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Kinetics and Mechanism of the Oxygenation of Potassium Flavonolate. Evidence for an Electron Transfer Mechanism

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The oxygenation of the potassium salt of flavonol (flaH) in absolute DMF leads to potassium *O*-benzoylsalicylate and carbon monoxide in 95% yield at 40 °C. Kinetic measurements resulted in the rate law $-d[flaK]/dt = k_2[flaK][O_2]$. The rate constant, activation enthalpy, and entropy at 313.16 K are as follows: $k_2/M^{-1} s^{-1} = (3.28 \pm 0.10) \times 10^{-1}$, $\Delta H^{\ddagger}/kJ\ mol^{-1} = 29 \pm 2$, $\Delta S^{\ddagger}/J\ mol^{-1}\ K^{-1} = -161 \pm 6$. The reaction fits a Hammett linear free energy relationship for 4′-substituted flavonols, and electron-releasing groups make the oxygenation reaction faster. The anodic oxidation wave potentials E^a of the 4′-substituted flavonolates correlate well with reaction rates. At more negative E^a values faster reaction rates were observed. EPR spectrum of the reaction mixture ($g = 2.0038$, $dH = 1.8$ G, $a_H = 0.9$ G) showed the presence of flavonoxyl radical as a result of a SET from the flavonolate to dioxygen.

Introduction

Biological oxygenation of natural substances by oxygenases are an important part of metabolic processes.[1-8] The structure and mechanism of many of these enzymes are still obscure, and only model reactions serve with some guidance so far as their chemistry is concerned.[9,10] The oxygenation of quercetin (**1a**) and 3-hydroxyflavones (flavonols, flaH, **1b**) catalyzed by quercetin 2,3-dioxygenase leads to oxidative cleavage of the heterocyclic ring to give the corresponding depsides (**2**) and carbon monoxide (Scheme 1).[11-19] Since it is a copper-containing

Scheme 1

a; R = OH
b; R = H
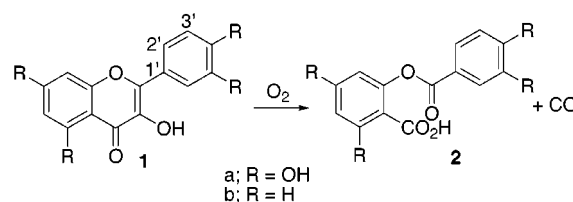
metalloenzyme, metal complexes with copper[20-30] and cobalt[31-34] have been used in model reactions. Autoxidation reactions of 3-hydroxyflavones in protic[35] and aprotic[36] solvents also resulted in enzyme-like products, and some efforts have also been made to elucidate the mechanism of the reaction. However, no kinetic studies

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were carried out. Attempts to detect or isolate intermediates of the oxygenation reaction have failed. We report here kinetic studies on the oxygenation of potassium flavonolates in DMF and EPR investigations on possible intermediates during the reaction.

Results and Discussion

Oxygenation of Potassium Flavonolate and EPR Studies. The potassium salts of flavonol and 4′-substituted flavonols (**3b**−**f**) were prepared in THF by reacting metallic potassium with the flavonols (**1**). The salts were characterized by elemental analysis, IR spectra, and UV−vis spectroscopy. In the salts, the C=O stretching frequencies[37] shift to lower wavenumbers by around 50 cm^{-1}, and the $\pi - \pi^*$ transition of the heterocyclic ring[38] undergoes bathochromic shifts up to 125 nm. The data are listed in the Experimental Section. Bulk oxygenation of the potassium salt of flavonol (**3b**) in DMF at 50 °C resulted in the formation of the potassium salt of the depside *O*-benzoylsalicylate (**4b**) in 76% yield. The formation of **4b** from **3b** requires dioxygen, which was measured by volumetry (no apparent dioxygen uptake was observed, because the absorption of oxygen and the liberation of carbon monoxide compensate each other). The GC analysis of the gas phase showed 0.87 mmol of CO (87%) evolved/1 mmol **3b**.
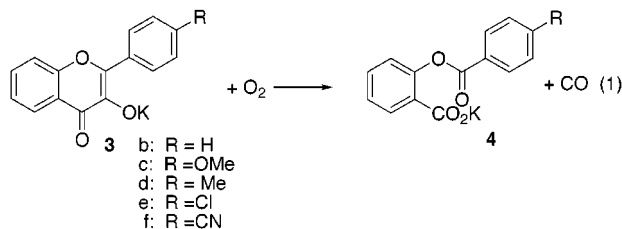
In DMF, the intense red color of the solution of **3b** turns to intense green on coming into contact with dioxygen. The UV−vis spectrum of the solution changes and a new intense band arises at 676 nm. This absorption has been assigned to the flavonoxy radical[39–42] formed in a single electron transfer from the flavonolate anion to dioxygen with the concomitant formation of superoxide anion.[43] The presence of the flavonoxy radical could also be confirmed by EPR spectroscopy. A weak EPR signal appeared in the solution of the flavonolate exposing to dioxygen at $g = 2.0038$, line broadness dH = 1.8 G, and coupling parameter of $a_H = 0.9$ G (Figure 1).

