Calixarene-Type Macrocycles by Oxidation of Phenols Related to Vitamin E**

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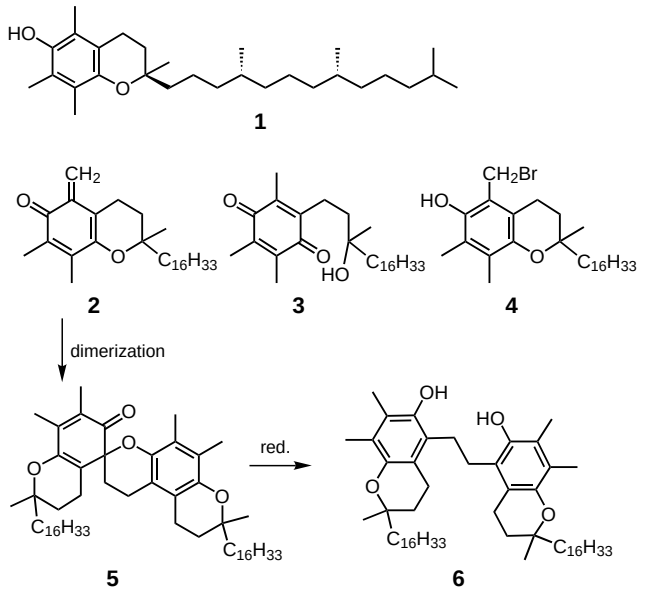
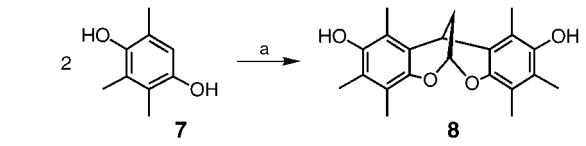
α-Tocopherol (**1**), the major component of vitamin E, is the biologically most active lipid-soluble phenolic antioxidant in mammalian tissues.[1] The two main reactions of vitamin E in vivo are formation of the relatively stable α-tocopheroxyl radical and its bimolecular self-reaction to give free α-tocopherol and *ortho*-quinone methide (*o*-QM) **2**. The latter reaction involves selective transfer of a H atom from the 5-methyl group[2] of one radical to the phenoxyl oxygen atom of the other radical.[3] The extremely high antioxidant behavior of α-tocopherol[4] has been attributed to the geometry of the pyran ring, which allows for optimum spin delocalization.[5]

With the "siamese twin" model compound **8**, which was obtained in good yield (76%) by condensation of trimethylhydroquinone (**7**) with 1,1,3,3-tetramethoxypropane (Scheme 1),[6] it became possible for the first time to "lock" the alicyclic chromane ring into a specific geometry (without disturbing the characteristic vitamin E structure by the introduction of large substituents). Any conformational change in one of the two chromanol moieties in **8**, which would influence the radical stability,[5] is accompanied by the reverse change in the second chromanol moiety, thus causing the opposite effect there. Computational results predict the formation of stable mono- and biradicals from **8** and a spin delocalization over both phenolic rings, despite the presence of a nonconjugated spacer. Preliminary EPR experiments have shown 7-line spectra ($g = 2.0048 \pm 0.0002$) resembling those of α-tocopherol, but exhibiting additional hyperfine structure.

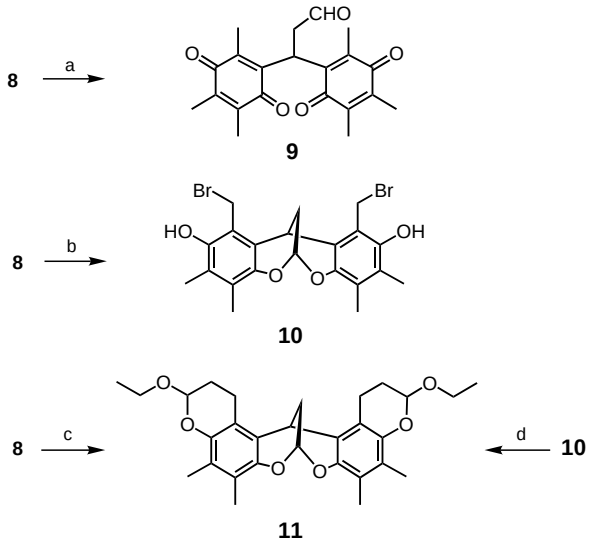


Scheme 1. Structure of α-tocopherol (vitamin E) and some of its characteristic reaction products.

