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DOI: 10.1039/C8DT03519A

Journal Name

COMMUNICATION

Catalytic and stoichiometric flavanone oxidations mediated by nonheme oxoiron(IV) complexes as flavone synthase mimics: kinetic, mechanistic and computational studies

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Ramona Turcas,[a] Balázs Kripli,[a] Amr A. A. Attia,[b] Dóra Lakk-Bogáth,[a] Gábor Speier,[a] Michel Giorgi,[c] Radu Silaghi-Dumitrescu,[*b] and József Kaizer[*a]

Abstract: The present study describes the first example of the stoichiometric and catalytic oxidation of flavanone by synthetic nonheme oxoiron(IV), and their precursor iron(II) complexes with *m*-CPBA as terminal oxidant. These models, including detailed kinetic, mechanistic and computational studies, may serve as a biomimics of flavone synthase (FS) enzymes.

Flavonoids are low molecular weight polyphenolic phytochemicals, derived from secondary metabolism of plants and play important role in various biological processes.[1] They are involved in UV-protection, flower coloration, interspecies interaction, and plant defence.[2] Flavanones, a type of flavonoids, are found in citrus fruits and have many beneficial pharmacologic properties, including antioxidant, anti-inflammatory, anticarcinogenic activities. Due to the antioxidant or putative anticancer activities of certain flavonoids, they also nutritional values and medicinal benefits to humans. For example, naringenin has been reported to be a good inhibitor of aromatase as a major strategy in the treatment of breast cancer[3]. Flavonoid biosynthesis is initiated by chalcone synthase, followed by the activity of chalcone isomerase. The resulting flavanones are precursors for different classes of flavonoids, including flavones, flavonols, and anthocyanins. The introduction of the C^2-C^3 double bond into flavanones to form flavones is an important reaction in the biosynthesis of flavonoids.[4] The therapeutic potential of flavones makes these compounds also valuable targets for drug design, including DNA approaches.[5] The oxidation of flavanones to flavones has been reported using stoichiometric reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[6a] DMSO/I2,[6b] selenium dioxide,[6c] nickel peroxide,[6d] disulfide,[6e] thallium(III) salts,[6f] and manganase acetate.[6g]

Oxidation reactions involving both heme and nonheme iron-dependent enzymes play a central role in flavonoid biosynthesis. The catalytic mechanism of both enzymes could be very similar with respect to the highly reactive iron-oxo complex generated at the active site and the subsequent oxidation of the substrate. However, the biosynthesis of flavones (**F**) from flavanones (**FH_2**) in plants was found to be catalyzed by two completely different flavone synthase proteins (FS I and FS II), which have totally distinct catalytic mechanisms (Fig. 1). FS I, a soluble Fe^{II}/2-oxoglutarate-dependent dioxygenase (Fe^{II}/2-OGD), abstracts hydrogens from C^2 and C^3 of a **FH_2**, to produce a **F** by direct non-concerted 2,3-desaturation without intermediate hydroxylation.[7] This reaction clearly differs from the mechanisms assumed for Fe^{II}/2-OGD flavonol synthase (FLS) or anthocyanidin synthase (ANS), which likely hydroxylate C^3 or C^2 of the substrate through a rebound process, followed by antiperiplanar water elimination. Thus, the catalytic action of FS I is clearly different from most of the known 2-oxoglutarate-dependent dioxygenases and could be referred to as 2-oxoglutarate-dependent dehydrogenation or desaturation.[8] In contrast, FS II (CYP93B), a membrane bound cytochrome P450 dependent monooxygenase (MO), has been presumed to catalyze the formation of a hypothetical 2-hydroxyflavanone (**A**) from a flavanone, the subsequent dehydration of which yields a flavone.[9]

In the present work, we carried out stoichiometric and catalytic flavanone oxidation reactions with spectroscopically

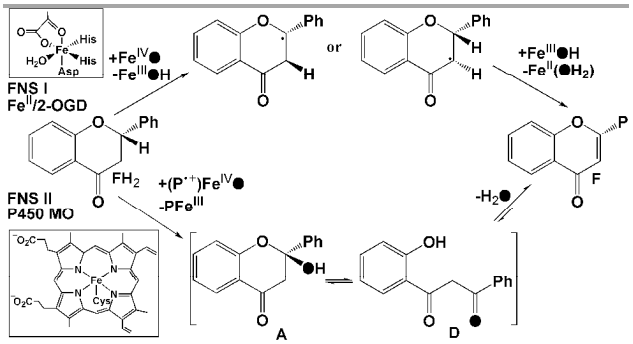

Fig. 1. Oxidation of flavanone by heme and nonheme flavone synthases, FS I and FS II.

