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The facile formation of trioxanaphthacenes by a [4 + 2] addition of flavonols to 1,2-benzoquinone

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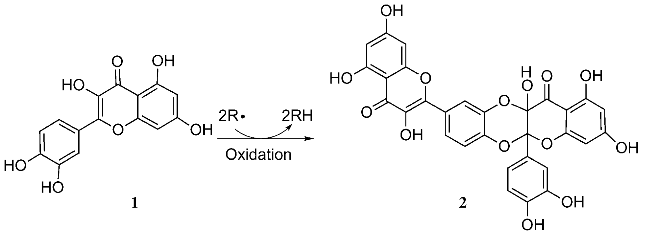
Abstract—Some 4′-substituted flavonols undergo [4 + 2] cycloaddition with 3,5-di-*tert*-butyl-1,2-benzoquinone to give trioxanaphthacenes.

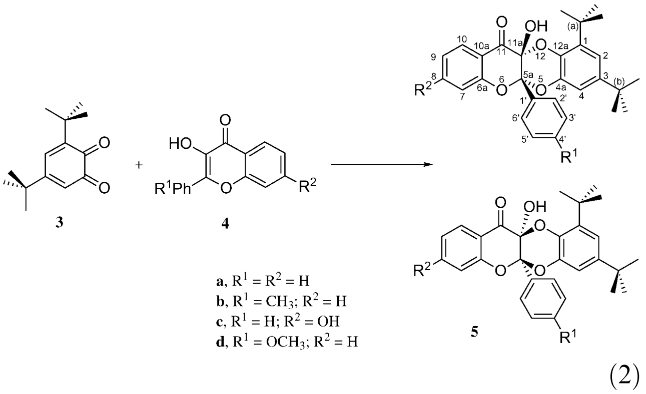
Quercetin is one of the most abundant natural flavonoids in edible fruits and vegetables. Flavonols have been recognized as antioxidants, scavenging dioxygen-derived radicals.[1–7] In recent years, their physiological potential has attracted much attention in relation to their role in cellular and extracellular antioxidant defences against oxygen radicals.[8–10]

In order to clarify which parts of the molecule contribute to the antioxidant activity, the reaction products of **1** accompanying the auto-oxidation of methyl linoleate, have been studied and the major product **2** has been found to be a novel doubly-linked oxidative dimer of **1**.[11] The structure of **2** indicated that the attack of radical species upon the molecule of **1** gave **2** via the elimination of hydrogen from the hydroxyl groups at the C-3, 3′- and 4′-positions. From this result, it was concluded that in homogenous medium, **1** acts mainly as a hydrogen-donating antioxidant and the hydroxyl groups at the C-3, 3′- and 4′-positions and the double bond at the C-2/C-3 are essential for the antioxidant activity (Eq. 1).

Looking for a reasonable explanation for this reaction (Eq. 1), we considered other possible pathways. In light of our previous studies on radical-initiated oxidation of catechols[12] we assumed that the first step is the two-electron oxidation of the catechol moiety of **1** resulting in the corresponding 3′,4′-quinone derivative, which then reacts with the C-2/C-3 double bond of **1** in a Diels–Alder reaction. To support this hypothesis, the reaction of 3,5-di-*tert*-butylquinone with several substituted flavonol derivatives was investigated (Eq. 2).[13]



(1)



(2)

Keywords: Quinones; Flavonols; Diels–Alder reaction.

