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The Hydroperoxyl Radical Scavenging Activity of Sulfuretin: Insights from Theory

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Abstract

Sulfuretin (**SFR**), which is isolated from *Rhus verniciflua*, *Toxicodendron vernicifluum, Dahlia, Bidens tripartite,* and *Dipterx lacunifera*, is one of the most important natural flavonoids. This compound is known to have numerous biological activities; among these, the antioxidant activity has not been thoroughly studied yet. In this study, the hydroperoxyl scavenging activity of **SFR** was examined by using density functional theory calculations. **SFR** is predicted to be an excellent $HOO^{\bullet}$ scavenger in water at pH = 7.40 with $k_{overall}$ = 4.75×10^7 $M^{-1}s^{-1}$, principally due to an increase in the activity of the anionic form following the single electron transfer mechanism. Consistently the activity of the neutral form is more prominent in the nonpolar environment with $k_{overall}$ = 1.79×10^4 $M^{-1}s^{-1}$ following the formal hydrogen transfer mechanism. Thus it is predicted that **SFR** exhibits better $HOO^{\bullet}$ antiradical activity than typical antioxidants such as resveratrol, ascorbic acid, and Trolox in the lipid medium. The hydroperoxyl radical scavenging of **SFR** in the aqueous solution is

~530 times faster than that of Trolox and similar to ascorbic acid or resveratrol. This suggests that **SFR** is a promising radical scavenger in physiological environments.

Keywords: Sulfuretin, DFT study, antioxidants, antiradical activity, flavonoids

1.Introduction

Sulfuretin (**SFR**, Figure 1) is a natural flavonoid present in numerous plant species, including *Rhus verniciflua*,[1,2] *Toxicodendron vernicifluum,*[3] *Dahlia, Bidens tripartite,* and *Dipterx lacunifera*.[4] This compound is known to have numerous biological activities such as amelioration of rheumatoid arthritis symptoms,[5] antimutagenic,[6] antiplatelet,[7] anticancer,[8,9] anti-inflammatory effects,[5,10] liver protection[11], anti-aging effect for skin,[12] anti-obesity effect[12] and antioxidant activity.[2,13-15]

Jung and co-workers reported that **SFR** presented strong antioxidant activity in the DPPH (2,2-diphenyl-1-picrylhydrazyl) assay and total anti-ROS (reactive oxygen species) activity with IC50 = 8.52 and 0.73 μM, respectively. The DPPH inhibition of **SFR** was about two times higher than that of L-ascorbic acid, whereas the total ROS inhibition is about five times stronger than Trolox. **SFR** also presented significant activity against $ONOO^-$ and $HO^\bullet$ radicals.[2] Chen et al. also reported that **SFR** has good DPPH, $ABTS^{\bullet+}$ (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) and $HO^\bullet$ radical scavenging activity that is higher than butylated hydroxytoluene (BHT).[14]

Although the antioxidant activity of **SFR** is widely examined experimentally,[2,14] there are no studies on the mechanism and kinetics of its antiradical activity, particularly in physiological environments. Computer calculations offer a convenient

way to predict the antioxidant activity of organic compounds in physiological media.[16-23] In this context and as a continuation of our previous studies,[18,24,25] we set out in this work to evaluate the HOO• antiradical activity of **SFR** by a combination of thermodynamic and kinetic calculations. This study also considered the effects of solvents on the antioxidant properties of **SFR** in comparison with some typical antioxidants.

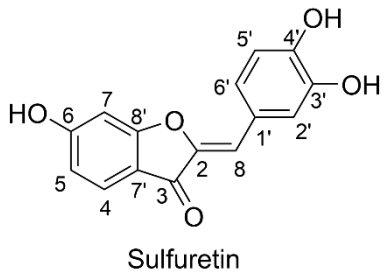

Figure 1. Molecular structure and atomic numbering of Sulfuretin (**SFR**).

