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From a Theoretical Concept to Biochemical Reactions: Strain-Induced Bond Localization (SIBL) in Oxidation of Vitamin E

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Abstract: The regioselectivity of the oxidation of α-tocopherol (the main component of vitamin E) to an *ortho*-quinone methide (*o*QM) has been explained in the literature mostly by the ill-defined term "Mills–Nixon effect". In this paper we describe the preparation of eleven α-tocopherol derivatives, different from each other by the sum of annulation angles, but keeping the electronic factors unchanged. These compounds underwent Ag_2O oxidation, forming two isomeric *o*QMs that were trapped by vinylmethyl ether. It was found that the isomeric product ratio changes smoothly as a function of the annulation angles, not abruptly from one regioisomer to the other on going from five- to six- and seven-membered rings, as predicted by the Mills–Nixon effect. The relative amounts of the products were determined at four different temperatures, and assuming that the product ratio represents the relative rates ratio, the relative enthalpy of activations could be obtained. Theoretically (at B3LYP/6-31G* theoretical level) four different intermediates were considered. Each of these underwent angular angles deformations to model the two regioisomers. At each deformation angle the energy difference between the two intermediates models was correlated to the experimental data for each of the four intermediates. It was found that the angle-deformed lithium (6-methyl-2-benzylium)phenolate correlated best ($R > 0.994$) to the experimental data. This study confirms that the regioselectivity of the two isomeric *o*QMs in the oxidation of α-tocopherol and related compounds is simply a function of angular strain, best explained by the SIBL (strain-induced bond localization) model. In addition, this study provides evidence that the highest energy intermediate in the oxidation of vitamin E is a phenolate–benzyl cation.

Keywords: density functional calculations · Mills–Nixon effect · natural products · quinone methide · strain-induced bond localization (SIBL) · vitamins

Introduction

Vitamin E, with its main component α-tocopherol (**1a**) as one of the most effective chain-breaking antioxidants, has manifold physiological functions as a lipophilic antioxidant in cellular membranes and lipidic tissues.[1] It is widely used in medical applications, and also finds wide use in a huge variety of healthcare products, food additives, and cosmetics.[2] Its oxidation pathways lead both in vivo and in vitro to an *ortho*-quinone methide (*o*QM) **2**, which is possibly the most prominent candidate within the class of biologically important *o*QMs.[3] Compound **2** undergoes immediate dimerization to the spiro dimer **3** as the final product. The formation of dimeric structures is irreversible and thus depletes the organism of the vitamin.

Even though the oxidation of α-tocopherol to its *o*QM is a rather "old" reaction,[4] the regioselectivity of this chemical process has not been understood until today. This is quite surprising considering the physiological and the economic importance of the vitamin. According to the litera-

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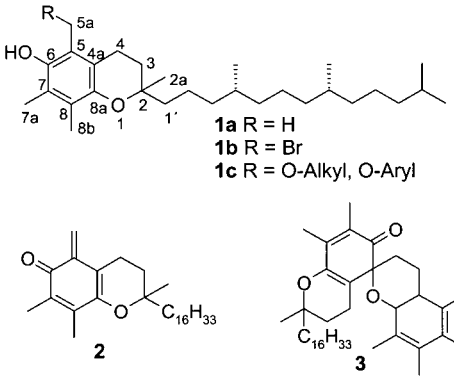


ture, formation of **2** proceeds with regioselective involvement of C5a ("up"-*o*QM); the isomeric compound with the *exo*-methylene group at C7a ("down"-*o*QM) is reportedly not observed.[5] The nearly complete regioselectivity in such reactions of α-tocopherol has been reflected in numerous reports;[6] the formation of regioisomers other than the up-*o*QM has been reported only very rarely.[6c] Oxidation of **1a** with silver oxide in non-aqueous media provided only **3**, thus proving the predominant formation of the up-*o*QM **2**. Bromination caused formation of 5a-bromo-α-tocopherol (**1b**), while other positions in the molecule were not affected.[7] Also in radical recombination products only the 5a-position is involved: reaction of α-tocopherol with radicals under simulated physiological conditions, for instance, produced 5a-substituted tocopherols (**1c**), while coupling products at the two other methyl groups were not found.[8] Usually, a very brief "explanation" is given for the regioselectivity observed: the so called "Mills–Nixon effect", mostly supported by a citation of the original reference from 1930.[9] A more rigorous explanation that is based on more modern concepts cannot be found.

The original work by Mills and Nixon, after which the effect is named, is based on three theories, today known as erroneous: 1) Aromatic systems consist of two bond-shift isomers that are in equilibrium. 2) The Van't-Hoff model of carbon. This implies that all the angles around the carbon atom are tetrahedral. Together with the first assumption, annulation of differently sized rings will shift the equilibrium between the equilibrating mesomers of benzene to the isomers that possesses the least strained angle, that is, as close to 109.5°. 3) The mechanism for electrophilic aromatic substitution is addition–elimination.

