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Synthesis and oxidation of 'non-annulated' vitamin E-like compounds

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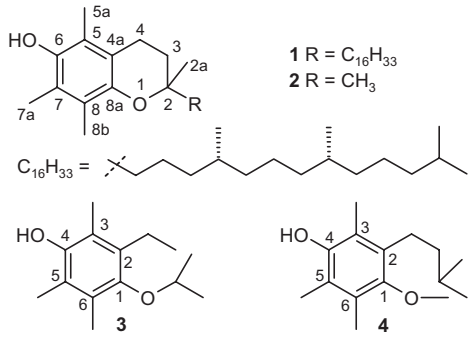
Abstract—Two model compounds (**3** and **4**) having the typical α-tocopherol-type substitution pattern of the aromatic ring, but lacking the annulated pyran ring, have been synthesized. Upon oxidation, the two possible *ortho*-quinone methides (*o*QMs) of each are formed in equal ratio. DFT calculations suggest that there is no angular strain in **3** and **4**, and each of the *o*QM pairs is of similar energy. These results prove that the commonly observed regioselectivity in oxidations of vitamin E-type model compounds is not an electronic substitution effect, but a consequence of annulation.

1. Introduction

Phenolic compounds derived from trimethylhydroquinone by annulation are commonly referred to as vitamin E-type antioxidants. They possess the typical substitution pattern of α-tocopherol (**1**),[1] that is, three aromatic methyl groups and a fourth substituent, which forms a ring structure with one of the oxygens. Oxidation of these compounds to *ortho*-quinone methides[2] (*o*QM) proceeds with peculiar regioselectivity, apparently exclusively involving C-5a (but not C-7a). In the pertinent literature, this behavior has been commonly explained by the so-called Mills–Nixon effect.[3] From this, it was predicted that *o*QM formation proceeds exclusively involving the 'upper' C-5a methyl group in benzopyranols, such as **1** and **2**, and exclusively involving the 'down' C-7a methyl group in benzofuranols. In a recent study,[4] we have shown that the Mills–Nixon theory from 1930 was based on the wrong premises, even though it seemed to provide the proper explanations for the vitamin E system. It was moreover shown that the prediction of complete regioselectivity in oxidations of vitamin E-type antioxidants was contradictory to experiment: the regioselectivity is instead a function of angular strain, changing gradually with the sum of the two annulation angles, but not abruptly with the size of the annulated ring. As a consequence, the oxidation regioselectivity of vitamin E-type phenols was fully explained by the theory of strain-induced bond localization (SIBL).[5]

Another older explanation attempt—mostly evoked together with the Mills–Nixon effect and still present in today's literature—has been postulating the electronic effects of the annulated six-membered ring to be the crucial factors in governing the oxidation regioselectivity of vitamin E-type antioxidants. Even though it seems difficult to imagine why the small difference of one CH_2 group—with regard to inductive effects—should be able to change the regioselectivity completely when going



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from six-membered to five-membered annulated rings, this explanation is still frequently used today.[6] It was the goal of the present study to test the validity of this hypothesis.

2. Results and discussion

The common vitamin E model compound 2,2,5,7,8-pentamethylchroman-6-ol (**2**) is oxidized in high (but not complete) regioselectivity. At room temperature, 98% of the 5a-*o*QM was found besides 2% of the 7a-*o*QM counterpart. The electronic influences of the annulated ring consist of inductive effects of the ring carbons on both C-4a and O-1. Assuming that these effects indeed govern the observed regioselectivity in oxidations, then any compound having similar alkyl substituents at both C-4a and O-1 should exhibit a comparable oxidation regioselectivity—independent of whether these substituents are joined in a ring structure or not. Thus, we have synthesized compounds **3** and **4** as two 'open ring' versions of **2**, which have similar substituents at C-4a and O-1, but no annulated ring. If indeed the electronic effects are responsible for the regioselectivity in oxidations of vitamin E derivatives, then both **3** and **4** should be oxidized in high regioselectivity to the *o*QM which involves the 3-methyl group, while the competitive *o*QM involving the 5-methyl group should be largely disfavored.

Compound **3** was obtained starting from 1-(5-acetoxy-2-hydroxy-3,4,6-trimethylphenyl)ethanone, which was readily obtained from TMHQ by treatment with BF_3–acetic acid complex. Claisen etherification of the free phenolic hydroxyl group followed by reduction of the keto group with simultaneous deacetylation afforded **3** in 73% yield[7] relative to the starting ethanone (Scheme 1). The synthesis of **4** in 33% overall yield[8] employed *O*-benzylated **2**, which underwent ring-opening by an intramolecular elimination process, followed by methylation of the liberated phenolic hydroxyl and simultaneous debenzylation and hydrogenation of the double bond.

