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Stabilization and First Direct Spectroscopic Evidence of the *o*-Quinone Methide Derived from Vitamin E

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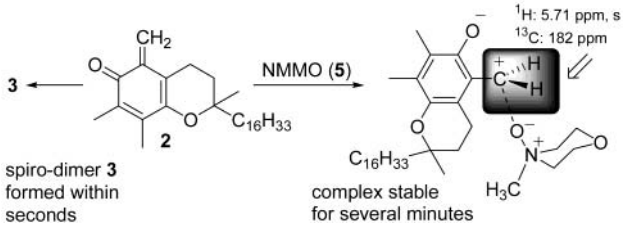
ABSTRACT



The *o*-quinone methide (2) derived from vitamin E (1) can be stabilized at low temperatures in a complex with the highly polar *N*-methylmorpholine-*N*-oxide (5). The lifetime of 2 can thus be prolonged from less than 10 s to several minutes. In the complex formed, 2 adopts a zwitterionic, aromatic structure with the exocyclic methylene group in perpendicular arrangement to the ring plane, stabilized by the negatively charged oxygen in 5.

o-Quinone methides (*o*-QMs) are frequently occurring intermediates, even though their use in synthesis is often hampered by their instability and short lifetime.[1] They are commonly generated in situ from the parent *o*-methylphenols. The same applies for a very prominent redox couple, namely, α-tocopherol (**1**) and its *o*-quinone methide (**2**). The latter has been early recognized as a key intermediate in vitamin E chemistry and vitamin E metabolism.[2] Its involvement had been concluded from the presence of characteristic reaction products, such as spiro-dimer **3**,[3] or from products of specific trapping reactions. The trapping of **2** in a hetero-Diels−Alder reaction with inverse electron demand succeeded with several electron-rich dienophiles, e.g., with ethyl vinyl ether leading to pyrano derivative **4**.[4,5]

Direct spectroscopic evidence for **2** is still lacking; also, the utilization of **2** in synthesis is rather limited, even though it would be highly desirable for the production of novel vitamin E congeners. Apart from the reduction back to vitamin E, which is physiologically important but of no value in synthesis, all attempts to employ **2** in synthesis evoke oxidative in situ generation, followed by scavenging in Diels−Alder processes. The main drawback of this approach is the necessity to apply the dienophilic trapping reagent in large excess, preferably as the solvent itself or as a major solvent component, which naturally limits the range of coreactants and accessible products.

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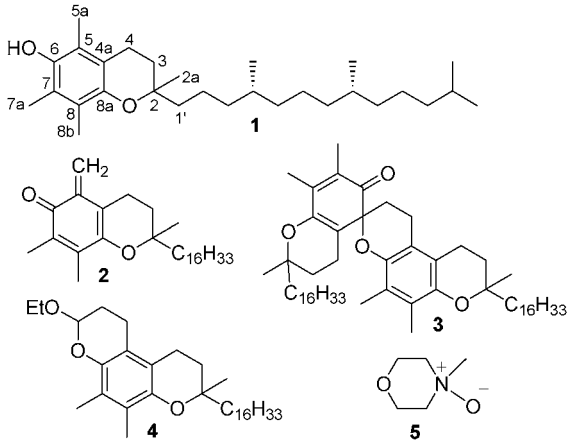


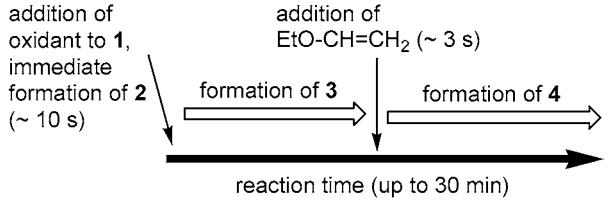
Oxidation of α-tocopherol (**1**) at −78 °C in CH_2Cl_2, with excess Ag_2O, the reagent of choice for *o*-QM generation, caused complete formation of spiro-dimer **3** within about 10 s. The dimer is the result of two molecules of **2** undergoing a hetero-Diels−Alder reaction, one reacting as the diene, and the other one as the dienophile.