From the viewpoint of the chemical behavior, it could reasonably be expected that all the characteristic reactions of vitamin E (Scheme 2) would occur twice in **8**. Oxidation of α-tocopherol (**1**) with $FeCl_3$ in aqueous methanol is known to afford the corresponding *p*-quinone.[7] Model compound **8** showed analogous oxidation behavior, and a bis(*p*-quinone) **9** (Scheme 3) was obtained. Bromination, which produces tocopheryl bromide **4** from α-tocopherol,[8] also proceeded twice in molecule **8** to afford dibromide **10**. Only dibrominated product **10** and unchanged starting material was found (but no monobromination product was formed) when substoichiometric amounts of Br_2 at $-78\,^{\circ}C$ were used. Bromination of the first chromanol part thus favors reaction of its "twin".



Scheme 2. a) $(MeO)_2CHCH_2CH(OMe)_2$, $CHCl_3/CF_3COOH$ (2/1), N_2, 24 h, 76%.



Scheme 3. a) $FeCl_3$ or $AgNO_3$, $MeOH/H_2O$ (5/1), 1 h, reflux, 84–86%; b) Br_2, *n*-hexane, 2 h, 100%; c) Ag_2O, CH_2=CHOEt, *n*-hexane, 4 h, reflux, 23%; d) CH_2=CHOEt, Ag_2O or NEt_3, CH_2Cl_2, $-10\,^{\circ}C$, 2 h, 86%.

The involvement of *o*-QM structures in the chemistry of **8** was demonstrated by trapping these intermediates with ethyl vinyl ether in a hetero-Diels–Alder reaction with inverse electron demand (Scheme 3). The oxidation of **8** with Ag_2O in non-aqueous media or treatment of dibromide **10** with bases

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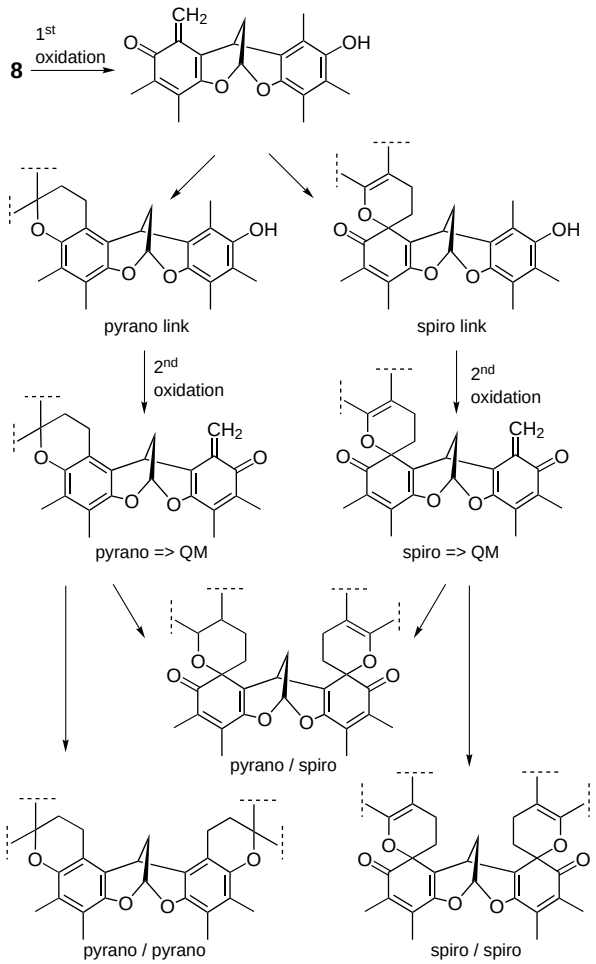
afforded the same trapping product **11**. Again, only the symmetric structure was obtained; reaction of only one "half" of the molecule was not observed.