Kinetic Measurements. The kinetic measurements on the oxygenation of potassium flavonolate (flaK) were followed by UV−vis spectroscopy at 465.5 nm at constant dioxygen pressure under pseudo-first-order conditions.[44] A typical concentration time profile can be seen in Figure 2, indicating that the reaction order with respect to the
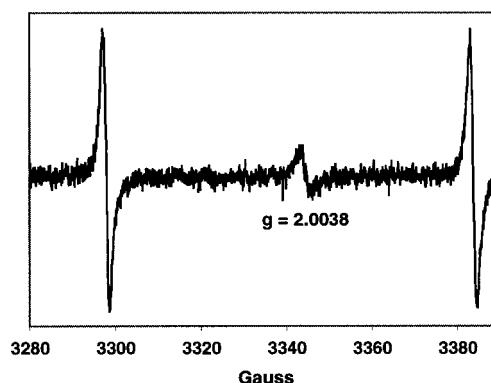
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Figure 1. EPR spectrum of a DMF solution of flaK after exposure to dioxygen (the two intense signals are from the Mn(II) standard).
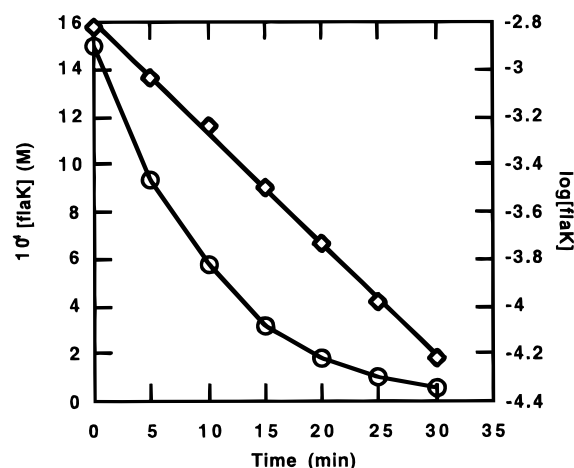
Figure 2. Time course of the oxygenation of potassium flavonolate.

substrate flaK is one. This could be also confirmed by the straight line obtained by plotting the reaction rate against the initial flaK concentration (Supporting Information, SFigure 1). The first-order dependence of the reaction rate on the dioxygen concentration was established by plotting the reaction rate against the O_2 concentration (Supporting Information, SFigure 2). On that basis, the rate equation is as follows (2):

$$\text{reaction rate} = k_2[\text{flaK}]\,[O_2] \qquad (2)$$

The rate constant at 313.16 K was found to be $k_2 = (3.28 \pm 0.10) \times 10^{-1}$ M^{-1} s^{-1} (Supporting Information, STable 1). From the temperature dependence of the reaction rates (Supporting Information, SFigure 3), the activation parameters $\Delta H^{\ddagger} = 29 \pm 2$ kJ mol^{-1}, $\Delta S^{\ddagger} = -161 \pm 6$ J mol^{-1} K^{-1} could be calculated. Addition of tetrabutylammonium perchlorate to flavonol (**1b**) in an equimolar amount accelerated the reaction rate by one-third ($k_2 = 5.18 \pm 0.16) \times 10^{-1}$ M^{-1} s^{-1}) due to onium catalysis of better ion separation.[45]

The influence of the 4′-substituted groups on the reaction rate of the oxygenation showed a linear Hammett plot with a reaction constant of $\rho = -0.73$ (Figure 3; Supporting Information, STable 2), indicating that electron-releasing groups result in enhanced reactions rates.