[a] Department of Chemistry, University of Pannonia, H-8201 Veszprém, Hungary E-mail: kaizer@almos.vein.hu.
[b] Department of Chemistry, Babes-Bolyai University, 1, Kogalniceanu Str., 400084 Cluj-Napoca, Romania
[c] Aix Marseille Université, CNRS, Centrale Marseille, Spectropole FR1739, 13397, Marseille, France

† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

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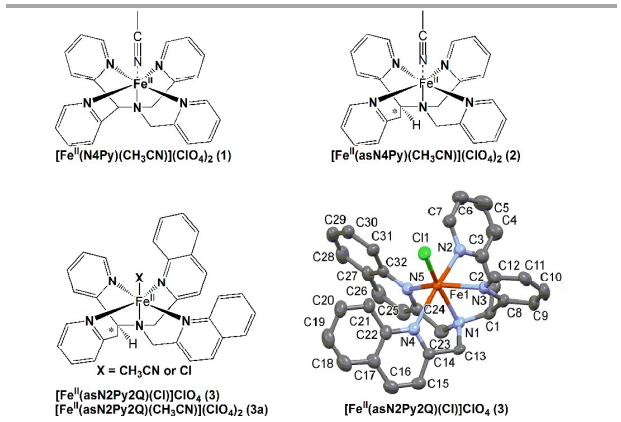

Fig. 2. Iron(II) complexes used in this study.

well characterized nonheme oxoiron(IV) intermediates, $[Fe^{IV}(O)(N4Py)](ClO_4)_2$ (**4**),[10] $[Fe^{IV}(O)(asN4Py)](ClO_4)_2$ (**5**),[11] $[Fe^{IV}(O)(asN2Py2Q)]^{2+}$ (**6**) and their precursor complexes, $[Fe^{II}(N4Py)(MeCN)](ClO_4)_2$ (**1**), $[Fe^{II}(asN4Py)(MeCN)](ClO_4)_2$ (**2**), $[Fe^{II}(asN2Py2Q)(MeCN)](ClO_4)_2$ (**3a**), $[Fe^{II}(asN2Py2Q)(Cl)]ClO_4$ (**3**) (Fig. 2). To the best of our knowledge, this study provides the first mechanistic details of oxoiron(IV)-mediated flavanone oxidation, which may serve as functional model of FS enzymes.