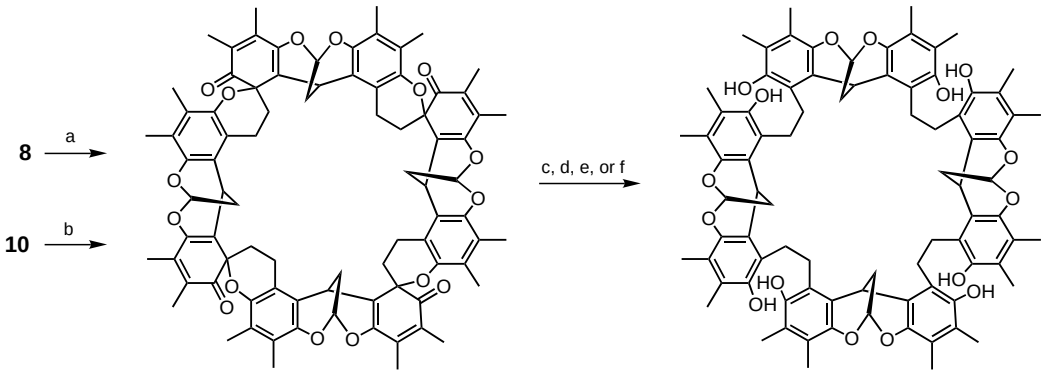
Both of the two chromanol units in **8** could be expected to undergo a reaction similar to the dimerization of tocopherol to form a spiro compound (Scheme 4).[9] After reaction of the first chromanol unit of **8**, for example, as a dienophile, the second half can react either as a dienophile or as a diene. Compound **8** would thereby be converted into a pyrano/spiro, a pyrano/pyrano, or a spiro/spiro couple. The second side of the two molecules of **8** attached to the first twin pair has again two options in reacting further, and so on. Thus, the same process that causes a dimerization of α-tocopherol to spiro compound **5** would result in a rather irregular oligomerization in the case of model compound **8**. In the materials produced in the latter case, the "monomeric" $C_{21}H_{20}O_4$ units are connected through spiro links, formed in sequential hetero-Diels--Alder reactions.



Scheme 4. Formation of pyrano/spiro, pyrano/pyrano, and spiro/spiro bridges by reaction of **8** as diene/dienophile, diene/diene, or dienophile/dienophile, respectively.

The reaction of *o*-QM precursors in refluxing toluene indeed afforded the expected complex oligomer mixtures: oxidation of **8** with Ag_2O gives tetramers ($M = 1349.5\ g\,mol^{-1}$) up to octadecamers ($M = 6058.7\ g\,mol^{-1}$), while dehydrobromination of **10** gave hexamers up to nonamers, with both oligomer "ends" still substituted with Br atoms. The generation of *o*-QM at room temperature afforded one major product together with smaller amounts of oligomers (up to the pentamer). At $-78\,^{\circ}C$, however, a single product was obtained in good yield (72%): the cyclic tetramer **12** ($M = 1345.6\ g\,mol^{-1}$), which contained exclusively pyrano/spiro (=spiro/pyrano) pairs, but no pyrano/pyrano or spiro/spiro couples, as the building blocks (Scheme 5).[10]

The selective formation of a pyrano moiety on the opposite side of a spiro structure (and vice versa) can be rationalized in terms of frontier orbital theory. The observed selectivity in the oligomerization is indicative of an electronic effect of the first link in the oxidized **8** on the *o*-QM unit located in the other half of **8**. Computational results[11] showed that reaction of the first twin in **8** as a diene (pyrano structure) results in an increase in the HOMO energy of the *o*-QM unit in the other half of the molecule by 0.25 eV. Therefore, the presence of a pyrano structure on one side increases the π-donor ability, and the *o*-QM unit on the other side will react as a dienophile, and thus form a spiro structure; thus, this reaction sequence results in a pyrano/spiro pair. By analogy, reaction of the first twin in **8** as a dienophile (spiro structure) decreases the LUMO energy of the *o*-QM on the opposite side by 0.21 eV, which leads to increased π-acceptor capability and subsequent reaction as a diene (pyrano structure) to form a spiro/pyrano



Scheme 5. a) Ag_2O, *n*-hexane, 96 h, 27%; b) morpholine, CH_2Cl_2, $-78\,^{\circ}C$, 1 h, 72%; c) ascorbic acid, MeOH/H_2O, 48 h, RT, 74%; d) $NaBH_4$, *i*PrOH, 3 h, RT, 26%; e) Zn, HCl (1M), MeOH, 3 h, RT, 93%; f) **8**, PhMe, reflux, 6 h, 8%.