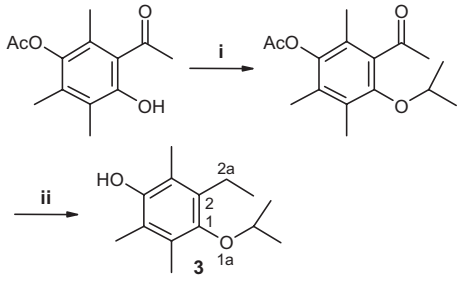
In order to obtain some more insight, **3** and **4** underwent full geometry optimizations at the B3LYP/6-311G* hybrid density functional level.[9] Since there are no annulations in these systems, the bond angles should be relaxed, that is, close to 120° at the aromatic ring. Indeed, the sum of the C-2a–C-2–C-1 and O-1a–C-1–C-2 bond angles (see Schemes 1 and 2) are 239.3° and 237.6° for **3** and **4**, respectively. Since these two systems are not isomeric, it is impossible to compare directly the heats of formation. However, the results of Eqs. 1 and 2 suggest that there is no special stability or instability comparing **3** and **4**.

$$\mathbf{3} + C_2H_6 \rightarrow \mathbf{4} + CH_4 \quad (1)$$

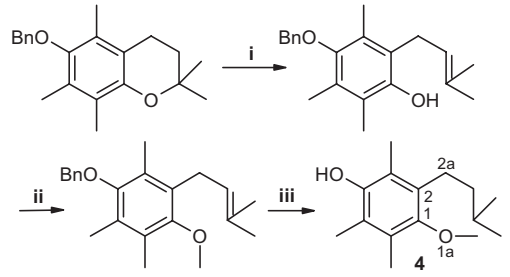
$\Delta E(\text{ZPE corrected}) = 2.5$ kcal mol^{-1}, $\Delta H = 3.1$ kcal mol^{-1}

$$\mathbf{3} + (CH_3)_2CHCH_2CH_3 + CH_3OH \rightarrow \mathbf{4} + C_2H_6 + (CH_3)_2CHOH \quad (2)$$

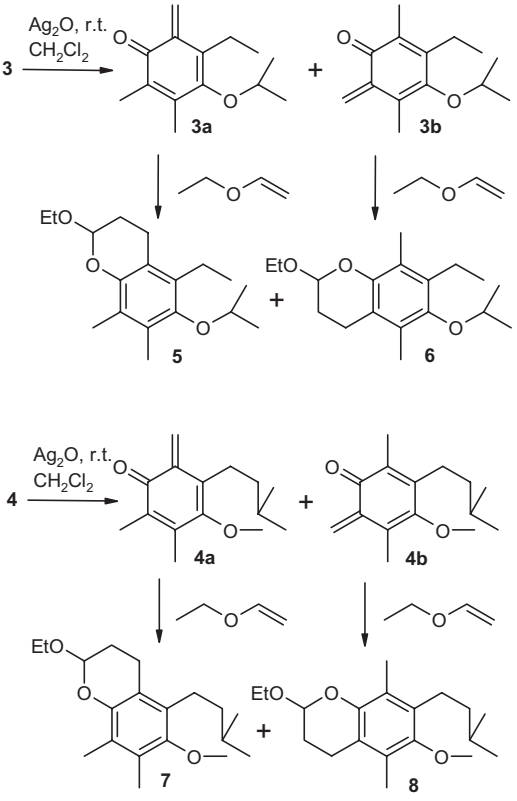
$\Delta E(\text{ZPE corrected}) = -3.8$ kcal mol^{-1}, $\Delta H = -3.7$ kcal mol^{-1}.



Scheme 1. Synthesis of 'non-annulated' vitamin E model compound **3**. Reagents and conditions: (i) Me_2CHBr, K_2CO_3, KI, acetone, rt, 24 h; (ii) Zn, HCl, 2 h, rt, 72%, overall.



Scheme 2. Synthesis of 'non-annulated' vitamin E model compound **4**. Reagents and conditions: (i) H_2SO_4, toluene, reflux, 10 min; (ii) MeOTf, 2 h, rt; (iii) H_2, Pd/C, 24 h, 33% overall.



Scheme 3. Oxidation of compounds **3** and **4**—as the 'non-annulated' versions of vitamin E model compound **2**—to *ortho*-quinone methides and trapping in a hetero-Diels–Alder reaction with ethyl vinyl ether.

Oxidation of both compounds **3** and **4** was carried out by either Ag_2O or elemental bromine at room temperature. For determination of the transient *ortho*-quinone methides, we used the fast trapping reaction in excess ethyl vinyl ether, as described in earlier work.[10] Upon oxidation, compound **3** afforded the two *o*QMs **3a** and **3b** which were trapped as **5** and **6** in a 48/52 ratio independent of the oxidant used, which proved that there was no oxidation regioselectivity at all.[11] In the case of compound **4**, the two *ortho*-quinone methides **4a** and **4b** were even formed in a perfect 50/50 ratio as reflected by the 50/50 ratio found for the two trapping products **7** and **8** (Scheme 3).

