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Redox Reactions of Quercetin and Quercetin-5'-sulfonic Acid with Fe^{3+} and Cu^{2+} Ions and with H_2O_2

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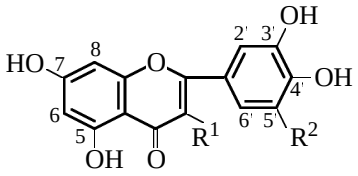
Abstract — Redox reactions of quercetin and quercetin-5'-sulfonic acid with Fe^{3+} and Cu^{2+} ions and with H_2O_2 were studied spectrophotometrically. Oxidation of the flavonoids occurs at the 3-OH and 4-OH groups. The redox reactions are largely influenced by pH. With Fe^{3+} ions, oxidation occurs in strongly acidic (pH 1–2), and with Cu^{2+} ions, in weakly acidic (pH 4–5) solutions. Oxidation of quercetin and quercetin-5'-sulfonic acid with Fe^{3+} and Cu^{2+} ions is accompanied by complexation. Hydrogen peroxide oxidizes the flavonoids at pH 1–3.5, and at pH > 4 oxidation is insignificant.

Flavonoids, especially polyhydroxyflavones, are natural antioxidants. The high biological activity of flavonoids is due to their capability for redox reactions and to complexation with metal ions. Flavonoids scavenge $OH^{\cdot}$ radicals and superoxide (O_2^-) anions; they also reduce some metal cations to lower oxidation states [1, 2].

The redox properties of flavonoids largely depend on the number and position of hydroxy groups in the molecule [3, 4]. Kopacz and Novak [5] showed that Fe^{3+} ions oxidize quercetin, quercetin-5'-sulfonic acid, and kaempferol at the 3-OH and 4'-OH groups to the quinone. In this work we determined the time required to attain the redox equilibrium and studied the influence of temperature on the reaction rate. We also studied the reactions of quercetin and quercetin-5'-sulfonic acid with Cu^{2+} ions and (for comparison) of quercetin, quercetin-5'-sulfonic acid, and rutin with H_2O_2. We determined the rate of the redox reaction of quercetin-5'-sulfonic acid with H_2O_2 in aqueous solutions. As metal cations we chose Fe^{3+} and Cu^{2+} playing an enormous role in biological processes in human and animal bodies. Biological oxidation processes are in many cases similar to oxidation reactions performed in a laboratory without enzymes. Enzymatic systems effecting oxidation usually contain transition metal ions. We studied the redox reactions with the metal ions at metal-to-flavonoid molar ratios of 1 : 1 and 1 : 2 and a constant ionic strength of 0.1. Experiments were performed in 50% methanol solutions, and in the case of the reaction of quercetin-5'-sulfonic acid with H_2O_2, in aqueous solutions, since quercetin-5'-sulfonic acid is readily soluble in water.

The structures of the flavonoids are shown below.



R^1 = OH; R^2 = H (quercetin), SO_3H (quercetin-5'-sulfonic acid).

The reactions of the flavonoids with metal cations involve two competing pathways: complexation and redox reaction. With Fe^{3+} at pH 1–3, the redox transformations of quercetin and quercetin-5'-sulfonic acid prevail. In these systems, the solutions decolorized, and the absorption maxima at 369 and 254 nm for quercetin, or at 366 and 256 nm for quercetin-5'-sulfonic acid decreased in intensity. However, a new band at 298 nm simultaneously appeared and grew in intensity (Fig. 1). At pH 4–6, the solution color did not fully disappear and only became weaker, and a bronze precipitate formed. All the solutions at pH 1–6 contained Fe^{2+} ions; their content grew as the solution acidity increased (Fig. 2). This indicates that quercetin and quercetin-5'-sulfonic acid are readily oxidized at low pH. At higher pH, complexation of Fe^{3+} ions occurs first and is followed by the redox reaction. The redox equilibrium at room temperature is attained very slowly (in two weeks).