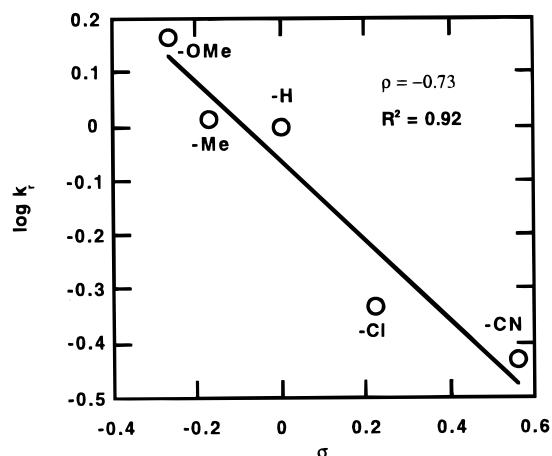(45) Starks, C. M.; Liotta, C. *Phase Transfer Catalysis*; Academic Press: New York, 1978; p 29.

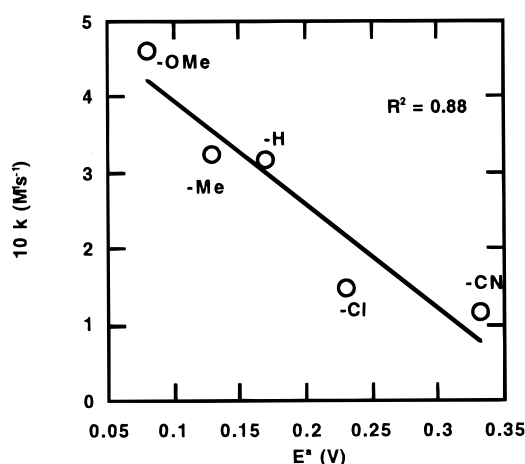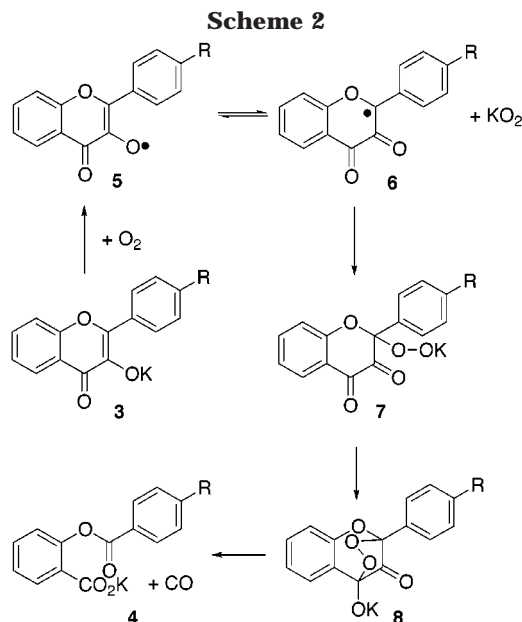**Figure 3.** Hammett plot of the oxygenation of potassium flavonolate.

Figure 4. Reaction rate vs anodic oxidation potentials profile of various 4′-substituted potassium flavonolates.

Scheme 2

The electrochemistry of the potassium flavonolates (**3b**−**f**) in DMF showed irreversible anodic oxidation waves (Supporting Information, SFigures 4−8). The data shown in SFigures 4-8 (Supporting Information) and compiled in STable 3 (Supporting Information) make clear that flavonolates with electron-releasing groups have a more negative anodic electron potential. The irreversibility of the redox peaks is due to the relatively unstable flavonoxy radical.[33] The linear correlation between the anodic oxidation potential and the reaction rate supports that a higher electron density on the flavonolate makes the electron transfer easier (Figure 4). The kinetic and the EPR data on the oxygenation reactions of the potassium salts of flavonolates show similar features as those of phenolates[46] and carbanions.[47] Since the reducing power of these anions is high and a direct electron-transfer results in radicals, from which the phenoxy radicals show a relative good stability while those formed from carbanions and flavonolates are less so. Despite the fact that the first electron reduction of dioxygen to superoxide ion is unfavorable ($E° = -0.62$ V vs NHE in DMF),[48] the reduction potentials of phenolates,[49] carban-

ions,[50] and flavonolates are more negative than that of O_2. The stability of the intermediate radicals depends on their delocalization of the unpaired electron. Due to that, the phenoxy radicals exhibit higher stability, while the stability of the flavonoxy radicals is low. The stability depends also on the solvents, and DMF was found to be the most appropriate one. The weak signal shows only a poor hyperfine structure due to either one or three equivalent hydrogen atoms. From the data, it can be concluded that it is not to assign to superoxide,[51] and it is not a carbon-centered radical[52] (the g value is higher than 2.003). We assume a structure where the unpaired electron resides mostly on the oxygen and to a less extent on the carbon atoms.