The newly synthesized and characterized, chiral N4Py-type ligand, *N,N*-bis(2-quinolylmethyl)-1,2-di(2-pyridyl)ethylamine (asN2Py2Q) (Scheme S1 and Fig. S1, ESI†), forms the monomeric iron(II) complex $[Fe^{II}(asN2Py2Q)(Cl)]ClO_4$ (**3**). The structure of **3** was revealed by X-ray structure analysis (Fig. 2, and Fig. S2, ESI†). The iron(II) centre in **3** is in a distorted octahedral geometry because of the coordination of all five N donor atoms of the ligand and of a chloride anion. The replacement of two pyridyl arms by 2-quinoline arms and the solvent molecule by chlorido anion results in a lengthening of the Fe-N_{div}, and Fe-N_{amine} bond distances by 0.2-0.3 Å, with respect to $[Fe^{II}(asN4Py)(MeCN)](ClO_4)_2$ and other N4Py-type ligand containing iron(II) complexes (Tables S1-S3, ESI†).[12] The significantly longer Fe-N bond lengths (2.2-2.4 Å) are in agreement with the presence of high spin Fe(II) centre in **3**. As a result of symproportionation of **3** into dichlorido and diperchlorato species, the ESI mass spectrum in acetonitrile shows peaks at m/z = 268.8 and m/z = 289.2 corresponding to the formulations $[Fe^{II}(asN2Py2Q)]^{2+}$ (calcd 268.6) and $[Fe^{II}(asN2Py2Q)(CH_3CN)]^{2+}$ (calcd 289.6), respectively, as well as peaks at m/z = 572.1 and m/z = 636.2 corresponding to the formulations $[Fe^{II}(asN2Py2Q)(Cl)]^{2+}$ (calcd 572.1) and $[Fe^{II}(asN2Py2Q)(ClO_4)]^{2+}$ (calcd 636.1), respectively (Fig. S3, ESI†). The UV-vis spectrum of **3** in acetonitrile obtained at 25˚C is dominated by the intense π-π* band at 300 nm (ε = 11 000 M^{-1} cm^{-1}), and an additional broad feature of low intensity between 320 and 460 nm (λ_{max} = 380 and 440 nm with ε_{max} = 1000 and 600 M^{-1} cm^{-1}, respectively) corresponds to a MLCT transition. The weak intensity is characteristic of high-spin iron(II) centre (Fig. S4, ESI†).[13] We have found earlier that $[Fe^{II}(N4Py)(MeCN)](ClO_4)_2$ (**1**) complex has a relatively high redox potential value ($E_{1/2}$ = 1.01 V vs. SCE). The replacement of a pyridyl moiety by a 2-pyridylethyl moiety resulted in almost the same value for complex **2** ($E_{1/2}$ = 0.95 V) (Fig. S5, ESI†), and two values can be observed ($E_{1/2}$ = 0.83 V and 1.22 V vs. SCE) for **3**, which may be explained by the presence of diperchlorato (**3a**) and dichlorido species, respectively, as a result of the symroportionation of **3**.[11a]

Similarly to the formation of $[Fe^{IV}(O)(N4Py)](ClO_4)_2$ (**4**) and $[Fe^{IV}(O)(asN4Py)](ClO_4)_2$ (**5**) species, the complex $[Fe^{IV}(O)(asN2Py2Q)]^{2+}$ (**6**) can be generated by the reaction of its precursor (**3**) with a single oxygen atom donor, such as iodosylbenzene (PhIO) or *m*-chloroperoxybenzoic acid (*m*-CPBA).[10,11] The reaction of **3** (**3a**) with excess (1.5 equiv) solid PhIO in acetonitrile at room temperature yields a green species (**6**) within 4 min, characterized by a 805 nm absorption band (ε ≈ 280 M^{-1} cm^{-1}) in the near IR region, which can be assigned as a ligand-field (d-d) transition centred on the low-spin (S = 1) Fe(IV) ion.[14] This species is much less stable ($t_{1/2}$ ≈ 1.5 h at 25°C) than those found for **4** ($t_{1/2}$ ≈ 60 h at 25°C) and **5** ($t_{1/2}$ ≈ 10 d at 25°C).[10,11] Its ESI-MS spectrum showed major peaks at m/z = 276.6 and 652.1, corresponding to the formulation $[Fe^{IV}(O)(asN2Py2Q)]^{2+}$ (m/z calcd 276.6) and $[Fe^{IV}(O)(asN2PyQ2)(ClO_4)]^{+}$ (m/z calcd 652.1), respectively (Fig. S6, ESI†).