In solutions containing Cu^{2+} ions and quercetin or quercetin-5'-sulfonic acid, at pH 1–3, there is virtually no redox reaction (insignificant changes in the absorption spectra), whereas at pH 3.5–6 complexation occurs, as indicated by a shift of the long-wave bands

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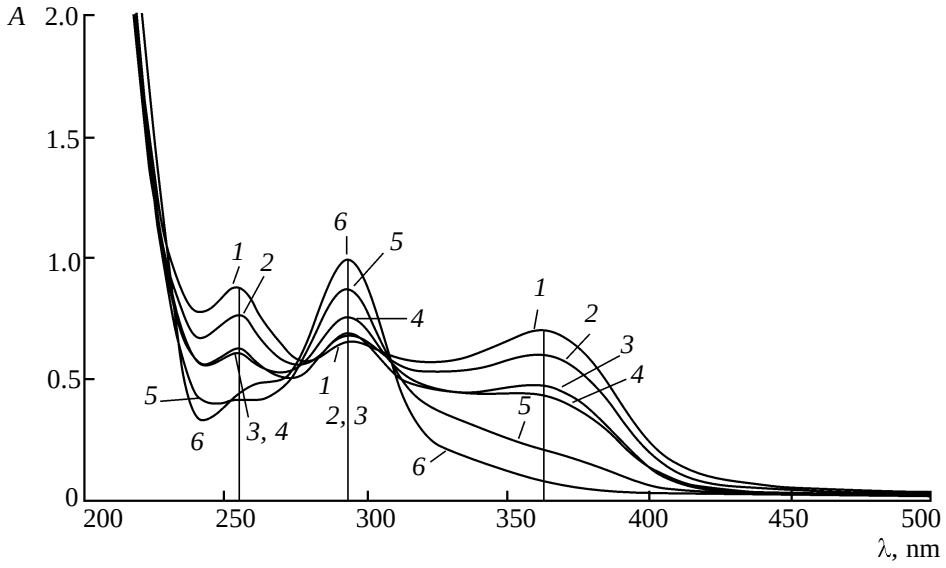


Fig. 1. Electronic absorption spectra of aqueous solutions of quercetin-5'-sulfonic acid, containing Fe(III). Time after mixing, h: (*1*) 1, (*2*) 24, (*3*) 120, (*4*) 168, (*5*) 336, and (*6*) 504; $c_M : c_L = 2 : 1$; pH 5.

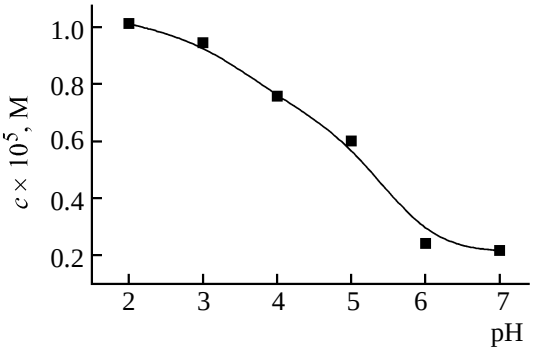


Fig. 2. pH dependence of the Fe(II) concentration ($c_M : c_L = 2 : 1$).

of quercetin (369 nm) and quercetin-5'-sulfonic acid (366 nm) to 425 nm. The coordinated ligand is subsequently oxidized to quinone (Fig. 3), the intensity of absorption bands of the complex decreases, and a new band of the oxidized flavonoid appears at 298 nm and grows in intensity. At the metal-to-ligand molar ratio 2 : 1, oxidation occurs more readily than at 1 : 1; the oxidation products are quinone and Cu^+ ions. The redox equilibrium at room temperature is attained slowly (in 3 weeks).

With 6% H_2O_2 as oxidant, quercetin and quercetin-5'-sulfonic acid are oxidized similarly to the reactions with the metal ions. Quercetin-5'-sulfonic acid in aqueous solution in completely oxidized in 24 h, after which the oxidized form decomposes. The redox reaction accelerates with temperature, with the equilibrium attained at 80°C. The Lambert–Beer law for aqueous solutions of quercetin-5'-sulfonic acid with H_2O_2 (after heating to 80°C and cooling to room temperature) is obeyed at the quercetin-5'-sulfonic acid concentration ranging from 2×10^{-5} to 7×10^{-5} M.

In this concentration range, the kinetics of the redox reaction of quercetin-5'-sulfonic acid with H_2O_2 can be monitored spectrophotometrically [6, 7]. For this purpose, five drops of 6% H_2O_2 were added to a 5×10^{-5} M aqueous solution of quercetin-5'-sulfonic acid with pH 2, and the absorption of λ 298 nm was monitored in time at room temperature. The rate constant of the redox reaction was determined from Eq. (2).

$$B + C \longrightarrow D, \quad (1)$$

$$-\frac{d[B]}{dt} = \frac{[dA]}{dt}\left(\frac{[B]_0 - [B]}{A_\infty - A_0}\right). \quad (2)$$

Here A is absorption; t, time; $[B_0]$ and [B], initial and final concentrations of quercetin-5'-sulfonic acid, respectively; A_0, initial absorption; and A_∞, final absorption.