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couple. Thus, a molecule **8** which has reacted as a diene on one side will react as dienophile on the other side, and vice versa, as a result of the significantly decreased HOMO – LUMO energy difference for these asymmetric pairs compared to the symmetric couples. Hence, pyrano/spiro (spiro/pyrano) pairs are formed exclusively.

The tetramer **12** bears not only structural resemblance to spiro compound **5**, but also exhibits surprisingly similar chemical behavior. Analogous to **5**, whose most important reaction is the reduction to the ethano-dimer **6** by the mild reductant ascorbic acid,[12] tetramer **12** was also reduced to the tetra-ethano derivative **13** (Scheme 5). Even though **13** contains tetracycles tethered by ethylene bridges, its structural appearance as well as solubility and analytical properties are quite close to those of calixarenes (Figure 1), which consist of monocyclic phenolic units linked by methylene groups. The formation of an inclusion complex was observed for **13** with, for example, *o*-$PhCl_2$ or anthracene.[13] The use of these aromatic guests also allows the study of the complexing properties of the novel macrocycles by UV and fluorescence spectroscopy.

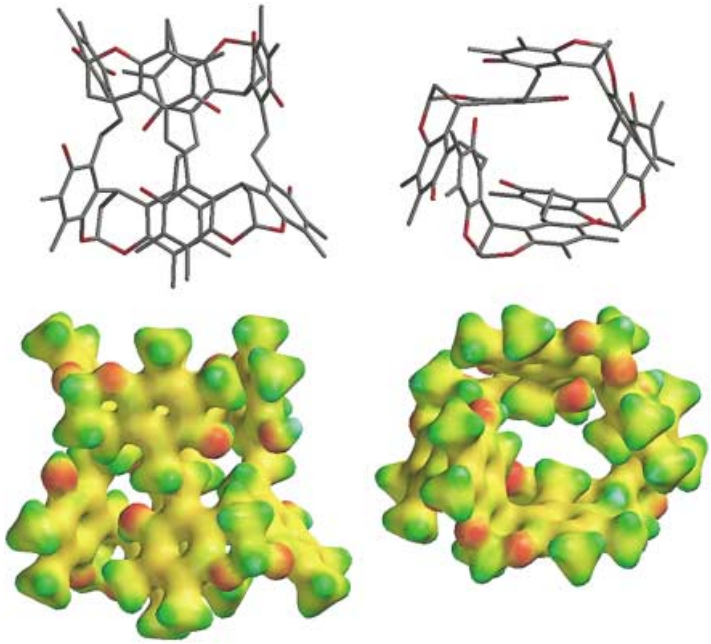

Figure 1. Energy-minimized structure of **13** with a calixarene-type 1,3-alternate conformation, based on computational results; hydrogen atoms in the top structures have been removed.

In conclusion, model compound **8** allows for deeper insights into the reactivity of tocopherols and tocopheroxyl radicals. In addition, the presented facile tertiary sequence of oxidation, multiple hetero-Diels – Alder reactions, and reduction provides an easy access to novel, complex calixarene-type macrocycles.

Experimental Section

8: White needles; m.p. 225 – 228 °C; ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 12.9, 13.5 (^{7a}C, ^{8b}C), 14.5 (^{5a}C), 26.1 (^{4}C), 28.5 (^{3}C), 91.2 (^{2}C), 120.4 (^{5}C), 121.4 (^{8}C), 123.1 (^{4a}C), 123.9 (^{7}C), 143.9 (^{8a}C), 147.3 (^{6}C); IR (KBr): $\tilde{\nu}$ = 3452 (br, OH), 2952 and 2870 (CH_3), 1639 (aromatic ring), 1080, 1209 cm^{-1} (^{Ar}C-O-C); elemental analysis calcd for $C_{21}H_{24}O_4$ (340.40): C 74.09, H 7.11; found: C 73.97, H 7.24.

