



Unveiling the chemistry behind bromination of quercetin: the ‘violet chromogen’



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ABSTRACT

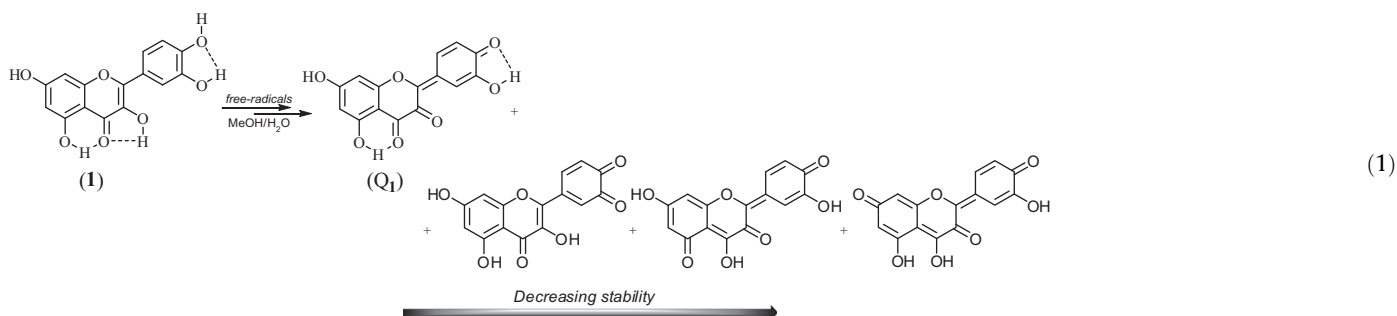
Bromination of quercetin with *N*-bromosuccinimide in neutral aqueous methanol occurs surprisingly in the *electron-deficient* A-ring only. Deprotonation of the acidic 7-OH is a major driver of this regioselective reaction. The increase of electron density makes in fact the quercetin anion suitable for an electrophilic attack by bromine at positions 8 and 6. Several pieces of evidence (NMR spectra and H/D exchange) are presented to substantiate the mechanism advanced. Bromoquinones/quinomethides produced in excess of *N*-bromosuccinimide are responsible for the formation of a stable ‘violet chromogen’.

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Quercetin (**1**) is a polyphenol belonging to the class of ‘flavonoids’ which are widely distributed in the plant kingdom and consequently in our daily diet.^{1,2} Quercetin has recognized biological properties^{3–5} and—as most phenols⁶—is able to slow down the process of oxidation of organic matter⁷ caused by dioxygen ³O₂ (peroxidation). This beneficial antioxidant property is due to the ability that quercetin has to chelate transition-metal ions and to quench peroxy radicals ROO•.^{6,7} The interest in the chemistry

and biology of quercetin is therefore notable, and in the last decades has shown no decline.⁸

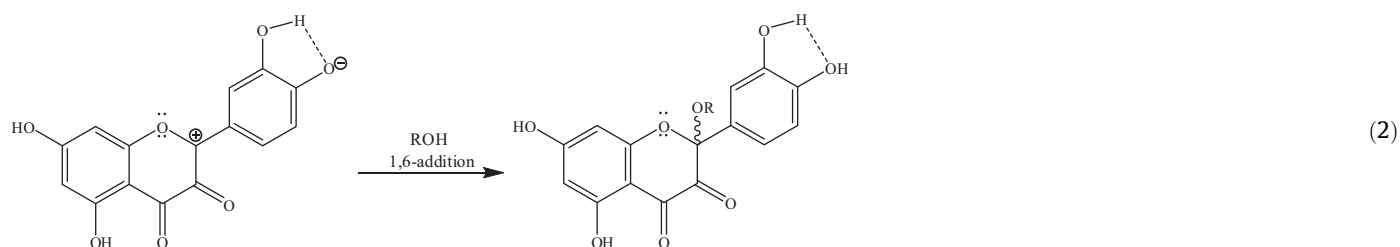
The oxidation chemistry of quercetin has long been investigated.^{9–11} The two-electron oxidation yields quinone/quinomethide compounds (Eq. (1)) that are intensely colored in purple ($\lambda_{\text{max}} \sim 525$ nm, in 80% by volume methanol/water).⁹ Density functional theory (DFT) calculations¹² show that the quinomethide Q₁ is more stable—and thus more abundant in solution—than the other three possible tautomers (Eq. (1)).



