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Stabilization of *ortho*-quinone methides by a bis(sulfonium ylide) derived from 2,5-dihydroxy-[1,4]benzoquinone

Anjan Patel [a], Thomas Netscher [b], Thomas Rosenau [a,*]

[a] *BOKU University, Department of Chemistry, Muthgasse 18, A-1190 Vienna, Austria*
[b] *Research and Development, DSM Nutritional Products, PO Box 3255, CH-4002 Basel, Switzerland*

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Abstract

The zwitterionic intermediates (**2a**) in the oxidation of *ortho*-alkylphenols (**1**) and bis(sulfonium ylide) **3** form reasonably stable 2:1-complexes (**4**), in which the *ortho*-quinone methide (*o*QM) moieties are not present in quinoid form with the exocyclic in-plane methylene group, but as zwitterionic, aromatic conformer having an out-of-plane exocyclic methylene group. The complex **7** derived from the α-tocopherol model compound PMC (**5**) was comprehensively characterized. As exemplarily demonstrated, the adducts can be advantageously employed in organic synthesis as 'stabilized *o*QMs'.

Keywords: *ortho*-Quinone methides; *ortho*-Alkylphenols; Aromaticity; Sulfonium ylides; Zwitterions

ortho-Quinone methides (*o*QMs, **2**), obtained from their parent *ortho*-methylphenols (**1**) by oxidation, are a class of chemical intermediates that have not been isolated directly. Their mere existence, however, is confirmed beyond any doubt as there is abundant indirect evidence for their in situ formation, which comes mainly from the identification of their reaction products, as well as from trapping reactions. In 1963, the first spectrophotometric observation of a chromophore with supposed *o*QM structure was reported.[1] Also in some other cases fast UV spectroscopy[2] at low temperatures was used to detect the occurrence of intermediates, which had stronger UV-absorption than starting materials and final products, and were consequently attributed to *o*QM-type structures. In the previous work, we had shown by the example of tocopherol-type compounds that zwitterionic structures (**2a**) are quite transitory intermediates in the formation of the *o*QMs (**2**) from the parent phenols.[3] Direct NMR spectroscopic evidence of an *o*QM was provided recently when the *o*QM derived from α-tocopherol was temporarily stabilized by interaction with the zwitterionic *N*-methylmorpholine-*N*-oxide at lower temperatures (−78 °C).[4]

Here, we would like to report the interaction of the zwitterionic precursors of *ortho*-quinone methides (**2a**) with bis(sulfonium ylide) **3** and the resulting formation of reasonably stable 2:1 complexes **4**, which were unaltered at −78 °C for 10 h and stable at room temperature under inert conditions for as long as 15–30 min. The *o*QM was produced by Ag_2O oxidation of the respective *ortho*-methylphenol in a solution containing 0.50–0.55 equiv of bis(sulfonium ylide) **3**. This compound is readily prepared from 2,5-dihydroxy-[1,4]benzoquinone by reaction with DMSO in acetic anhydride.[5] Although the species interacting with the ylide is actually the zwitterionic oxidation intermediate **2a** and not the *o*QM itself, the term 'stabilized *o*QM' will be used in the following for complexes **4**. Model experiments were carried out with the α-tocopherol model 2,2,5,7,8-pentamethylchroman-6-ol (PMC, **5**), which upon oxidation formed the zwitterionic structure **6a** that in turn reacted with bis(sulfonium ylide) **3** to form the 2:1 complex **7**.

* Corresponding author. Tel.: +43 1 360066071; fax: +43 1 360066059.
E-mail address: thomas.rosenau@boku.ac.at (T. Rosenau).