Using these working hypotheses Mills and Nixon explained why electrophilic substitution of 5-hydroxyindan yielded the 4-substituted system, whereas 6-hydroxytetralin yielded the 7-substituted system.

Applying the Mills-Nixon explanation to vitamin E, it is usually argued that the annullation of a pyran or furan structure[10] to the methyl-substituted phenol ring causes bond localization in the aromatic part of the corresponding benzochromanol/benzofuranol. Upon oxidation, only one of the two possible *o*QMs is formed; this transformation requires as little rearrangement of the π-frame (double bonds) as possible.[11] In benzopyrans such as vitamin E, the three double bonds in the aromatic ring are positioned so that one is placed at the annullation site: the *ortho*-quinone methide will thus be formed involving C5a (the up-*o*QM). In the related benzofuran antioxidants, the three aromatic double bonds are positioned in a way that the annullation bond is a single bond: the favored *ortho*-quinone methide will be the one with "down" structure. According to this hypothesis, which is accepted throughout the literature, chromanol systems form up-*o*QMs exclusively, while benzofuranols produce only down-*o*QMs. Clearly, this explanation, resting on erroneous theories, is unacceptable.

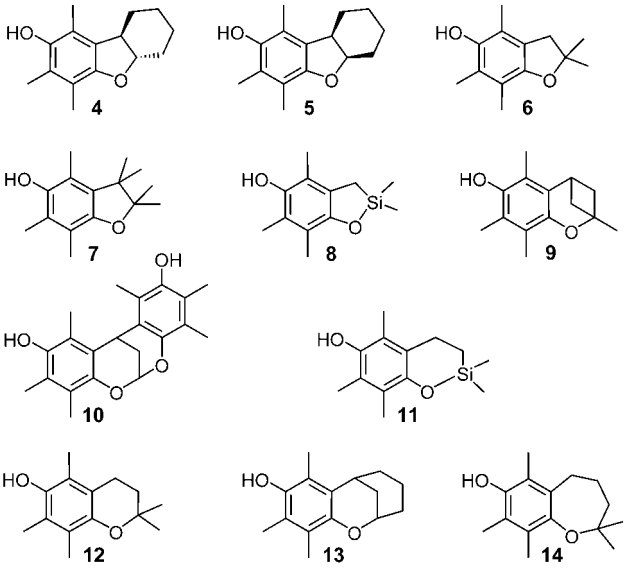
As a consequence of our studies on *o*QM formation in tocopherol-related antioxidants, and especially the observation that room-temperature oxidation of **1a** produced **2** in large excess (98–99%), but not exclusively, we set out to clarify the regioselectivity in antioxidants of the vitamin E type by a combined experimental and theoretical study. Our approach is based on measuring the ratio between the "down" and "up" products of the oxidation reaction for a series of 2,3,6-trimethylphenols annulated at the 4,5-positions, with different cycles that always have an oxygen atom bound to the 4-position and a carbon atom to the 5-position, thus keeping the electronic effects constant and changing only the angular strain of the systems. Then, a comparison to a theoretical model in which only pure angular strain is introduced was made, and the factors governing the regioselectivity were sorted out. Since the oxidation of vitamin E derivatives is irreversible, the product ratio reflects the relative rates to obtain the "up" and "down" oxidation products. Thus, the rate-determining transition states for the different substrates should have been compared. Since the mechanism of the reaction has not been established as yet, the following assumptions were used as working hypotheses. 1) The rate-determining step is endothermic. Thus, the intermediate that is formed after the rate-determining step should closely resemble the transition state leading to it (Hammond postulate). 2) Electron transfer mechanisms probably operate both in vitro and in vivo. However, they are probably fast relative to possible steps that lead to closed-shell intermediates.

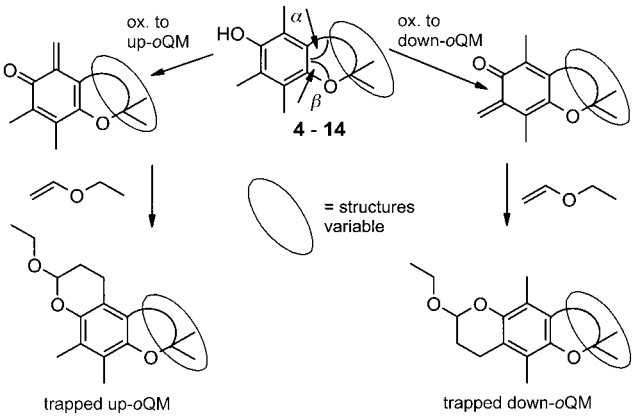
Thus, several possible closed-shell anions and cations were considered as intermediates. These ions were calculated with artificially imposed angle deformations (see below), and the results were correlated to the experimental data.