The second-order rate expression suggests that the rate-determining step is the reaction between the flavonolate ion and dioxygen. In the first step, the flavonoxy radical and superoxide ion are formed. The reaction is entropy driven, and the Hammett plot shows that a higher electron density on the flavonolate ion leads to faster reaction rates. This is also valid for the redox properties of the flavonolates; electron-releasing groups in the 4′-position increase the negative electrode potential of the flavonolates, which may be correlated with their participating HOMO orbitals in a similar manner as found by the catechols.[54] The linear correlation between the anodic wave of the CV spectra and the reaction rates of the various 4′-substituted flavonolates are a good proof for that. All the consecutive reactions of the flavonoxy radical and superoxide ion are shown in Scheme 2. In a radical−radical coupling reaction, the flavonoxy radical and the superoxide ion react with the deprotonated peroxidic species **7**. This undergoes then an intramolecular nucleophilic attack at the 4-C=O position to give the

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endoperoxide **8**, which after fast decomposition and release of carbon monoxide results in *O*-benzoylsalicylate (**4**). All attempts to isolate or detect the endoperoxide **8** failed, suggesting that this type of endoperoxides (**8**) is very unstable if compared to other endoperoxides[54] where the elimination of CO is not easily feasible. In the case of **8**, the homolytic cleavage of the O—O bond and simultaneous elimination of CO seems to be very facile. Until now, no endoperoxides of this general stucture (**9**) could be isolated or characterized.
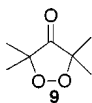
From the results obtained, the conclusion may be drawn that the oxygenolysis of the flavonolate ion in aprotic solvents has a single electron transfer (SET) mechanism[55] and it obeys the second-order rate equation followed by a fast radical—radical coupling reaction of the flavonoxy radical and superoxide ion to give a deprotonated hydroperoxide species, which after an intramolecular A_N reaction on 4C=O leads to an unstable endoperoxide of the structure **8**, and its decomposition results then in the *O*-benzoylsalicylate and carbon monoxide. Further work is in progress to isolate endoperoxides of the type **9** for studies of their thermal decomposition in order to understand the chemistry of this unusual reaction.

Experimental Section

Materials and Methods. All manipulations were performed under a pure dinitrogen or argon atmosphere unless otherwise stated using standard Schlenk-type inert gas techniques.[56] Solvents used for the reactions were purified by literature methods[57] and stored under argon. 3-Hydroxyflavone,[35] 3-hydroxy-4′-methoxyflavone,[58] 3-hydroxy-4′-methylflavone,[58] 3-hydroxy-4′-chloroflavone,[58] and 3-hydroxy-4′-cyanoflavone[58] were prepared according to literature methods. Diazomethane was freshly prepared according to the literature in ether and immediately used for the methylation reactions.[59]

Potassium Flavonolate (flaK, 3b). Potassium (0.195 g, 5 mmol) and flavonol (1.119 g, 5 mmol) in anhydrous tetrahydrofuran (50 mL) were stirred under argon for 5 h until dihydrogen evolution ceased. The orange-colored precipitate was filtered, washed with ether, and dried in a vacuum to give the potassium flavonolate (**3b**) (1.24, 90%): mp 229—32 °C; IR (KBr) 1592, 1556 cm^{-1}; UV—vis (DMF) (λ_{max}, log ϵ) 465.5 (4.186), 293.5 (2.995), 261.0 (3.061), 240.0 (3.111). Anal. Calcd for $C_{15}H_9O_3K$: C, 65.45; H, 3.27. Found C, 65.78; H, 2.98.

The other 4′-substituted flavonolate salts of potassium were prepared in an identical manner. **4′-OMe-flaK (3c)** (1.38 g, 90%): mp 210—13 °C; IR (KBr) 3214, 2837, 1593, 1565 cm^{-1}; UV—vis (DMF) (λ_{max}, log ϵ) 464.5 (4.082), 302.0 (3.964), 264.0 (4.089), 240.0 (3.111). Anal. Calcd for $C_{16}H_{11}O_4K$: C, 62.73; H, 3.62. Found: C, 63.12; H, 3.59. **4′-Me-flaK (3d)** (1.24 g, 85%): mp 208—210 °C; IR (KBr) 2866, 1593, 1567 cm^{-1}; UV—vis (DMF) (λ_{max}, log ϵ) 464.5 (4.085), 297.3 (3.951), 263.0 (4.019). Anal. Calcd for $C_{16}H_{11}O_3K$: C, 66.19, H, 3.82. Found: C, 65.83, H, 3.52. **4′Cl-flaK (3e)** (1.24 g, 80%): mp 214—18