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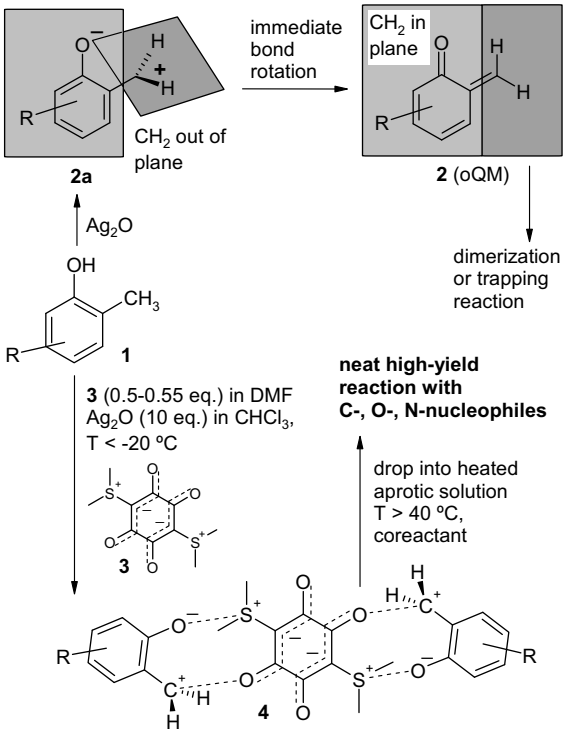
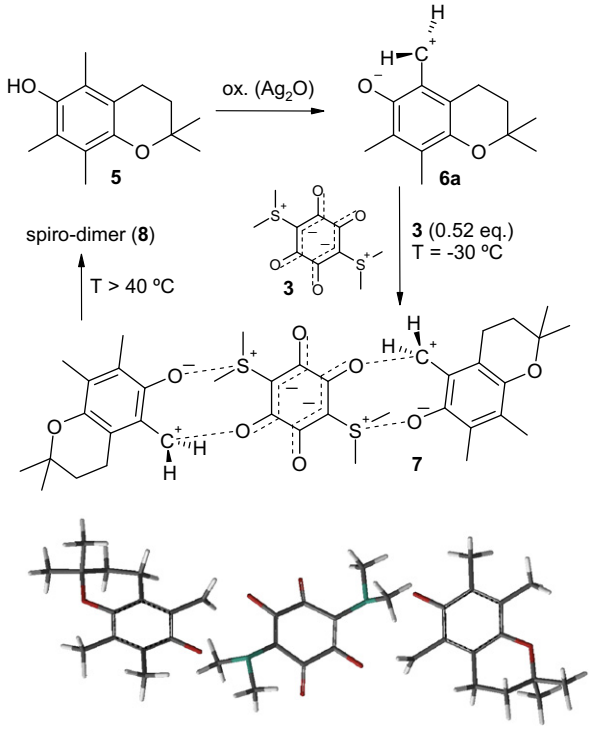
In the complexes formed, both *o*QMs adopt a zwitterionic, aromatic structure (**2a**) with the exocyclic methylene group in perpendicular arrangement to the ring plane, stabilized by the negatively charged oxygen in **3**. Simultaneously, the negatively charged oxygens in the *o*QM parts interact with the positively charged sulfur to provide additional stabilization. Thus, the stabilized *ortho*-quinone methides are evidently not present in their 'traditional' quinoid form with the exocyclic in-plane methylene group, but as zwitterionic, aromatic structure having an out-of-plane exocyclic methylene group. It should be noted that the latter structure is *not* a resonance structure of the *o*QM as such canonic structures differ *only* in the arrangement of multiple bonds. However, the aromatics in **4** and the *o*QMs (**2**) are distinguished by a different conformation of the exocyclic methylene group in addition. Formation of **2** from **2a** as present in complex **4** requires rotation of the methylene group into the ring plane, which is coupled to the immediate aromatic-to-quinone conversion.

The electrostatic interactions in complexes **4** were obviously sufficient to 'favor' the zwitterionic structure (**2a**) in a manner that formation of the quinoid structure (**2**) was 'suspended', so that all reactions typical of *o*QMs in their quinoid form (such as spiro-dimerizations or trapping in [4+2]-cycloadditions, e.g., with ethyl vinyl ether)[6] were suppressed or at least slowed down. Decomposition of the complex was immediate by fast heating to 40 °C or above, best achieved by slowly adding a cold solution of the complex into a heated solution of the coreactant. This causes disintegration of the complex, immediate rotation of the methylene group into the ring plane and thus formation of the *o*QM which then shows the 'classical' chemistry of such compounds (Scheme 1).