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Table 1. ^{1}H and ^{13}C NMR data of derivatives **5a–d** produced via reaction shown in Eq. 2

Position	**5a**[a] δ ^{1}H (ppm)	**5a** δ ^{13}C (ppm)	**5b**[a] δ ^{1}H (ppm)	**5b** δ ^{13}C (ppm)	**5c**[b] δ ^{1}H (ppm)	**5c** δ ^{13}C (ppm)	**5d**[a] δ ^{1}H (ppm)	**5d** (minor) δ ^{13}C (ppm)
1	—	138.2	—	138.1	—	137.3	—	137.9 (138.1)
2	7.03 m (1H)	117.6	7.01 m (1H)	117.5	6.93 m (1H)	116.5	7.06 (7.01) m (1H)	117.4 (117.5)
3[b]	—	144.9	—	144.8	—	143.7	—	144.7 (144.8)
4	7.07 m (1H)	112.8	7.05 m (1H)	112.8	6.93 m (1H)	112.1	6.85 (7.05) m (1H)	112.8 (112.8)
4a	—	139.7	—	139.7	—	139.9	—	140.1 (139.8)
5a	—	100.8	—	100.8	—	100.2	—	100.8 (100.7)
6a	—	159.4	—	159.4	—	159.7	—	159.5 (159.4)
7	7.11 m (1H)	118.2	7.09 m (1H)	118.2	6.44 m (1H)	102.9	7.06 (7.09) m (1H)	118.3 (118.2)
8	7.60 m (1H)	138.2	7.58 m (1H)	138.1	—	166.4	7.58 m (1H)	138.9 (138.1)
9	7.10 m (1H)	122.4	7.08 m (1H)	122.3	6.57 m (1H)	111.8	7.08 m (1H)	122.3 (122.3)
10	7.89 m (1H)	127.9	7.87 m (1H)	127.8	7.66 m (1H)	129.4	7.87 m (1H)	127.9 (127.8)
10a	—	117.3	—	117.3	—	110.7	—	117.5 (117.3)
11	—	186.7	—	186.7	—	184.9	—	186.7 (186.8)
11a	—	88.8	—	88.8	—	90.0	—	88.8 (88.9)
12a	—	136.7	—	136.7	—	137.1	—	136.3 (136.7)
1′	—	133.7	—	130.7	—	134.7	—	126.0 (125.6)
2′,6′	7.66 m (2H)	128.1	7.54 m (2H)	128.1	7.64 m (1H)	127.7	7.59 m (1H)	129.7 (129.7)
3′,5′	7.30 m (2H)	128.2	7.10 m (2H)	128.8	7.37 m (1H)	128.0	6.80 (6.82) m (1H)	113.4 (113.5)
4′	7.33 m (1H)	129.8	—	139.9	7.37 m (1H)	129.7	—	160.5 (160.4)
R_1	—	—	2.30 s (3H)	21.1	—	—	3.76 s (3H)	55.2 (55.2)
R_2	—	—	—	—	8.61 s (1H)	—	—	—
t-Bu-a(C-1)	—	35.0	—	35.0	—	34.2	—	35.1 (35.0)
t-Bu-Me(C-1)	1.27 s (9H)	29.7	1.25 s (9H)	29.7	1.24 s (9H)	29.6	1.45 (1.26) s (9H)	29.9 (29.7)
t-Bu-b(C-3)	—	34.6	—	34.5	—	34.6	—	34.5 (34.6)
t-Bu-Me(C-3)	1.32 s (9H)	31.5	1.30 s (9H)	31.4	1.25 s (9H)	31.3	1.28 (1.31) s (9H)	31.4 (31.5)
–OH	5.06 s (1H)	—	5.07 s (1H)	—	NA	—	4.99 s (1H)	—
	(5.00 s (1H))[c]		(4.99 s (1H))[d]	—	NA	—	(5.07 s (1H))[e]	—

[a] In $CDCl_3$.

[b] In DMSO-d_6.

[c] Minor species (~10%).

[d] Minor species (~10%).

[e] Minor species (~47%).