°C; IR (KBr) 1593, 1567 cm^{-1}; UV—vis (DMF) (λ_{max}, log ϵ) 464.5 (4.003), 292.5 (3.845), 265.0 (3.952). Anal. Calcd for $C_{15}H_8$-ClO_3K: C, 57.97; H, 2.59. Found: C, 57.32; H, 2.28. **4′-CN-flaK (3f)** (1.13 g, 75%): mp 218—22 °C; IR (KBr) 2225, 1596, 1573 cm^{-1}; UV—vis (DMF) (λ_{max}, log ϵ) 486.5 (3.811), 296.0 (3.636), 267 (3.834). Anal. Calcd for $C_{16}H_8NO_3K$: C, 63.77; H, 2.68; N, 4.65. Found: C, 63.32; H, 2.78; N, 4.25.

Oxygenation of Potassium Flavonolate (3b). FlaK (0.476 g, 2 mmol) in DMF (10 mL) was treated with dioxygen (0.1 MPa) at 50 °C for 8 h, yielding a green solution. The mixture was poured into ice-cooled dilute hydrochloric acid and extracted with ether. Unchanged **1b** was precipitated (0.11 g, 23%). After removal of **1b**, the extract was dried (Na_2SO_4) and evaporated to give **2b** as crystals (0.37 g, 76%): mp 131—33 °C; IR (Nujol) 1739, 1700 cm^{-1}; The GC—MS analysis of **2b**, after treatment with etheral diazomethane, shows the presence of *O*-benzoylsalicylic acid methyl ester: GC—MS *m/z* 256 (M$^+$, 3), 225 (1), 105 (100). The GC analysis of the gas phase shows the presence of 1.73 mmol of CO (87%).

The other 4′-substituted flavonolate salts of potassium were reacted in an identical manner. **2c** (0.49 g, 90%): mp 141—143 °C; IR (Nujol) 3216, 2835, 1740, 1695 cm^{-1}; GC—MS *m/z* 286 (M$^+$, 4), 255 (1), 135 (100). **2d** (0.44 g, 85%): mp 134—137 °C; IR (Nujol) 2864, 1737, 1684 cm^{-1}; GC—MS *m/z* 270 (M$^+$, 5), 239 (2), 119 (100). **2e** (0.33 g, 60%): mp 123—125 °C; IR (Nujol) 1743, 1687 cm^{-1}; GC—MS *m/z* 290 (M$^+$, 8), 259 (4), 139 (100). **2f** (0.16 g, 30%): mp 118—122 °C; IR (Nujol) 2227, 1720, 1707 cm^{-1}; GC—MS *m/z* 281 (M$^+$, 11), 208 (6), 139 (100).

Instrumentation. Infrared spectra and electronic spectra were recorded as λ_{max} (cm^{-1} and nm, respectively). GC analyses were performed with a flame-ionization and TCD detector with a CP SIL 8CB and molecular sieve 5A column. GC—MS measurements were recorded at 75 eV. CV measurements were carried out with a Pt working electrode in DMF solution at room temperature with ca. 10^{-3} M solutions, NBu$_4$ClO$_4$ as supporting electrolyte, and scan rate 100 mV s^{-1}. The potential values are relative to the NHE using an Ag/AgCl reference electrode. Microanalyses were carried out by Microanalytical Service of the University of Veszprém.

Kinetic Measurements. Reactions of flaK with O$_2$ were performed in DMF solutions. In a typical experiment, flaK was dissolved under argon atmosphere in a thermostated reaction vessel with an inlet for taking samples with a syringe and connected to a mercury manometer to regulate constant pressure. The solution was then heated to the appropriate temperature. A sample was then taken by syringe, and the initial concentration of flaK was determined by UV—vis spectroscopy measuring the absorbance of the reaction mixture at 465.5 nm (log ϵ = 4.186) [λ_{max} of a typical band of flaK]. The argon was then replaced with dioxygen, and the consumption of flaK was analyzed periodically (ca. every 5 min). Experimental conditions are summarized in STable 1 (Supporting Information). The temperature was determined with an accuracy of ±0.5 °C; the concentrations of KFla were measured with a relative mean error of ca. ±2%; the pressure of dioxygen was determined with an accuracy of ±0.5%. The O$_2$ concentration was calculated from literature data[60] taking into account the partial pressure of DMF[61] and assuming the validity of Dalton's law.

Supporting Information Available: Kinetic diagrams, cyclic voltammograms, and tables of kinetic data and anodic potentials for **3b**—**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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