Free Radical Scavenging by Natural Polyphenols: Atom *versus* Electron transfer

Florent Di Meo,[†] Vincent Lemaur,[‡] Jérôme Cornil,[‡] Roberto Lazzaroni,[‡] Jean-Luc Duroux,[†]

Yoann Olivier,[‡] Patrick Trouillas.[†,‡,§,*]

[†] Laboratoire de Chimie des Substances Naturelles EA-1069, Faculté de Pharmacie, Université de Limoges, 2 rue du Docteur Marcland, Limoges CEDEX, France.

[‡] Service de Chimie des Matériaux Nouveaux, Université de Mons - UMONS, Place du Parc 20, 7000 Mons, Belgium.

[§] Regional Center of Advanced Technologies and Materials, Department of Physical Chemistry, Faculty of Science, Palacký University, 17. listopadu 1192/12, 77146 Olomouc, Czech Republic.

S1. Thermodynamics of HAT between quercetin and the CH3OO• radical

The thermodynamic balance of reaction (5) between quercetin and LOO$^\bullet$ free radicals is favorable for HAT from the 3-, 3'- and 4'-OH groups and unfavorable for the 5- and 7-OH groups (Table S1a). The hierarchy established by DFT calculations is influenced by the solvent (PCM calculations). It is 4'-OH ≈ 3-OH < 3'-OH < 5-OH ≈ 7-OH and 4'-OH < 3'-OH < 3-OH < 7-OH < 5-OH in polar and non-polar solvents, respectively. The shift in BDE due to the solvent is particularly highlighted for the 3- and the 5-OH groups. This is explained by the relatively large dipoles of the ArO$^\bullet$ radicals obtained after HAT from these two groups (9.3 and 9.2 D, respectively). For 3'- and 4'-OH, in the B ring, the dipole moments are only 1.1 and 2.6 D and the solvent effect is weak. An intermediate shift is obtained in a polar solvent for the 7-OH group with an intermediate dipole moment (6.1 D).

The free scavenging of $^\bullet$OH radicals is very favorable with all OH groups (the ΔG° values range from -28.8 to -43.7 kcal/mol) (Table S1a). This confirms the experimental evidence that, due to its high reactivity, the $^\bullet$OH radical is not specific (most hydroxyl groups can potentially scavenge it) and it cannot therefore be used to establish a relevant hierarchy between groups and compounds.

The reaction with RO$^\bullet$ is slightly less favorable but is still exoergic for all OH groups of quercetin (Table S1a). The reactivity of quercetin with the carbon-centered free radicals (e.g.,

L˙) is intermediate between RO˙ and ROO˙. The reaction is favorable with all groups of quercetin but is close to the thermodynamic equilibrium with 5- and 7-OH. From the ΔG estimates of reaction (5) with quercetin, the hierarchy in terms of the free radical scavenging capacity is ˙OH > $CH_3O˙$ > ˙CH_2OH > $CH_3OO˙$. This is in good agreement with the experimental and physiological observations.

S2. **Discussion on kinetic solvent effect (KSE)**

The PCET mechanism is known to exhibit kinetic solvent effects (KSE). It has been well-described that intermolecular interaction, namely between phenolic OH groups and solvent may decrease rate constants. Rate constants in HBA (H bond acceptor) solvents can be efficiently corrected according to the following equation:[27,35,67]

$$\log(k^{Solvent}_{ArOH/R^{\bullet}}/M^{-1}s^{-1}) = \log(k^{0}_{ArOH/R^{\bullet}}/M^{-1}s^{-1}) - 8.3\alpha_2^H \beta_2^H$$

where k^o is the rate constant in a non HBA solvent, α_2^H predicts H-bonding capacity of ArOH and β_2^H describes the HBA capacity of the solvent. In polar solvents, β_2^H is around 0.5 (e.g., 0.4 for alcohol); and for phenol α_2^H is around 0.6. Therefore according to Eq. (14) the KSE-corrected rate constant can be reduced by more than 10^2. However in our case, most of the OH groups, except 7-OH, are involved in strong intramolecular H-bonding (with the neighbouring group for 3'-OH and 4'-OH, and with the keto group for 3-OH and 5-OH).[10,24] It has been shown that in such cases, KSE is lowered since intermolecular interactions with solvent are weakened.[27,29] E.g. α_2^H is around 0.25 for guaiacol (2-methoxyphenol).[27] Taking a value of 0.5 for β_2^H, the rate constant of PCET from guaiacol would only be divided by 10. In non-polar solvents, β_2^H is much lower and KSE is of minor importance in our case. Taking explicitly the solvent into account would have required a huge computational effort. Therefore PCM-type solvent is a perfect choice for non-polar solvents. For polar solvents it properly takes polarizable effects into account but we are aware that KSE is not fully determined, inducing a slight overestimation of PCET rate constants in our case.