The catalytic activities of the four ferrous complexes $[Fe^{II}(N4Py)(MeCN)](ClO_4)_2$ (**1**), $[Fe^{II}(asN4Py)(MeCN)](ClO_4)_2$ (**2**), $[Fe^{II}(asN2Py2Q)(Cl)]ClO_4$ (**3**) and $[Fe^{II}(asN2Py2Q)(MeCN)](ClO_4)_2$ (**3a**) were studied in the oxidation of flavanone, utilizing *m*-CPBA as co-oxidant. The oxidation reactions were carried out under standard catalytic conditions (3:225:1000 ratio for catalyst:oxidant:substrate) in acetonitrile at room temperature (Table S4, ESI†). The large excess of substrate was used to minimize over-oxidation of the product and get an evidence for the formation of possible intermediates. It took less than 10 min to have about 9-26% yields (based on oxidant) for the iron(II)-catalyzed reactions. These reactions were also examined on varying the time period between 10-30 minutes, where we observed the flavone yield attained a peak after 10 minutes of reaction and remained the same even after 30 minutes. Much smaller yield (~1.6%) was obtained for the $Fe(ClO_4)_2$ salt. The iron(II)-catalyzed reactions of flavanone produced flavones (**F**) as expected and major product in all cases in addition to two minor products. The GC-MS/MS search proposed names for two of the minor products: 2-hydroxy-2-phenyl-chroman-4-one (**A**, 2-hydroxyflavanone) and its opened tautomeric form 1-(2-hydroxy-phenyl)-3-phenyl-propane-1,3-dione (**D**) (Fig. S7-S9, ESI†). Complex **1** together with *m*-CPBA (75 equiv.) oxidizes flavanone, and a turnover number (TON) of 10.9 for **F**, 1.05 for **D** and 0.1 for **A** was obtained with an overall yield of 16.13%. Complex **2** produced an overall yield of 9.42%, TON for **F**=6.93, TON for A=0.02, TON for **D**=0.11, and complex **3** produced an overall yield 17.9%, TON for **F**=13.4, TON for A=0.03, TON for **D**=0.74. Significantly higher yield (26%; TON for **F**=19.5, TON for A=0.02, TON for **D**=0.54) was observed for **3a**. It is important to mentione that the amount of 1,3-dione (**D**) can be increased in the presence of H_2O (**3a**: 27.6%; TON for **F**=16.5, TON for A=0.04, TON for **D**=11.1), suggesting an equilibrium step during the flavone formation. An increase in the yield of flavone was observed when the amount of catalyst **3** was increased from 1 to 5 mM per 1 M $\mathbf{FH_2}$ (Table S4, ESI†). In the absence of catalyst (blank experiments) no flavone formation was detected under our conditions. The TON values also significantly increased on

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increasing the concentration of the oxidant *m*-CPBA. The turnover number is calculated from the ratio of the amount of the reacted flavanone to the amount of the catalyst. The ligand framework influenced the catalytic activities of these complexes, their values indicate that the relative reactivities of iron(II) complexes are in the order of **3a** > **3** > **1** > **2**. The finding (GC/MS) that the investigated catalysts catalyzed the formation of both the theoretical tautomers (**A** and **D**) of the acid-labile intermediate of flavone strongly supports the hypothesis that flavone biosynthesis proceeds via 2-hydroxylation of flavanone. Similarly to our results, a cytochrome P450 monooxygenase has been presumed to catalyze the formation of a hypothetical 2-hydroxyflavanone (**A**) from a flavanone, the subsequent dehydration of which yields a flavone. Further insight into the nature of the oxidizing species was obtain via ^{18}O-labeling experiments by the use of $H_2{}^{18}O/H_2{}^{16}O$ (40:60%), where ~40% ^{18}O incorporated into the oxidized products (**D** and **A**, Table S4, Fig. S10-S11, ESI†). Compound **1**, **2** and **3** (**3a**) produce a brown solution after dissolution which become green on addition of the oxidant *m*-CPBA, and fade of the color when substrate was added. UV/Vis spectrophotometry was used to identify the possible reactive intermediate of the iron(II)-catalyzed oxidation processes. The reaction of **1**, **2** and **3** with *m*-CPBA resulted in the formation of a transient oxoiron(IV) species **4**, **5** and **6** with a broad absorbance maxima in the range 680-810 nm suggesting that the oxidation of flavanone takes place through higher valent metal oxo species formation. To get direct evidence for the involvement of the high-valent oxoiron(IV) intermediates observed in the catalytic reactions, the oxidation potential of **4**, **5** and **6** has been studied at 25°C in HAT process with flavanone in dry acetonitrile. Complex **4** was generated by the reaction of **1** with 1.5 equiv. of PhIO (<40 min), and the rate of its rapid decomposition (λ_{max} = 695 nm, ligand-field (d-d) transition centered on the low-spin (S = 1) iron(IV) ion),[11a] which coincided with the regeneration of **1** (λ_{max} = 380 and 449 nm), was measured as a function of the concentration of added flavanone. The yield of flavone was almost quantitative (~70-80%), indicating that the UV-vis spectral change corresponds to the HAT process. An isobestic point was observed at 560 nm, suggesting that there were no long-lived intermediates in the conversion of the green species into the Fe^{II} product. Furthermore, no shifts have been observed in the λ_{max} value of **4** after the addition of flavanone, excluding any complexation with the oxidant (Fig. 3). Similar spectral behaviour has been observed for the reaction between flavanone and **5**. The absorption band at 705 nm changed to new bands at 398, 409, and 513 nm (**2**) with a well-defined isosbestic point at 560 nm (Fig. S12, ESI†). The reaction of **6** was followed at 805 nm (Fig. S13, ESI†). Pseudo-first-order fitting of the kinetic data allowed us to determine k_{obs} values for the reactions of **4**-**6** (Table 1, Table S5-S7, ESI†), and product analysis of the resulting solutions with GC and GC-MS revealed that flavone (with a small amount of 1,3-dione, 5-10%) was produced with high yields in all the reactions (>70%, based on the intermediates generated), and ^{18}O from $H_2{}^{18}O$ was shown to be incorporated into the 1,3-dione with ~100%, probably via the formation of labeled high-valent Fe=O units. The rates in the presence of a large excess of flavanone (200-600 equiv.) obeyed pseudo-first order kinetics, and the pseudo-first order rate constants (k_{obs}) increased proportionally with the substrate concentration (Fig. S14-S16, ESI†), leading us to determine second-order rate constants (k_2). These values (0.024-1.92 × 10^{-2} M^{-1} s^{-1}) are much smaller than that was obtained for the oxidation of benzyl alcohol (9.9 × 10^{-2} M^{-1} s^{-1} at 25°C in CH_3CN) by **4**.[15] Finally, the activation parameters of activation energy, enthalpy, entropy, and Gibbs energy ($\Delta H^{\neq}$, $\Delta S^{\neq}$, and $\Delta G^{\neq}$) were calculated from the plots of log(k) (and log(k/T)) versus 1/T over the temperature range of 293 to 308 K (Table 1, Table S17-S19, ESI†). The large negative activation entropies are typical of associative processes, which indicate that the transition state is better organized than the prior step. Based on kinetic and activation parameters the relative reactivity of oxoiron(IV) complexes is in the order of **6** > **4** > **5**. Similar trend has been observed for their precursor complexes in the catalytic reactions: **3** > **1** > **2**.