Results and Discussion

Eleven benzopyranol and benzofuranol derivatives with different ring strain (**4**–**14**) were synthesized and comprehensively characterized.

These test candidates possess structures as close to the common benzopyranol/benzofuranol antioxidants as possible, but exhibit different angular strain ($\alpha+\beta$ values, see Scheme 1), which cover an angle range of ~219° (for **4**) to





Scheme 1. Oxidative formation and trapping of two different possible types of *ortho*-quinone methides (*o*QMs) derived from vitamin E type antioxidants.

~246° (for **14**).[12] The model compounds were oxidized to the corresponding *o*QMs,[13] which were trapped by reaction with ethyl vinyl ether present in large excess as a solvent component, in a hetero-Diels–Alder process with inverse electron demand. Product analysis provided the ratio between the two *o*QMs intermediates.[14] Under the assumption that both *o*QMs are formed from the respective two distinct intermediates and the trapping is not the rate-determining step, the ratio X between the trapped up-*o*QMs and down-*o*QMs reflects their relative concentrations and hence the relative formation rates. Thus, the relative activation energies for the formation of the two intermediates can be obtained [Eq. (1)]. A plot of $\Delta\Delta G^{\neq}$ versus temperature yielded $\Delta\Delta H^{\neq}$.

$$\Delta\Delta G^{\neq} = -RT\ln X \qquad (1)$$

The results (Table 1) proved that the regioselectivity, that is, the ratio X, was not a function of the ring size alone: it changed *gradually*, not abruptly, when going from six- to five-membered ring systems, in contrast to what has been assumed so far. The up-*o*QMs were increasingly favored when going from small $\alpha+\beta$ values to large ones, with down-*o*QMs showing the opposite trend. Note that there is a distinct correlation between $\alpha+\beta$ values and the differences in activation enthalpies.

According to the theory that is based on the original Mills–Nixon effect, oxidation of benzofuranol **8**, for example, should produce the down-*o*QM in high or even complete regioselectivity; the experiments showed, however, that the up-*o*QM structure is still more favored. On the other hand, compound **9**, which has a six-membered annullated ring, should exclusively afford the up-*o*QM, but gave about 30% of down-*o*QM product. These two examples disprove the notion that vitamin E-related benzofuranols form only one *o*QM (down-*o*QMs), while chromanol-type tocopherol models give only the opposite one (up-*o*QMs).

To be able to assign the reasons for the regioselectivity of the reaction its mechanism should be known. Unfortunately, the detailed mechanism of the *o*QM formation from vitamin E type antioxidants is not established. There are, however, some considerations that can help in eliminating some of the possible mechanisms. First, the stochiometric difference between the starting material and the product is two hydrogen atoms. Since the most acidic proton is the phenolic proton, it is probable that the phenolate is an intermediate, probably stabilized by a counterion (e.g., Ag^+). The next step may be deprotonation of one of the methyl groups to form a dianion, which may yield the product either by two single-electron transfers to two Ag^+ or by a single two-electron process. A second alternative is an abstraction of a hydride from one of the methyl groups of the phenolate to form the respective benzyl cation, which, when not stabi-

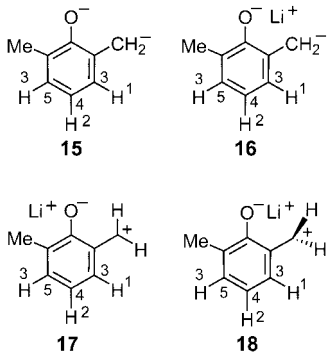
Table 1. Relative amounts of up-*o*QM in the oxidation of **4**–**14** at different temperatures.

	$\alpha+\beta$[12]	up-*o*QM [%, 195 K]	up-*o*QM [%, 273 K]	up-*o*QM [%, 298 K]	up-*o*QM [%, 343 K]	ΔH [kcal mol^{-1}]	R
4	219	0.02	0.3	0.5	0.9	3.49±0.12	0.99834
5	221	0.1	0.9	1.3	2.3	2.86±0.08	0.99926
6	221	4.3	10.4	11.7	14.9	1.22±0.04	0.99904
7	223	38.4	41.3	42.0	43.3	0.18±0.01	0.99649
8	231	57.6	55.5	55.0	54.3	−0.109±0.002	0.99951
9	233	77.1	70.4	69.2	66.9	−0.458±0.009	0.99964
10	239	98.8	96.6	95.2	93.1	−1.61±0.09	0.99670
11	240	99.3	97.3	96.1	94.2	−1.96±0.06	0.99918
12	242	99.9	99.2	98.8	97.9	−2.768±0.005	0.99978
13	244	100.00[a]	99.8	99.6	99.3	−3.24±0.12	0.99856
14	246	100.00[a]	99.96[b]	99.93[b]	99.8	−4.77±0.13	0.99925

[a] 99.999 used for calculation. [b] Second decimal estimated.

lized by a counterion, is actually a zwitterionic resonance form of the product *o*QM. It is also reasonable to assume that the slowest step (i.e., the rate-determining step) is the removal of the second hydrogen atom (as a proton or a hydride), and thus the isomeric product ratio is determined at this step. This assumption holds even if electron-transfer (ET) processes precede or follow the proton or hydride removal, since ET processes are expected to be faster. It is also likely that this process is endothermic, and therefore the resulting ion closely resembles the rate-determining transition state.