Complex **7**, formed by Ag_2O oxidation of PMC (**5**) in the presence of **3**, was isolated at −30 °C as an amorphous addition product.[7] It showed the exact ratio of 2:1 between **3** and **6a**. Unfortunately, despite extensive trials, all attempts to obtain (micro)crystalline **7** suitable for X-ray or neutron scattering failed. A reliable image of the structure of the complex (Scheme 2) was obtained by refining a quantum-chemical prediction (DFT, B3LYP 6-31G* level of theory) of the crystal structure until optimum agreement with powder diffraction data was reached.[8] Proton NMR spectroscopy of complex **7** in DMSO-d_6 at 0 °C showed a singlet (2H) at 5.85 ppm, corresponding to the exocyclic methylene group. This peak showed a heteronuclear correlation to a carbon at 191.8 ppm, and HMBC cross peaks at 129.9 ppm ($^2J_{H-C}$), 117.2 ppm ($^3J_{H-C}$), and 154.1 ppm ($^3J_{H-C}$). The proton resonances of the 7a-CH_3, 8b-CH_3 methyl groups and the 4-CH_2 methylene group at 11.8, 12.0, and 20.4 ppm indicated the presence of an aromatic system.[9] The high down-field shift of the carbon resonance at 191 ppm for the exocyclic methylene group is especially indicative of a cationic species,[10] and the peak at 154 ppm for C-5 agrees with a phenolate carbon, but not with a quinoid carbonyl carbon.[11] Also the bis(sulfonium ylide) moiety was influenced, albeit rather weakly. The four magnetically equivalent methyl groups in bis(sulfonium ylide) resonating at 3.02 ppm in DMSO-d_6 appeared as two



Scheme 1. Oxidation of *ortho*-alkylphenols (**1**) to the *ortho*-quinone methide (**2**) via transient zwitterionic intermediates (**2a**) that can be stabilized by forming complexes (**4**) with 2,5-dihydroxy[1,4]benzoquinone-derived bis(sulfonium ylide) **3**.



Scheme 2. Formula and molecular structure of the 2:1 complex **7**, formed between the zwitterionic *o*QM precursor derived from pentamethylchromanol **5** and bis(sulfonium ylide) **3**.

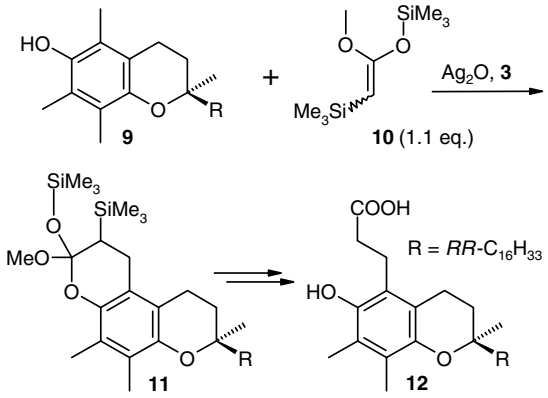
singlets at 2.94 ppm and 2.98 ppm in complex **7**. A fully formed σ-bond between the phenolic oxygen and the benzylic methylene group can be excluded based on the NMR data. However, through-space stabilization of the charges is likely to be an important contribution to the stability of the complex.

Compound **7** passes LC setups as single entity, but will show signs of degradation at rt, so that it is best used at lower temperatures. Purification of the *o*QM complexes is unnecessary as their formation was near quantitative in all cases if a slight excess of **3** and excess oxidant (5 equiv of freshly prepared Ag_2O) was used.[12] Decomposition of **7** by heating in aprotic media to 40 °C afforded **3** and spiro-dimer **8** quantitatively. In the presence of coreactants, the zwitterionic forms of the *o*QMs can be conveniently derivatized as discussed in the following.

The stabilization of *o*QMs was preliminarily employed in organic synthesis—an apparently very promising application which, however, has yet to be fully exploited.[8] The general advantage is that *o*QMs can now be used and handled like stable, stoichiometrically usable, dosable reagents. They can be reacted in a controlled way without the danger of immediate self-dimerization or other uncontrolled side reactions. Preparation of the complexes and their further conversion can be separated, so that the derivatization of the preformed, stabilized *o*QMs can be carried out at later times, in different vessels or reaction media, and under different reaction conditions. This way, high yield conversions *o*QMs with coreactants in equimolar amounts appear to become generally possible for the first time, although it is advisable to optimize the conditions for complex formation for each *o*QM used. By contrast, *o*QMs were so far almost exclusively employed in trapping-like scenarios, that is, the coreactant was present in a large excess consuming the *o*QM immediately upon its formation.