In conjunction with our studies on the reaction mechanisms of tertiary amine *N*-oxides[6] and novel tocopherol-type antioxidants,[7] we observed a certain "induction period" of the spiro-dimer formation when *N*-methylmorpholine-*N*-oxide (NMMO, **5**) was present. At lower temperatures the amine *N*-oxide stabilized the *o*-QM **2** in such a way that further reactions (dimerization or trapping) were significantly retarded. Oxidation of **1** by Ag_2O in the presence of 1 equiv of **5** relative to **1** at −78 °C gave complete spiro-dimer formation only after about 20 min, as compared to about 10 s in the absence of **5**.

The observed stabilizing effect is not due to a retarded oxidation of the starting material **1**. When the oxidant was removed after 20 s while maintaining the low temperature throughout, the outcome of the reaction was unchanged: spiro-dimerization was completed after about 20 min, and no starting material was left. This proves that the oxidation of **1** proceeded almost immediately even in the presence of **5**, but the resulting *o*-QM **2** was somehow "held in suspension" by the NMMO, before it could react further by dimerization.

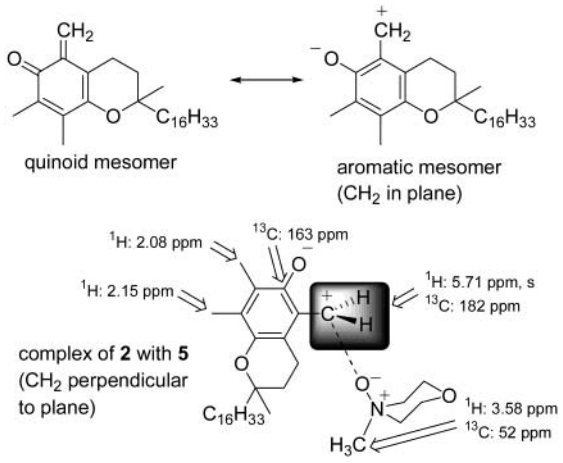
To determine the degree of conversion of **1** into **2** at a certain point in time we used the quick addition of a large excess of ethyl vinyl ether into the reaction mixture. Material that had already undergone oxidation and dimerization would be present as spiro-dimer **3**. In contrast, tocopherol, which had not yet dimerized, was trapped to afford **4**.[8] Thus, the amounts of **3** and **4** present after a certain reaction time are a direct measure of **2** having formed and dimerized up to this point. This procedure, once elaborated, produced quite consistent results, which even allowed recording reaction kinetics (see Scheme 1).

Scheme 1



NMR spectroscopy at low temperature confirmed an interaction between the *o*-QM **2** and NMMO (**5**) (cf. Scheme 2 and Table 1). The prominent signal of the proton spectrum

Scheme 2



is a singlet (2H) at 5.71 ppm, corresponding to the exocyclic methylene group. This peak had a HMQC correlation at 182 ppm, and HMBC cross-peaks at 129 ($^2J_{H-C}$), 118 ($^3J_{H-C}$), and 163 ($^3J_{H-C}$) ppm. The proton resonances of the C-7a and C-8b methyl groups and the C-4 methylene group indicated the presence of an aromatic system,[9] and the ^{13}C NMR data also indicates an aromatic resonance structure,

Table 1. NMR Data (^1H in ppm/^{13}C in ppm, $CDCl_3$) of Selected Atoms/Groups in Tocopherol **1**, *o*-QM **2**, and Spiro-Dimer **3**

atom/group	α-tocopherol (**1**)	*o*-QM **2**	quinoid moiety in spiro-dimer **3**
5a-CH_x	2.18/11.2	5.71/182	1.88/23.6
5-C	- - -/118.5	- - -/129	- - -/80.8
6-C	- - -/144.4	- - -/163	- - -/202.4
7a-CH_3	2.13/12.1	2.15/12	1.73/16.6
8b-CH_3	2.12/11.8	2.08/12	1.64/16.8
4-CH_2	2.62/20.8	2.60/23	1.82/23.4

