a negative potential to carry out the biological reductions of riboflavin.

Reist *et al.* (1960) prepared the non-redox analogues of riboflavin as potential anticancer agents. Replacement of the N_5-nitrogen of dihydroriboflavin (1,5-dihydro-7,8-dimethyl-10-ribitylisoalloxazine) by a methylene group (III) would be expected to have a profound effect on the redox potential as compared to riboflavin. Similarly, replacement of the N_5-nitrogen of dihydroriboflavin by an isopropylidene group (IV) fixes the molecule in the dihydro form, thus eliminating the redox system completely.



Although compound IV is derived from dihydroriboflavin (II) rather than from riboflavin, the redox enzyme system employing riboflavin coenzymes utilizes both the oxidized and reduced forms; thus, analogues of either I or II should be effective antagonists.

Craig *et al.* (1960) studied a series of substituted phenothiazine with regard to potentiometric titration, electrode potentials, and their correlation with anthelmintic activity. They measured them in the biological assay using mixed infestation of *Syphacia obvelata* and *Aspicularis tetraptera* in mice. From these studies, it appeared that two factors were necessary for their activity, namely, the ability to form a high proportion of a stable semiquinone radical (as measured by the index potential in aqueous CH_3COOH) and the presence of free 3 or 7 position.



In addition to the two factors mentioned above, Craig *et al.* (1960) also noted that only these compounds with electrode potential in the range of 550–850 mV in aqueous CH_3COOH had significant activity. If the toxic or paralyzing effect of the phenothiazines was due to an inhibition by the semiquinone of the oxidation–reduction system in the parasite, it would seem reasonable that active phenothiazines would

have reduction potentials corresponding to those of oxidation–reduction enzyme system or the system which they inhibit. At similar potentials, the semiquinone concentration would be maximal, and thus facilitates or competes with the electron transfers in the enzyme system involved.

For example, it has been suggested that the semiquinone of chlorpromazine is responsible for the inhibition of certain oxidoreductase *in vitro* and some of the biological activities of phenothiazines correlate with the formation of their semiquinones *in vivo*.