The calculated rate constant of the redox reaction is 2.5×10^{-9} mol l^{-1} s^{-1}, i.e., the reaction is slow.

In the spectra of reaction mixtures of rutin with H_2O_2 in 50% methanol and in aqueous solution at pH 2, virtually no changes were observed in 2 weeks. This means that rutin in which the 3-OH group is

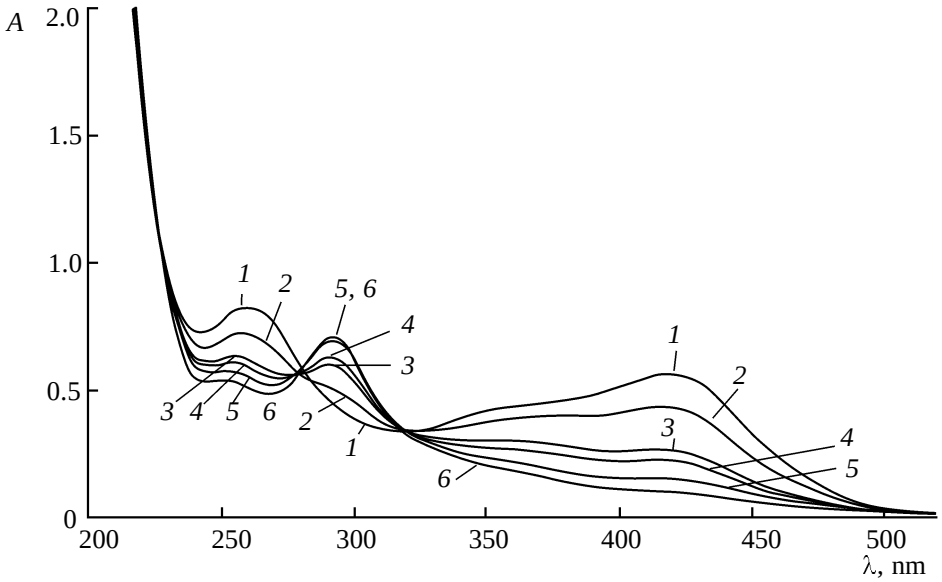
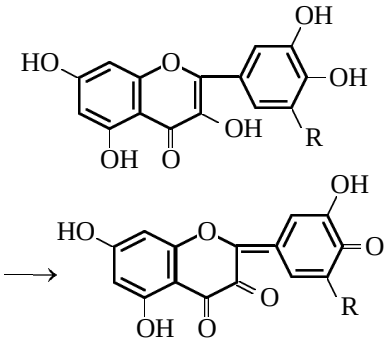


Fig. 3. Electronic absorption spectra of aqueous solutions of quercetin-5'-sulfonic acid, containing Cu(II). Time after mixing, h: (*1*) 1, (*2*) 24, (*3*) 120, (*4*) 168, (*5*) 336, and (*6*) 504; $c_M : c_L = 2 : 1$; pH 5.

blocked by a carbohydrate moiety is not oxidized under these conditions. This fact, in turn, suggests that oxidation of quercetin and quercetin-5'-sulfonic acid in acidic solutions occurs at the 3-OH and 4-OH groups, yielding a quinone:



R = H (quercetin), SO_3H (quercetin-5'-sulfonic acid).

The reaction mechanism is difficult to determine unambiguously; it may be ionic or radical. The complexation occurring in solutions with metal ions additionally complicates the redox reactions. It should be noted, however, that both with the cations (Fe^{3+}, Cu^{2+}) and with H_2O_2 a single oxidized form of the flavonoid is formed, with a strong absorption maximum at about 298 nm.

EXPERIMENTAL

Quercetin was purchased from Chemapol, and rutin, from Koch–Licht. Quercetin-5'-sulfonic acid was prepared as described in [8]. Two series of 50% methanol solutions of $Fe(NO_3)_3$ with quercetin and quercetin-5'-sulfonic acid were prepared. The $Fe(NO_3)_3$ concentration was 4.5×10^{-5} and 8×10^{-5} M. The absorption spectra were recorded at various pH values, reaction times, and temperatures (20–80°C) on a Specord UV-Vis spectrophotometer in the range 200–700 nm. The ionic strength was 0.1; it was adjusted with 1 M $NaClO_4$. The pH was adjusted with 0.1 M $HClO_4$ and NaOH.

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