(6) NMMO is used on the industrial scale as a solvent for cellulose to produce the Lyocell fiber type. The cellulose/NMMO mixtures need to be stabilized during dissolution and further processing against degradation reactions, before being spun. For a review, see: Rosenau, T.; Potthast, A.; Sixta, H.; Kosma, P. *Prog. Polym. Sci.* **2001**, *26*(9), 1763−1837.

(7) (a) Rosenau, T.; Potthast, A.; Elder, T.; Lange, T.; Sixta, H.; Kosma, P. *J. Org. Chem.* **2002**, *67*(11), 3607−3614. (b) Rosenau, T.; Potthast, A.; Hofinger, A.; Kosma, P. *Angew. Chem., Int. Ed.* **2002**, *41*(7), 1171−1173.

cf. Table 1. The downfield shifted signal at 182 ppm for the exocyclic methylene group is especially indicative of a cationic species,[10] and the peak at 163 ppm for C-5 strongly disagrees with a quinoid carbonyl carbon.[11] Also the NMMO moiety was influenced by the interaction with **2**. The *N*-methyl group, giving $^{1}H/^{13}C$ resonances at 3.26/60.8 ppm for pure NMMO ($CDCl_3$), appears now at 3.58/52 ppm.

These results allow an interesting conclusion: the stabilized *o*-quinone methide was evidently not present in its "traditional" quinoid form but in a form that results from its zwitterionic, aromatic resonance structure by rotation of the exocyclic methylene group. A singlet for this group will only be obtained when the two protons are magnetically equivalent, which is the case if the group is arranged perpendicular to the ring plane. With the $^{5a}CH_2$ group standing perpendicular to the ring (out-of-plane), the positive charge is localized at C-5a and cannot dissipate into the aromatic ring, so that **2** is forced into an aromatic structure.[12] Normally, the relatively low rotational barrier[13] of the perpendicular CH_2 group is very easily overcome, the methylene protons align in the ring plane, and the positive charge is immediately compensated under formation of the more stable quinoid resonance structure. In the presence of NMMO, however, the negatively charged *exo*-oxygen of NMMO is evidently able to stabilize the aromatic resonance structure by interactions (supposedly mainly of Coulomb type) with the positively charged C-5a methylene group, so that **2** and **5** form a complex (Scheme 2). The primary effect of the proximity of the negative charge is an increase in the rotational barrier of the exocyclic, cationic methylene group. This results in an impeded rotation into its in-plane form, which means impeded formation of the quinoid resonance form of **2**, and thus delayed dimerization to **3**.

Figure 1 shows the reaction kinetics for the decomposition of the complex between **2** and **5**, which causes formation of the spiro-dimer **3** or pyrano adduct **4**.[14] The stabilizing effect of NMMO, which prevents immediate dimerization of **2**, is clearly demonstrated. The reaction follows a first-order kinetics, which indicates that the decomposition of the *o*-QM−NMMO complex is rate-determining, the subsequent

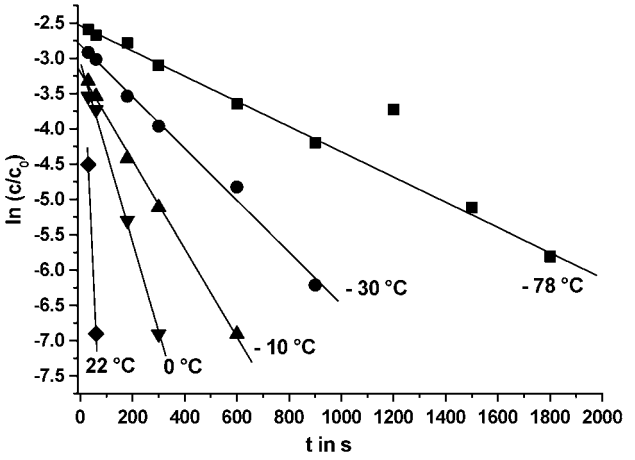


Figure 1. First-order kinetics of the decomposition of the complex between **2** and **5** at different temperatures, followed by trapping of released **2** with ethyl vinyl ether.