2. Computational Details

All calculations were carried out with Gaussian 09 suite of programs[26]. M06-2X/6-311++G(d,p) model chemistry was used for all calculations.[27-29] It was demonstrated before that the M06-2X functional is one of the most reliable methods to study thermodynamics and kinetics of radical reactions, particularly in physiological environments.[19,28,30,31] The solvation model density (SMD) method was used for including the effects of water and pentyl ethanoate in the computations.[17,18,24,32-34] The kinetic calculations were performed following the quantum mechanics-based test for the overall free radical scavenging activity (QM-ORSA) protocol,[17,34] using the conventional transition state theory (TST) and 1M standard state at 298.15 K.[18,34-40] The details of the method are shown in Table S1, SI.

3. Results and discussion

3.1. The HOO• antiradical activity of SFR in the gas phase

Thermodynamic evaluation

For SFR that contains OH and moieties, the antioxidant activity may follow either of the four main mechanisms: the formal hydrogen transfer (FHT), the sequential proton loss electron transfer (SPLET), the single electron transfer proton transfer (SETPT), and radical adduct formation (RAF).[41,42] The first three pathways are defined by the following thermodynamic parameters: bond dissociation enthalpy (BDE), proton affinity (PA), and ionization energy (IE), respectively. The Gibbs free energy change of the addition reaction is calculated directly for the RAF mechanism. Thus, the BDE, IE, and PA values of **SFR** were first calculated in the gas phase, and the results are shown in Table 1.

As per Table 1, the lowest BDE value was predicted for O4'–H at 77.5 kcal/mol. This value is lower than that of natural antioxidants such as viniferifuran (82.7 kcal/mol)[43], resveratrol (83.9 kcal/mol)[43], puerarin (87.3 kcal/mol),[44] and vanillic acid (85.2 kcal/mol).[45] The lowest PA and IE values are about 4.14 and 2.25 times higher than the BDE value. Thus, based on the computed data, the antioxidant activity of **SFR** is predicted to favour the FHT pathway, at least in apolar and low-dielectric environments.

Table 1. The calculated thermodynamic parameters (BDEs, PAs, and IEs) of **SFR** in the gas phase

Positions	BDE	PA	IE
O6–H	90.7	323.4	174.6
O3'–H	80.5	327.9	
O4'–H	77.5	320.9	

To confirm that FHT is indeed the preferred pathway, the HOO• antiradical activity of **SFR**, the Gibbs free energy of the **SFR** + HOO• reaction was calculated according to each of the four mechanisms: FHT, single electron transfer (SET, the first step of the SETPT mechanism), the proton loss (PL, the first step of the SPLET), and RAF (Table 2). It was found that the HOO• antiradical activity of **SFR** is only clearly spontaneous for FHT atO3'(O4')–H bonds and RAF at the C8 position (ΔG^o <0), whereas the RAF reaction at C2 with ΔG^o = 1.1 kcal/mol can not be clearly excluded based on thermodynamics alone and therefore it was also included in the kinetic study. The other reactions are clearly not spontaneous with high positive ΔG^o values. The ΔG^o values for the reactions following the SP and SET pathways are much higher than those of the FHT mechanism. Thus the calculated data suggest that the HOO• antiradical activity of **SFR** may follow either FHT or RAF mechanism (at O3'(4')–H and C2/C8 positions, respectively), and these pathways should be investigated in the kinetic study.

Table 2. Calculated ΔG^o (kcal/mol) of the **SFR** + HOO• reactions according to the FHT, SA, RAF, and SET mechanisms in the gas phase.

Positions	**FHT**	**SP**	**SET**	**RAF**
O6–H	4.8	170.8		–
O3'–H	–4.9	176.1		–
O4'–H	–7.7	169.2	152.1	–
C2	–	–		1.1
C8	–	–		–4.6

Kinetic study

Based on the above results, the kinetics of the **SFR** + HOO• reaction in the gas phase was investigated for the thermodynamically favourable positions and mechanisms according to the (QM-ORSA) protocol[17], and the data are presented in Table 3 and Figure 2.

Table 3. Calculated ΔH (kcal/mol), activation Gibbs free energies (ΔG≠, kcal/mol), tunneling corrections (κ), k_{Eck} (M^{-1} s^{-1}) and branching ratios (Γ, %) for the HOO• + SFR reaction in the gas phase.