In four examples, the potential of the stabilization approach in synthesis was demonstrated. 5-(γ-Tocopheryl)propionic acid (**12**) was previously prepared in 72% yield by the reaction of the *o*QM derived from α-tocopherol (**9**) with *O*-methyl-*C*,*O*-bis-(trimethylsilyl)-ketene acetal (**10**), which was used as 'trapping agent' in large excess.[13] By introducing the stabilized *o*QM into a solution of only 1.1 equiv of the ketene acetal at 40 °C a near-quantitative reaction to *ortho*-ester derivative **11** was observed after which two subsequent hydrolysis steps afforded **11** in 93% overall yield.[14] In this case, the *o*QM released from the stabilized zwitterionic form reacted in the 'classical' [4+2]-cycloaddition way as electron-deficient hetero-analogous diene (Scheme 3).

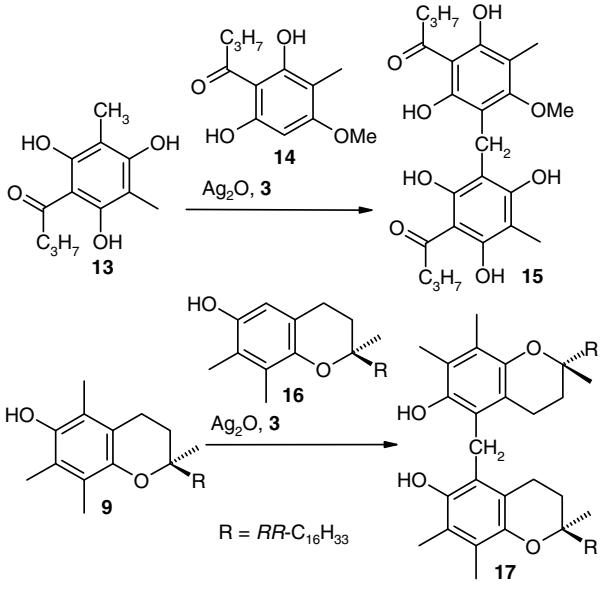
In a second example, the stabilized *o*QMs reacted as *C*-alkylating agents. The anthelmintic margaspidin (**15**),[15] was synthesized by introducing a solution of the stabilized *o*QM from *O*-nor-methylaspidin (**13**) into a warm solution of aspidin (**14**). The *o*QM liberated from the former acted as alkylating agent toward the latter, and the target **15**[16] was obtained in a satisfying 84% yield which compared



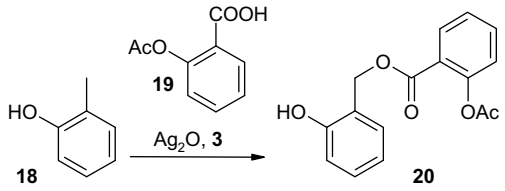
Scheme 3. High-yield synthesis of 5-(γ-tocopheryl)propionic acid (**12**) employing the stabilized *o*QM derived from α-tocopherol in a hetero-Diels–Alder reaction with inverse electron demand.

favorably to the existing tedious isolation approaches (Scheme 4). A similar alkylation approach was used to provide bis(5-γ-tocopheryl)methane (**17**),[17] a vitamin E oxidation product and model compound which could be synthesized so far in dissatisfying yields only. Applying the ylide-stabilized form of the *o*QM derived from α-tocopherol (**9**) as the alkylating agent toward equimolar amounts of γ-tocopherol (**16**), a non-optimized 78% yield of **17** was obtained,[18] which illustrated quite nicely the potential of the stabilized *o*QMs as reagents in synthesis (Scheme 4).

As the fourth example, *o*-hydroxybenzyl *O*-acetyl-salicylate (saligenin *O*-acetyl-salicylate, **20**), the aglycon in salicoylsalicin, was synthesized which was so far not available from high-yield syntheses.[19] This compound is closely related to the β-glucosidase inhibitor salicortin, which is



Scheme 4. High-yield synthesis of margaspidin (**15**) and bis(5-γ-tocopheryl)methane (**17**) employing ylide-stabilized *o*QMs as alkylating agents in Friedel–Crafts-type reactions.



Scheme 5. High-yield synthesis of (*O*-acetylsalicyl)saligenin (**20**) via the stabilized *o*QMs from *ortho*-cresol undergoing nucleophilic substitution.

also an insecticide and a model for 'biological' *o*QMs. The present stabilization allowed the reaction of the stabilized *o*QM from *ortho*-cresol (**18**), in an O-alkylation process, with 1.5 equiv of acetylsalicylic acid (**19**) to saligenin derivative **20** in 82% isolated yield[20] (Scheme 5).