Table S3: Gibbs energies (kcal/mol) of the free radical scavenging of $CH_3OO^\bullet$, $CH_3O^\bullet$, $^\bullet CH_2OH$ and $^\bullet OH$ by quercetin in polar and non polar media, following the (a) CPET, (b) ET-PT and (c) SPLET mechanisms

(a) CPET

OH group	$CH_3OO^\bullet$			$CH_3O^\bullet$			$^\bullet CH_2OH$			$HO^\bullet$	
	Non polar	*polar*		*non polar*	*polar*		*non polar*	*polar*		*non polar*	*polar*
3-OH	-3.5	-8.1		-22.2	-26.5		-13.3	-14.1		-38.3	-40.6
3'OH	-5.0	-4.0		-23.7	-22.3		-14.9	-9.9		-39.8	-36.4
4'-OH	-9.0	-8.4		-27.6	-26.8		-18.8	-14.4		-43.7	-40.9
5-OH	12.4	2.7		-6.2	-15.7		2.6	-3.3		-22.3	-29.8
7-OH	2.7	3.7		-16.0	-14.7		-7.1	-2.3		-32.0	-28.8

(b) ET-PT

Reaction		$CH_3OO^\bullet$			$CH_3O^\bullet$			$^\bullet CH_2OH$			$HO^\bullet$	
		non polar	*polar*		*non polar*	*polar*		*non polar*	*polar*		*non polar*	*polar*
2	Quercetin	81.9	29.0		72.6	21.8		117.3	72.7		59.8	7.0
	3-OH	-85.4	-37.2		-94.7	-48.3		-130.7	-86.8		-98.1	-47.6
	3'OH	-86.9	-32.9		-96.2	-44.1		-132.2	-82.7		-99.6	-43.4
3	4'-OH	-90.9	-37.4		-100.2	-48.6		-136.2	-87.1		-103.5	-47.9
	5-OH	-69.5	-26.3		-78.8	-37.5		-114.7	-76.0		-82.1	-36.8
	7-OH	-79.2	-25.3		-88.5	-36.5		-124.5	-75.0		-91.9	-35.8

(c) ET reaction in SPLET

Reaction	Compound[a]	$CH_3OO^\bullet$			$CH_3O^\bullet$			$^\bullet CH_2OH$			$HO^\bullet$	
		non polar	*polar*		*non polar*	*polar*		*non polar*	*polar*		*non polar*	*polar*
	$[QOH-H_3]^-$	21.3	5.4		12.0	-1.7		56.7	49.2		-0.8	-16.6
	$[QOH-H_{3'}]^-$	27.4	8.7		18.1	1.6		62.9	52.5		5.3	-13.3
5	$[QOH-H_{4'}]^-$	27.9	9.3		18.6	2.1		63.4	53.0		5.8	-12.7
	$[QOH-H_5]^-$	32.1	13.5		22.9	6.4		67.6	57.3		10.1	-8.5
	$[QOH-H_7]^-$	35.0	18.9		25.7	10.9		70.5	61.9		12.9	-3.9

[a] [QOH-H3]-, [QOH-H3']-, [QOH-H4']-, [QOH-H5]-, [QOH-H7]- correspond to the deprotonation of quercetin on 3-OH, 3'-OH, 4'-OH, 5-OH, 7-OH, respectively.

Table S4: Energies (eV) of (a) free radical SOMOs and (b) quercetin MO in water and benzene. MO energies have been performed within HF theory with Def2-TZVPP quality basis set.

MO	QOH		QOH-3H+	QOH-5H+	QOH-7H+	QOH-3'H+	QOH-4'H+
	Benzene	*Water*	*Water*				
HOMO	-8.0	-8.0	-6.6	-7.3	-7.4	-7.0	-6.7
HOMO-1	-9.0	-9.0	-8.6	-8.1	-8.4	-8.2	-8.7
HOMO-2	-9.4	-9.3	-8.9	-9.0	-8.7	-8.9	-8.9
HOMO-3	-9.6	-9.6	-9.2	-9.2	-9.2	-9.5	-9.4
HOMO-4	-10.5	-10.5	-9.7	-10.1	-10.3	-10.2	-10.0
HOMO-5	-12.3	-12.3	-10.4	-10.4	-10.9	-10.8	-10.7
HOMO-6	-12.7	-12.7	-11.9	-11.6	-11.6	-12.2	-12.1
HOMO-7	-13.6	-13.6	-12.3	-12.1	-12.0	-12.2	-12.2
HOMO-8	-13.9	-13.9	-12.7	-13.4	-13.4	-12.8	-12.9
HOMO-9	-14.4	-14.3	-13.5	-13.6	-13.6	-13.1	-13.7

Table S5: Energy differences (eV) between HOMO and HOMO-n at HF and DFT levels.

QOH-4'H+	HF			KS
	SVP	DZVP (cc-pVDZ)	Def2-TZVP	KS/DZ
HOMO	0.0	0.0	0.0	0.0
HOMO-1	-2.2	-2.1	-2.0	-1.3
HOMO-2	-2.4	-2.3	-2.2	-1.5
HOMO-3	-2.9	-2.9	-2.7	-1.6
HOMO-4	-3.4	-3.4	-3.3	-2.0
HOMO-5	-3.9	-4.0	-4.0	-2.2
HOMO-6	-5.6	-5.4	-5.4	-2.9
HOMO-7	-5.6	-5.6	-5.6	-3.7

QOH-3'H+	HF			KS
	SVP	DZVP (cc-pVDZ)	Def2-TZVP	KS/DZ
HOMO	0.0	0.0	0.0	0.0
HOMO-1	-1.4	-1.5	-1.2	-0.9
HOMO-2	-2.2	-2.3	-1.9	-1.5
HOMO-3	-2.7	-2.9	-2.5	-1.6
HOMO-4	-3.4	-3.5	-3.2	-2.0
HOMO-5	-3.7	-3.5	-3.8	-2.4
HOMO-6	-5.3	-5.4	-5.2	-2.9
HOMO-7	-5.5	-5.5	-5.3	-3.6
HOMO-8	-6.0	-6.1	-5.9	-4.0