Mechanism	Positions	ΔH	ΔG≠	κ	k_{Eck}	Γ
FHT	O3'–H	2.3	11.6	39.6	8.43×10^{5}	23.0
	O4'–H	2.0	11.2	72.1	2.83×10^{6}	77.0
RAF	C2	7.1	17.1	1.5	2.83	0.0
	C8	8.6	17.7	1.5	9.03×10^{-1}	0.0
$k_{overall}$					**3.67×10^{6}**	

It is apparent that the HOO• antiradical activity of **SFR** occurs mostly by the H-abstraction of the O4'–H bond (ΔG≠ = 11.2 kcal/mol; k_{Eck} = 2.83×10^{6} M^{-1} s^{-1}; Γ = 77.0 %). That is more than three times higher contribution than the hydrogen abstraction of the O3'–H bond (ΔG≠ = 11.6 kcal/mol; k_{Eck} = 8.43×10^{5} M^{-1} s^{-1}; Γ = 23.0 %). In contrast, the addition of the radical does not make any contribution (Γ = 0%) at either the C2 or C8 positions. This result is in good agreement with previous studies in phenolic compounds.[46-48] We can conclude that the HOO• antiradical

activity of **SFR** is dominated by the FHT mechanism at the O3'(4')-H bond; therefore, this is further analyzed in physiological environments.