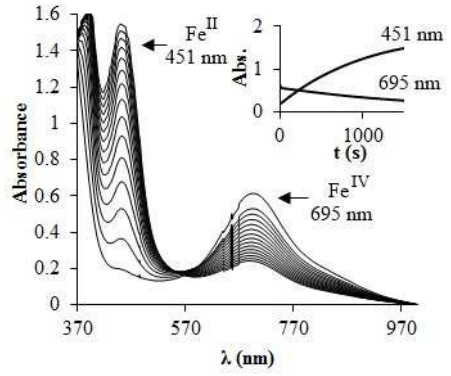

Fig. 3. UV-vis spectral change of **4** (1.5 mM) upon addition of 500 equiv. flavanone at 298 K. Inset shows time course of the decay of **4** monitored at 695 nm.

Two reaction mechanisms were mainly investigated by DFT calculations (Fig. S20-S22, ESI†). The first proposed reaction mechanism involves the hydroxylation of flavanone by $[Fe^{IV}(O)(N4Py)]^{2+}$ forming 2-hydroxyflavanone through H-atom abstraction followed by the elimination of H_2O and the formation of $[Fe^{II}(N4Py)(MeCN)]^{2+}$ and flavone.[16] DFT results using the M06-L functional show that abstracting a H-atom from flavanone's C^2 atom entails an energy barrier of ~14 kcal/mol, as shown by (TS1) in Fig. 4, leading to $N_4PyFe^{3+}OH^-$ with Fe-O bond length of 1.80 Å and ~1 spin unit on Fe; the resulting product is exothermic by 3.6 kcal/mol relative to the starting structure. The transition state leading to the hydroxide rebound to flavanone's C^2 (TS2) was found endergonic by a favorable 7.4 kcal/mol and the product (2-hydroxyflavanone and $[Fe^{II}(N4Py)(MeCN)]^{2+}$) is exothermic by 7.2 kcal/mol. This step is then followed by the elimination of H_2O forming the