It was shown that the *o*QM, which is formed upon oxidation of the phenol, is similar to the intermediate which is formed after the rate determining step, which, in turn, contains the rate determining transition state.[4] Thus, the two possible *o*QMs for **3** and **4** (**3a**/**3b** and **4a**/**4b**, respectively) were calculated. The energy differences between **3a** and **3b** and **4a** and **4b** are small: **3b** is by 0.1 kcal mol^{-1} more stable than **3a** (ZPE corrected ΔE, both have the same ΔH), and **4b** is by 0.4 kcal mol^{-1} more stable than **4a** (both ZPE corrected ΔE and ΔH), that is, within the limitations of the theoretical method each pair shows a comparable stability. The equal stability of the different *o*QM isomers is perhaps best demonstrated by comparing the energy of the isodesmic equations 3a with 3b, and 4a with 4b. Within 0.2 kcal mol^{-1}, each pair of equations shows the same energy. Thus, it is clear from the calculations that in the non-annulated systems there is no preference for one of the two possible *o*QMs, in strong contrast to the situation in the annulated systems.

$$\mathbf{3} + \mathbf{4a} \rightarrow \mathbf{4} + \mathbf{3a} \quad (3a)$$

ΔE(ZPE corrected) $= -0.9$ kcal mol^{-1}, $\Delta H = -0.9$ kcal mol^{-1}

$$\mathbf{3} + \mathbf{4a} \rightarrow \mathbf{4} + \mathbf{3b} \quad (3b)$$

ΔE(ZPE corrected) $= -0.7$ kcal mol^{-1}, $\Delta H = -0.8$ kcal mol^{-1}

$$\mathbf{3} + \mathbf{4b} \rightarrow \mathbf{4} + \mathbf{3b} \quad (4a)$$

ΔE(ZPE corrected) $= -0.3$ kcal mol^{-1}, $\Delta H = -0.4$ kcal mol^{-1}

$$\mathbf{3} + \mathbf{4b} \rightarrow \mathbf{4} + \mathbf{3a} \quad (4b)$$

ΔE(ZPE corrected) $= -0.5$ kcal mol^{-1}, $\Delta H = -0.4$ kcal mol^{-1}.

These results clearly disprove the notion that electronic substituent effects exerted on the aromatic ring via C-4a and O-1 determine the regioselectivity in oxidations of vitamin E-like compounds. The observed regioselectivity is due to the annulation of the aromatic system to an alicyclic ring, rather than due to mere substitution at C-4a and O-1. The effect of the annulation strain on the oxidation selectivity, that is, the ratio of the two possible *ortho*-quinone methides, can be smoothly explained by the SIBL model as mentioned above.[4]

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7. 3-Ethyl-4-isopropoxy-2,5,6-trimethylphenol (**3**), fluffy precipitate of white, long needles, mp 123–125 °C. ^{1}H NMR: δ 1.21 (t, 3H, CH_2–CH_3, $^3J = 7.6$ Hz), 1.28 (d, 6H, CH–$(CH_3)_3$, $^3J = 6.2$ Hz), 2.03, 2.09, 2.14 ($3\times$s, 3×3H, $3\times CH_3$), 2.61 (q, 2H, CH_2–CH_3, $^3J = 7.6$ Hz), 4.25 (sept, 1H, CH–$(CH_3)_3$, $^3J = 6.2$ Hz), 4.55 (s, 1H, OH). ^{13}C NMR: δ 11.8, 12.1, 12.9 ($3\times CH_3$), 13.2 (CH_2–CH_3), 19.8 (CH_2–CH_3), 22.0 (CH–$(CH_3)_3$), 75.7 (CH–$(CH_3)_3$), 114.8, 118.3, 119.1, 120.1, 145.6, 146.9 (^{Ar}C). Anal. Calcd for $C_{14}H_{22}O_2$ (222.33): C, 75.63; H, 9.97. Found: C, 75.47; H, 9.86.
8. 4-Methoxy-2,3,6-trimethyl-5-(3-methyl-butyl)phenol (**4**), white powder, mp 131–132 °C. ^{1}H NMR: δ 1.07 (d, 6H, CH–$(CH_3)_2$, $^3J = 7.0$ Hz), 1.60 (q, 2H, CH–CH_2), 1.71 (m, 1H, $CH(CH_3)_2$), 2.05, 2.06, 2.12 ($3\times$s, 3×3H, $3\times CH_3$), 2.58 (t, 2H, ^{Ar}C–CH_2, $^3J = 7.3$ Hz), 6.12 (s, 1H, OH). ^{13}C NMR: δ 12.1, 12.1, 12.8 ($3\times CH_3$), 20.4 (^{Ar}C–CH_2), 21.0 (CH–$(CH_3)_2$), 27.1 (CH–$(CH_3)_2$), 44.4 (CH–CH_2), 56.9 (OCH_3), 115.4, 117.6, 119.3, 121.1, 145.9, 148.2 (^{Ar}C).

Anal. Calcd for $C_{15}H_{24}O_2$ (236.35): C, 76.23; H, 10.24. Found: C, 75.99; H, 10.20.

9. (a) Gaussian 03, Revisions B.05 and C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004; (b) All the systems under study underwent analytical frequencies calculations to ensure minima ($N_{imag} = 0$) and for obtaining zero point energies (ZPE) and thermochemical parameters.
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11. If the small deviation from the 50/50 ratio is seen as a faint indication of regioselectivity, then it is opposite to the postulated effect.