processes, i.e., dimerization or reaction with ethyl vinyl ether, being fast and thus of no influence on the rate law. Further experiments revealed a strong temperature dependence of the stabilizing effect, which is very small at 0 °C and nearly undetectable at room temperature. This allows estimation of the activation parameters for the formation of free **2** from the NMMO complex: With a $\Delta H^{\ddagger}$ of 47 kJ·mol^{-1}, the reaction is comparable to the cleavage of a strong hydrogen bond.

The observed stabilizing effect of **5** on **2** can favorably be applied in syntheses involving the tocopherol-derived *o*-QM **2**. For instance, in a previous approach toward γ-tocopher-5-yl-propionic acid[15] we had to use the valuable *O*-methyl-*C*,*O*-bis(trimethylsilyl)-ketene acetal in extreme excess (as solvent component) to trap the thermally generated intermediate **2** in order to achieve acceptable yields (72%). Using the NMMO-stabilized **2**, the same conversion succeeded with merely 2 equiv of the dienophile in even better yield (78%).

Preliminary experiments have shown that NMMO (**5**) can be replaced by trimethylamine *N*-oxide with similar results, while long-chain tertiary amine *N*-oxides seem to be less effective. NMMO monohydrate and semisesquihydrate are ineffective, which seems plausible as the negatively charged *exo*-oxygen in these amine *N*-oxide hydrates is blocked by intermolecular hydrogen bonds and thus not free to interact with **2**. Also, the stabilizing effect in the case of other *o*-QMs, such as the one derived from the vitamin E model compound 2,2,5,7,8-pentamethylchroman-6-ol, was much smaller, which indicates that the isoprenoid side chain in **1** and **2** must have a contributing effect.

Future work will be aimed at exploiting the stabilized *o*-QM **2** in the synthesis of tocopherol derivatives and at correlating the experimental findings with computational results.

(8) The rate constant for the reaction of **2** to **4** is about 10 times larger than that of the spirodimerization to **3**. As ethyl vinyl ether is added in more than a 100-fold molar excess relative to **1**, the trapping reaction becomes about 3 orders of magnitude faster than the dimerization, so that the formation of spiro-dimer **3** after addition of ethyl vinyl ether into the reaction system can be neglected.

(9) As a result of the ring current effect, the resonances of the protons at C-7a, C-8b, and C-4 experience a downfield shift in tocopherol (**1**), which seems still to be operating in the complex between **2** and **5** (Table 1).

(10) The ^{13}C resonances of carbocations can range between 100 to above 300 ppm. See: Kalinowski, H. O.; Berger, S.; Braun, S. *^{13}C NMR-Spektroskopie*; Georg Thieme Verlag: Stuttgart, 1984; p 370.

(11) ^{13}C resonances of quinoid carbons are usually found between 180 and 195 ppm. See: ref 10, p 281.

(12) The structure of **2** in the complex with the perpendicular CH_2 group is not a resonance form of quinoid **2**, as rotating the methylene group breaks the resonance.

(13) For the issue of planar and perpendicular benzyl cations and the corresponding rotational barriers, see: Dorigo, A. E.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 6942−6948.

(14) After addition of ethyl vinyl ether at certain reaction times and workup, the ratio **3**/**4** was determined by NMR. The amount of **4** corresponded to the amount of stabilized **2** still present at the time of CH_2═CH−OEt addition. No other compounds than **3** and **4** were detected.

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