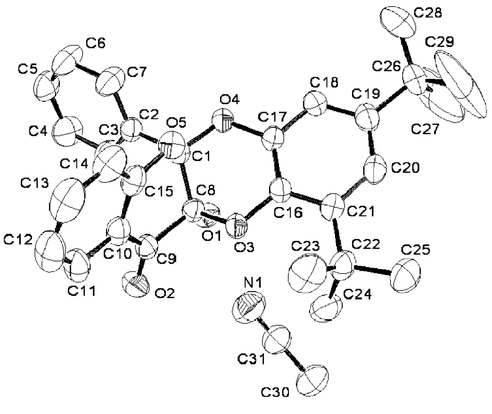

Figure 1. Solid-state structure of **5a**.

A solution of di-*tert*-butyl-1,2-benzoquinone **3** and flavonol **4a** in dry toluene was refluxed under argon for 10 h. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol. After the Diels–Alder reaction 1,3-di-*tert*-butyl-5a-phenyl-11a-hydroxy-5,6,12-hexahydro-5,6,12-trioxanaphthacene-11-one **5a** was obtained as a racemic mixture (90% major species), based on the ^{1}H and ^{13}C NMR measurements (Table 1) in 55% yield. The X-ray single-crystal structure of **5a** (5a*S*,11a*S* and 5a*R*,11a*R* diastereomers) was determined,[14] and its computer-generated drawing is shown in Figure 1. The structural determination with spectral evidence of 4′- and 7′-substituted products (**5b–d**) and their composition are also summarized in Table 1.

The results obtained show that the substituted flavonols are able to act as dienophiles by the use of their C-2/C-3 double bonds in the reaction with *o*-quinones in good yields. On this basis it seems reasonable to suggest that in the auto-oxidation of quercetin, as described by Hirose and co-workers, initially the catechol moiety is 2e oxidized to the *o*-quinone, which undergoes subsequent Diels–Alder reaction with quercetin leading to the trioxanaphthacene.

Acknowledgements

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13. *General procedure*: A solution of di-*tert*-butyl-1,2-benzoquinone (0.220 g, 1 mmol) and the appropriate flavonol (1 mmol) in dry toluene (10 mL) was refluxed under argon for 10 h. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol. Compound **5a**: 55%; mp 162–164 °C. Anal. Calcd for $C_{29}H_{30}O_5$: C, 75.96; H, 6.59. Found: C, 75.82; H, 6.34. Compound **5b**: 53%; mp 188–192 °C. Anal. Calcd for $C_{30}H_{32}O_5$: C, 76.25; H, 6.83. Found: C, 75.98; H, 6.68. Compound **5c**: 88%; mp 198–203 °C. Anal. Calcd for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37. Found: C, 73.11; H, 6.18. Compound **5d**: 62%; mp 229–232 °C. Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 73.44 H, 6.42.
14. X-ray quality single crystals were obtained by slow evaporation of a C_2H_5OH solution of **5a**. Measurement was made on a Nonius CCD diffractometer with graphite monochromatized Mo-K_α radiation ($\lambda = 0.71070$ Å). The structure was solved by direct methods and refinement, based on F^2, was made by full-matrix least-squares techniques. *Crystal data for* **5a**: CHO, 482.56, triclinic, *P*-1, $a = 9.1030(7)$, $b = 11.1974(5)$, $c = 14.4257(9)$, $\alpha = 72.556(3)°$, $\beta = 83.137(3)°$, $\gamma = 88.707(4)°$, $V = 1392.58(15)$ Å^3, $Z = 2$, $\rho_{\text{calcd}} = 1.151$ g cm^{-3}, $\mu = 0.07$ mm^{-1}, $F(000) = 477$, $\theta_{\text{max}} = 26.33°$ ($0 \leqslant h \leqslant 11$, $-13 \leqslant k \leqslant 13$, $-17 \leqslant l \leqslant 17$). Final residuals (for 346 parameters) were $R_1 = 0.0668$ and $wR_2 = 0.1677$ for 4984 reflections with $I > 2\sigma(I)$, GOF = 1.072. Residual electron density was 0.375 and -0.244 e Å^{-3}. The CIF file with data for **5a** has been deposited at the Cambridge Crystallographic Data Centre, CCDC 247752.