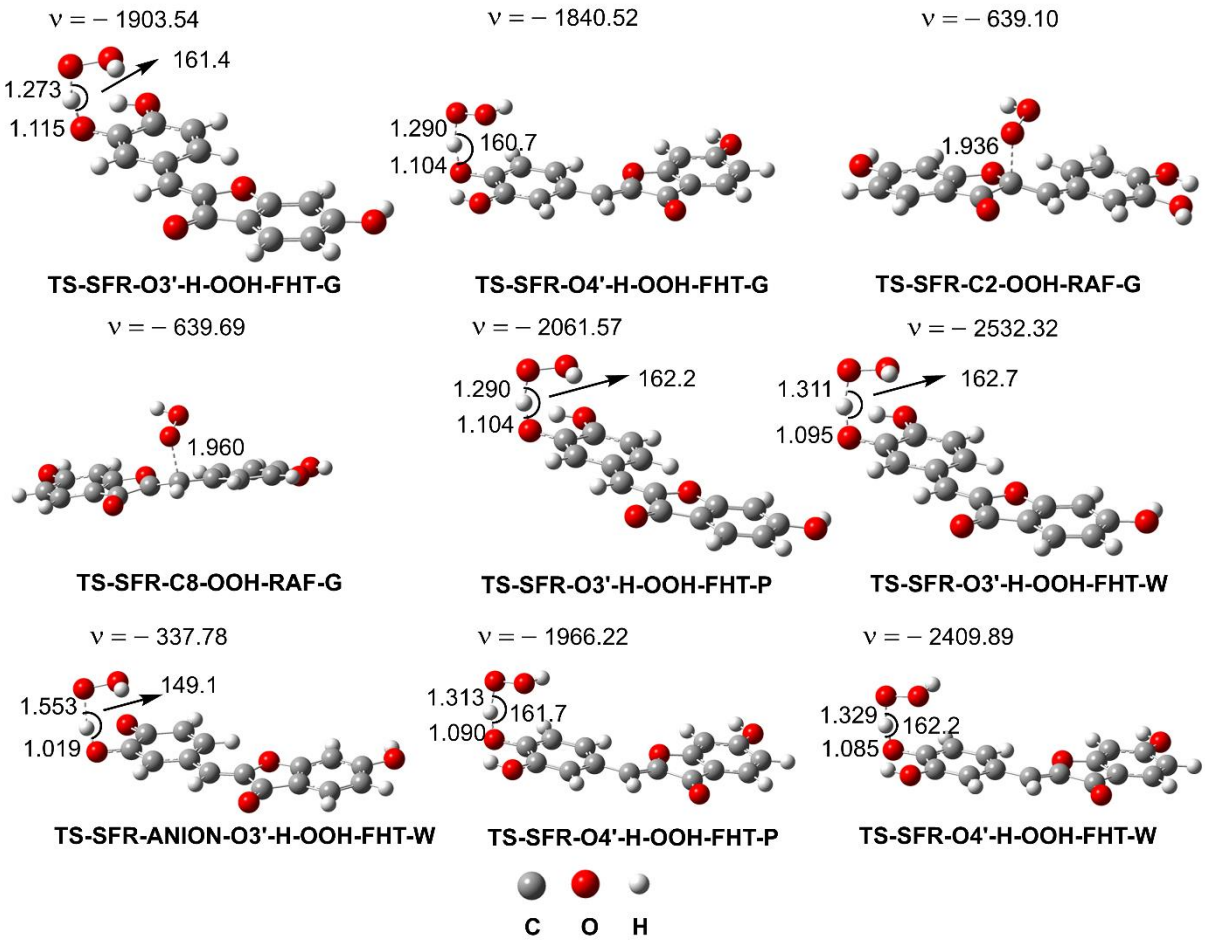

Figure 2. The optimized transition state (TS) structures following the FHT and RAF mechanisms of the **SFR** + HOO• reaction (G: gas phase; W: water; P: pentyl ethanoate).

3.2. The HOO• antiradical activity of SFR in physiological environments.

Acid-base equilibrium

Previous studies showed that the deprotonation of the OH bonds plays a key role in the HOO• antiradical activity of phenolic compounds in the aqueous solution.[30,34,49] The spontaneous dissociation of acidic moieties practically eliminates the activation energy barrier of the first step of the SPLET mechanism, simplifying it to direct electron transfer, and for this reason, this pathway can become energetically

favoured in aqueous solution for the dissociated species. Thus, in this study, the deprotonation of **SFR** must also be considered. The proton affinity values (Table 1) showed that the site most likely to dissociate is the O4'–H bond. Thus, this bond was used to calculate the pKa of **SFR**. The pKa was computed following the literature[49,50] and the results are shown in Figure 3. The calculated pKa value was 7.47. Thus, under physiologically relevant conditions (pH = 7.40) **SFR** has both neutral (HA, 54.0%) and anionic (A^-, 46.0%) forms. Therefore, in the physiological environments, these states were used for the kinetic investigation.

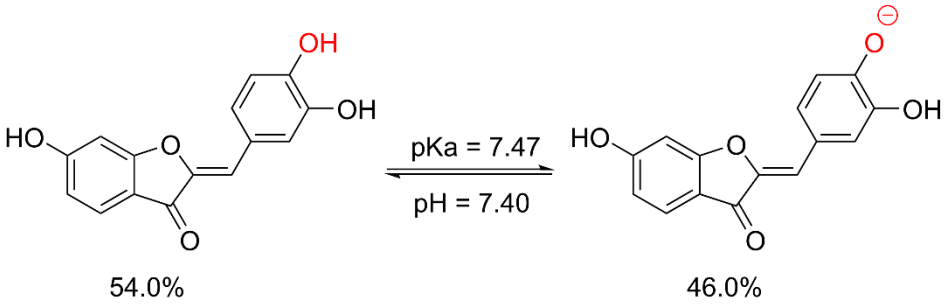

Figure 3. The acid dissociation equilibrium of **SFR**

Kinetic study

Based on the kinetic study results in the gas phase, the $HOO^{\bullet}$ antiradical activity in nonpolar environments was modeled by the hydrogen transfer mechanism at the O3'(O4')–H bonds. In an aqueous environment, the SET mechanism was also investigated for the deprotonated state of **SFR**. The overall rate constants ($k_{overall}$) were computed following the (QM-ORSA) protocol,[17,33] (Table 4) according to equations 1 and 2.

In the lipid medium

$$k_{overall} = \Sigma k_{app}(\text{FHT(O–H)-neutral}) \quad (1)$$

In water at pH = 7.40:

$k_{overall} = \Sigma k_f(\text{FHT-neutral}) + k_f(\text{SET-anion}) + k_f(\text{FHT(O3'–H)-anion})$ (2)

Table 4. Calculated $\Delta G^{\neq}$ (kcal/mol), tunneling corrections (κ), the nuclear reorganization energy (λ, kcal/mol) rate constants (k_{app}, k_f, and $k_{overall}$ $M^{-1}\,s^{-1}$), molar fractions (f) and branching ratios (Γ, %) at 298.15 K, in the **SFR** + HOO• reaction in pentyl ethanoate and water solvents.