13: White powder; m.p. > 350 °C; ^{13}C NMR (75.47 MHz, [D_6]DMSO, 90 °C): δ = 12.1 (^{7a}CH_3), 12.6 (^{8b}CH_3), 18.5 (^{4}CH), 27.6 (^{3}CH_2), 32.1 (^{5a}CH_2), 90.4 (O-^{2}CH-O), 119.5 (^{5}C), 120.6 (^{8}C), 122.2 (^{4a}C), 123.0 (^{7}C), 143.0 (^{8a}C), 146.4 (^{6}C); IR (KBr): $\tilde{\nu}$ = 3474 (br, OH), 2956, 2865 (CH_3), 1597 (aromatic ring), 1076, 1211 cm^{-1} (^{Ar}C-O-C); positive-ion MALDI-TOF MS: *m*/*z* calcd for $C_{84}H_{87}O_{16}Na$ [*M* – H+Na]$^+$: 1375.51, found: 1375.62; elemental analysis calcd for $C_{84}H_{88}O_{16}$ (1353.63): C 74.54, H 6.55; found: C 74.72, H 6.82.

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[1] a) L. J. Machlin, *Vitamin E: a Comprehensive Treatise*, Marcel Dekker, New York, **1980**; b) L. Packer, J. Fuchs, *Vitamin E in Health and Disease*, Marcel Dekker, New York, **1993**; c) A. Kamel-Eldin, L. A. Appelquist, *Lipids* **1996**, *31*, 671 – 699.

[2] The increased reactivity of ^{5a}CH_3 relative to ^{7a}CH_3 and ^{8b}CH_3 in all types of homolytic or heterolytic reactions, the so-called "Mills – Nixon effect", is typical of α-tocopherol: a) J. M. Behan, F. M. Dean, R. A. Johnstone, *Tetrahedron* **1976**, *32*, 167 – 174; b) N. L. Frank, J. S. Siegel, *Adv. Theor. Interesting Mol.* **1995**, 209 – 260.

[3] a) G. W. Burton, K. U. Ingold, *Acc. Chem. Res.* **1986**, *19*, 194 – 201; b) V. W. Bowry, K. U. Ingold, *J. Org. Chem.* **1995**, *60*, 5456 – 5467.

[4] See, for example, a) G. W. Burton, L. Hughes, K. U. Ingold, *J. Am. Chem. Soc.* **1983**, *105*, 5950 – 5951; b) ref. [1c].

[5] S. Nagaoka, K. Mukai, *J. Phys. Chem.* **1992**, *96*, 8184 – 8187.

[6] The use of trifluoroacetic acid as the co-solvent (30 vol %) was crucial to direct the course of the reaction.

[7] P. Schudel, H. Mayer, J. Metzger, R. Rüegg, O. Isler, *Helv. Chim. Acta* **1963**, *46*, 636 – 648.

[8] a) T. Rosenau, W. D. Habicher, *Tetrahedron* **1995**, *51*, 7919 – 7926; b) T. Rosenau, C. L. Chen, W. D. Habicher, *J. Org. Chem.* **1995**, *60*, 8120 – 8122.

[9] a) W. A. Skinner, R. M. Parkhurst, *J. Org. Chem.* **1964**, *29*, 3601 – 3603; b) D. R. Nelan, C. D. Robeson, *J. Am. Chem. Soc.* **1962**, *84*, 2963 – 2965; c) H. M. Fales, *J. Chem. Soc. Perkin Trans. 2* **1990**, 1005 – 1010.

[10] The ^{13}C NMR spectra recorded at 370 K show only the 21 resonances of the spiro/pyrano-linked tetramer with characteristic resonances at δ = 80.4 (^{sp}C), 195.5 (C=O), and 25.3/34.4 (pyrano link). Spiro/spiro- or pyrano/pyrano-linked tetramers would give twice the number of signals.

[11] DFT calculations (pBP/DN**) were carried out on the structures pyrano ⇒ QM, spiro ⇒ QM, and starting QM (Scheme 4).

[12] D. R. Nelan, C. D. Robeson, *J. Am. Chem. Soc.* **1962**, *84*, 2963 – 2965.

[13] The ^{13}C NMR resonances of the guests experienced a pronounced high-field shift (8 ppm for C-5/C-6 in *o*-$PhCl_2$, 2.4 and 3 ppm for C-1 and C-9, respectively, in anthracene), whereas the ^{1}H NMR signals for both aromatic compounds shifted less than 0.55 ppm. The guests can be released by refluxing the inclusion complex for 24 h in ethanol. In contrast to the aromatic compounds, enclosed EtOH can be removed by prolonged drying in vacuo.

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