In all four examples, the formation of the dimerization products of the *o*QMs was below 6%, which is remarkable as the formation of (spiro-)dimers is usually the main reaction path of *o*QMs in the absence of large excess of 'external' coreactants. Further studies will have to exploit the stabilization approach for organic synthesis. Similarly, more general stabilization approaches, using the interaction of ionic species (as e.g., present in ionic liquids) with the zwitterionic oxidation intermediate **2a**, will have to be tested.

Acknowledgment

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7. *Complex* **7**. ^{1}H NMR (DMSO-d_6, 400 MHz, 4 mg/0.6 mL, 0 °C): δ 1.27 (s, 6H, 2 × 2a-CH_3), 1.28 (s, 6H, 2 × 2a-CH_3), 1.76 (t, 2H, $^{3}J = 6.9$ Hz, 2 × 3-CH_2), 2.02 (s, 6H, 2 × 8b-CH_3), 2.11 (s, 6H, 2 × 7a-CH_3), 2.61 (t, 4H, $^{3}J = 6.9$ Hz, 2 × 4-CH_2), 2.94 (s, 6H, 2 × –S^{+}–Me), 2.98 (s, 6H, 2 × –S^{+}–Me), 5.85 (s, 4H, 2×, 5a-CH_2^{+}), ^{13}C NMR (DMSO-d_6, 100 MHz, 18 mg/0.7 mL, 0 °C): 11.8 (7a-CH_3), 12.0 (8b-CH_3), 20.4 (4-CH_2), 24.2 (S–Me), 24.4 (S–Me), 26.6 (2a-CH_3), 27.3 (2a-CH_3), 32.4 (3-CH_2), 72.4 (2-C), 94.0 (C–S in ylide), 116.2 (8-C), 117.2 (4a-C), 127.0 (7-C), 129.9 (5-C), 151.4 (8a-C), 154.1 (6-C), 172,2 (C–O in ylide), 191.8 (5a-CH_2^{+}) 8.81, 123.01, 125.76, 145.04, 147.28. Anal. Calcd for $C_{38}H_{48}O_8S_2$ (696.9): C, 65.49; H, 6.94; S, 9.20. Found: C, 65.42; H, 7.02; S, 9.02. It should be noted that at rt, complex **7** is degraded into an equimolar mixture of **3** and equimolar amounts of the spiro-dimer **8**, which has the same net composition. However, the correct microanalysis of that resulting mixtures proves the purity of the parent complex **7** as well.
8. A comprehensive account of the structure of the complexes along with computational treatments and synthetic applications will follow in due course.
9. Due to the ring current effect, the resonances of the protons at C-7a, C-8b, and C-4 experience a down-field shift in tocopherol (**9**) and related derivatives, which evidently seems to be still operative in the complex between **2** and **6a**.
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: Stuttgart, 1984; p 370.
11. ^{13}C resonances of quinoid carbons are usually found between 180 and 195 ppm, see Ref. 9, p 281.
12. *General experimental procedure for the preparation of stabilized o-QMs* (**4**): Freshly prepared silver oxide (5 mmol) was suspended in ethyl acetate or chloroform (150 mL) at temperatures between −10 °C and −30 °C, maintaining this temperature throughout. A rt solution of bis-ylide **3** (0.55 mmol) in DMSO (5 mL) was added at once. The mixture was stirred vigorously and a solution of the *ortho*-alkylphenol (1 mmol) in EtOAc or chloroform, respectively, was added dropwise over about 10 min. After completion of the addition the mixture was stirred for another 10 min and filtered through a cooled filter to remove silver and excess silver oxide. In some cases the clear filtrate, which is usually yellow, might be colored gray to black by colloidal silver compounds, which does not influence reactivity or reaction behavior. The cooled solution of the stabilized *o*QM was used for further reactions. The *o*QMs were liberated by fast heating to 40 °C, advantageously by dropping the solution into a solvent heated to 40 °C which contained the coreactant.
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14. NMR data were identical to those in Ref. 12. Purity: Anal. Calcd for $C_{31}H_{52}O_4$ (488.75): C, 76.18; H, 10.72. Found: C, 76.06; H, 11.01.
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