Table 1. Kinetic parameters determined in the oxidation of flavanone by oxoiron(IV) complexes in acetonitrile at 25°C.[a]

Complex	$t_{1/2}$ (h)	k_2 ($10^{-3}M^{-1}$ s^{-1})	flavone (%)	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J mol^{-1} K^{-1})	$\Delta G^{\neq}$ (kJ mol^{-1})
4	60	0.57±0.03	80	63±4	-93±13	90.9
5	233	0.24±0.01	80	70±3	-75±9	92.2
6	1.5	19.2±1.1	80	48±2	-121±8	83.7

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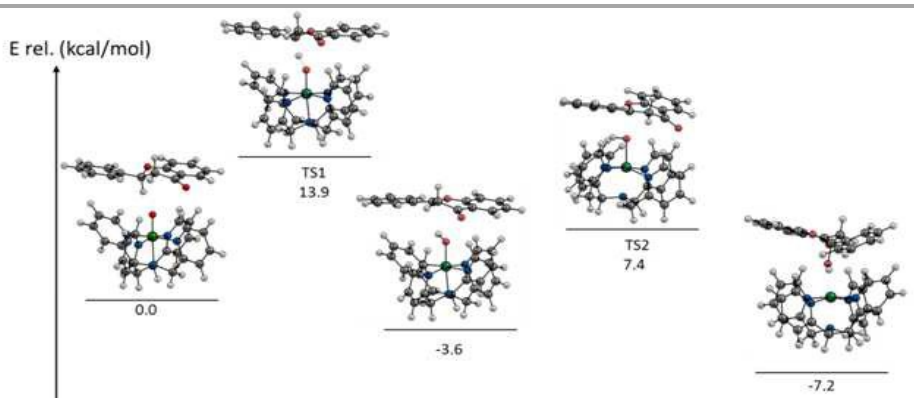

Fig. 4. M06-L/def2-TZVP DFT results for the proposed reaction mechanism (1) involving the formation of 2-hydroxyflavanone through H-atom abstraction from flavanone's C^2 by $[Fe^{IV}(O)(N4Py)]^{2+}$ to form the enzyme-like product flavone.

enzyme-like product flavone. A different pathway was also investigated where the H-atom abstraction occurs at flavanone's C^3 (cf. Fig. S21, ESI†), much higher energy barriers were obtained (~30 and 18.5 kcal/mol for TS1 and TS2 respectively) rendering such pathway unfavorable compared to the former. The second reaction mechanism entails a one-step two H-atom abstractions leading to flavone + Fe^{2+} (H_2O) with no hydroxylation involved. This mechanism is shown in Fig. S22 (ESI†). Abstraction of a second H-atom from flavanone was found to cost ~40 kcal/mol, which (together with the detection of 2-hydroxyflavanone as an experimental intermediate) makes this reaction pathway unlikely.

In this study we have demonstrated, that iron(II) complexes with N4Py-type ligands are active and selective catalysts in the oxidation of flavanone. The experimental and computational results clearly indicated the formation of a high-valent metal-oxo intermediate ($Fe^{IV}O$), and its role in the oxidation process, including a rebound mechanism with the formation of 2-hydroxyflavanone contrary with the dissociation process suggested by Nam for substrates with stronger C-H bonds.[16] This system is the first biomimics of FS enzymes.

Notes and references

‡ Deposited CIF file: CCDC 1841256.

§ This work was supported by a grant from The Hungarian Research Fund (OTKA) K108489, and GINOP-2.3.2-15-2016-00049.

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Catalytic and stoichiometric flavanone oxidations mediated by nonheme oxoiron(IV) complexes as flavone synthase mimics: kinetic, mechanistic and computational studies

Ramona Turcas, Balázs Kripli, Amr A. A. Attia, Dóra Lakk-Bogáth, Gábor Speier, Michel Giorgi, Radu Silaghi-Dumitrescu,* and József Kaizer*

Stoichiometric and catalytic oxidation of flavanone by synthetic nonheme oxoiron(IV), and their precursor iron(II) complexes with *m*-CPBA, as biomimics of flavone synthase (FS) enzymes have been carried out.