Mechanism		Pentyl ethanoate				Water					
		$\Delta G^{\neq}$	κ	k_{app}	Γ	$\Delta G^{\neq}$	κ	k_{app}	f	k_f**	Γ
SET						6.6	15.6*	8.90×10^{7}	0.460	4.09×10^{7}	86.2
HAT	O3'–H	15.0	106.9	6.90×10^{3}	38.5	16.0	744.5	9.20×10^{3}	0.540	4.97×10^{3}	0.0
	O4'–H	14.9	163.1	1.10×10^{4}	61.5	15.5	202.8	5.30×10^{3}	0.540	2.86×10^{3}	0.0
	O3'–H (anion)					7.8	1.2	1.42×10^{7}	0.460	6.53×10^{6}	13.7
$k_{overall}$				**1.79×10^{4}**						**4.75×10^{7}**	
*: λ; **: $k_f = f.k_{app}$; $\Gamma = k.100/k_{overall}$											

As shown in Table 4, the HOO• antiradical activity of **SFR** in the polar solvent is excellent with the $k_{overall}$ = 4.75×10^{7} $M^{-1}\,s^{-1}$. Similarly, in the lipid medium, **SFR** exhibits good activity with $k_{overall}$ = 1.79×10^{4} $M^{-1}\,s^{-1}$. It was found that the SET of anion A^- plays a principal role (k_f = 4.09×10^{7} $M^{-1}\,s^{-1}$, Γ= 86.2 %) in the radical scavenging activity of **SFR**. The H-abstraction of the anion state contributes about 13.7% to the overall rate constants. The rate constants for the H-abstraction of O3'(O4')–H bonds against HOO• radical are k_f = 4.97×10^{3} and 2.86×10^{3} $M^{-1}\,s^{-1}$, respectively; however, these reactions do not make any contributions (~ 0%) to the activity of **SFR**. Based on the results, **SFR** is better HOO• radical scavenger than typical antioxidants Trolox, ascorbic acid and resveratrol in both lipid phase (reference lipid

phase activities: $k_{overall}$ = 3.40×10^3 M^{-1} s^{-1},[33] $k_{overall}$ = 5.71×10^3 M^{-1} s^{-1},[17] and $k_{overall}$ = 1.31×10^4 M^{-1} s^{-1}, [46] , respectively) and aqueous medium. In aqueous solution the HOO• antiradical activity of **SFR** is ~530 times faster than that of Trolox (k = 8.96 ×10^4 M^{-1} s^{-1})[33] and fairly similar to the other well-known natural antioxidants, i.e., ascorbic acid (k = 9.97 ×10^7 M^{-1} s^{-1})[17] and resveratrol (k = 5.62 ×10^7 M^{-1} s^{-1}).[46] Thus, the results suggest that **SFR** is a promising antioxidant in physiological media.

4. Conclusion

The hydroperoxyl radical scavenging activity of Sulfuretin was investigated using the DFT calculations. The results showed that **SFR** has excellent HOO• antiradical activity with $k_{overall}$ = 4.75×10^7 M^{-1} s^{-1} in water at pH = 7.40 by the SET pathway of the anion state, and good/moderate HOO• scavenging activity in lipid environment ($k_{overall}$ = 1.79×10^4 M^{-1} s^{-1}) by the FHT mechanism *via* the O3'(O4')-H bonds. The hydroperoxyl antiradical activity of **SFR** is better than Trolox, ascorbic acid, and resveratrol in the lipid medium. This activity of **SFR** is ~ 530 times faster than that of Trolox and relatively similar to ascorbic acid and resveratrol in the polar environment. Thus, **SFR** can be a useful natural antioxidant in physiological environments.

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The Authors' Contributions section

N.T.H, D.T.M.H, D.P.H and H.V.T carried out the molecular lab work, participated in data analysis, carried out sequence alignments, participated in the design of the study and

drafted the manuscript; L.P.H carried out the statistical analyses and collected field data; A.M and Q.V.V. conceived of the study, designed the study, coordinated the study and helped draft the manuscript. All authors gave final approval for publication.

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