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In protic solvents, the survival of the above quinone/quinomethide species (reaction 1) is however very limited. In fact, in 80% methanol/water (v/v) the half-life of Q_1 is 2.5 s only.⁹ Q_1 can be regarded as a resonance-stabilized benzylic carbocation which readily undergoes a proton-assisted (Michael-type) nucleophilic addition of solvent (ROH) at position 2 (and 3) (Eq. (2)).^{13,14} Discoloration of the solution follows this reaction as a consequence of the interruption of the conjugation between the rings B and A+C (Eq. (2)). At room temperature, the reaction in 80% methanol/water (v/v) is over, that is the purple color disappears, in a few tens of seconds.⁹



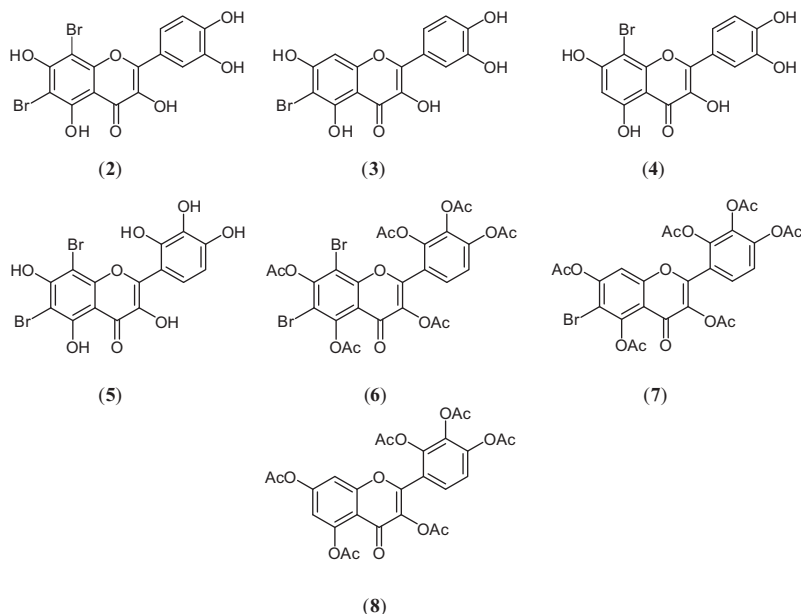
The aforementioned instability of Q_1 in protic solvents, however, seems to contrast with a report of 1992 in which the authors affirm that a methanolic solution of quercetin upon treatment with a neutral aqueous solution of *N*-bromosuccinimide (NBS) produced instantaneously an intense ‘violet chromogen’ ($\lambda_{\max} \sim 510$ nm) which was stable for at least 15 min.¹⁵ Later, the procedure was slightly modified and it was reported that the violet color persisted without decaying for more than one hour.^{16,17} Interestingly, solutions of this oxidized quercetin reagent were used to titrate ascorbic acid and several antibiotics (cefoperazone sodium, cefazolin

sodium, and ceftriaxone sodium) with a simple and accurate spectrophotometric test.^{16,17}

The authors of these works attributed the violet color to the formation of quercetin quinones/quinomethides, in particular to Q_1 .^{15,16} This hypothesis has been reconfirmed until recently¹⁶ after about 20 years from the first observation. Our data, however, do not support this conclusion because Q_1 disappears very quickly in methanol/water mixtures (see above). *What is (are) therefore the compound(s) responsible for this persistent and intense violet color?* While answering this question we chanced upon a few derivatives of quercetin (bromoquercetins and

2'-hydroxy-6,8-dibromoquercetin, see Scheme 1) worthy of being mentioned because we discovered they possess singular properties that will be reported in a forthcoming Letter. Although a few of these compounds are already known,¹⁸ the syntheses we now report (see Supplementary data) are particularly simple and environmentally-friendly deserving therefore consideration.

First, we verified that upon treatment of a methanol solution of quercetin with aqueous NBS in a mole ratio of 1:4, respectively, the solution became immediately violet and the color persisted for



Scheme 1. Quercetin bromoderivatives obtained by treating a methanol solution of quercetin with aqueous NBS followed by reduction with $\text{Na}_2\text{S}_2\text{O}_4$ at room temperature. The acetates were obtained by treating the reaction mixtures with acetic anhydride/pyridine.

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