Four possible models for the intermediates were considered:[15] model compounds **15** and **16** mimic proton abstraction, whereas **17** and **18** mimic the hydride abstraction.[16] These ions underwent H-C-C angle deformations to mimic the angular strain imposed by the annulation of the ring; H1-C3-C4 and H2-C4-C3 (γ) to mimic the ions leading to the up-*o*QM product and H2-C4-C5 and H3-C5-C4 (δ) to mimic the ions leading to the down-*o*QM product, according to the SIBL principle.[17]



The benzyl anions **15** and **16** did not show any correlation to the obtained products. Both benzyl cations **17** and **18** showed good correlations to the experimental data (see below). The perpendicular cation **18** is stabilized by through-space interaction between the phenoxide oxygen atom and the benzylic positive center, whereas **17** is stabilized by resonance. Although **18** was predicted to be an intermediate (based on trapping experiments and assigned by NMR spectroscopy),[18] in our hands **17** was more stable than **18** by 25–50 kcal mol^{-1} (depending on γ and δ) and therefore we consider here only **17**.[19] Table 2 shows the energy differences between δ- and γ-bent **17** as a function of the bending angle. Since the calculated and the experimental systems do not possess the same angles, a graphic comparison (Figure 1) is given as a correlation between the experimental $\Delta\Delta H^{\neq}$ values per degree (Table 2, 4th column) and the calculated data within the similar angle range (Table 2) as ΔE per degree.

The good correlation between the experimental $\Delta\Delta H^{\neq}$ derived from the up/down ratio and the simple theoretical model used ($R > 0.994$) suggests that the regioselectivity of the "up" and "down" product formation in the oxidation of

Table 2. Energy difference [kcal mol^{-1}] between γ- and δ-bent **17**.

Angle[a]	ΔE[b]	ΔE per degree[c]	ΔE per degree[d]
180	10.42	0.05787	
200	6.21	0.03106	
220	3.20	0.01455	0.01595
226	2.40	0.01063	0.01292
232	1.61	0.00692	0.00552
238	0.65	0.00273	0.0008072
240	0.56	0.00235	−0.0004713
244	0.085	0.000349	−0.00196
250	−0.69	−0.00276	−0.00674
256	−1.47	−0.00574	−0.00817
260	−2.01	−0.00772	−0.01144
262	−2.25	−0.0086	−0.01328
268	−3.10	−0.01159	−0.01939
274	−3.90	−0.01422	
280	−4.77	−0.01703	

[a] 2γ, 2δ, in degrees. [b] $E(\gamma$-bent **17**$)-E(\delta$-bent **17**), in kcal mol^{-1}. [c] Theoretical data. [d] Experimental data taken from Table 1, columns 2 and 8.

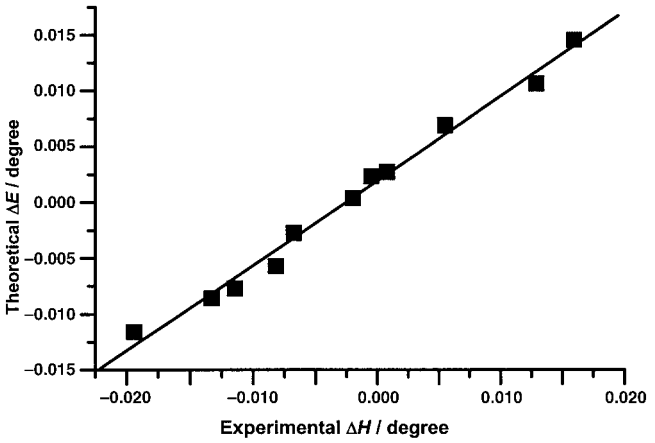
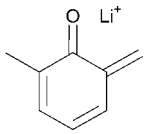


Figure 1. Comparison of experimental and theoretical (computational) results.

α-tocopherol and related compounds is simply a function of angular strain. Natural resonance theory (NRT)[20] analysis of the data suggests that the main resonance structure responsible for the charge localization is the quinoid structure that has a C3−C4 double bond and a C4−C5 single bond (**19**).[20] Small γ and δ values increase C3−C4 and C4−C5



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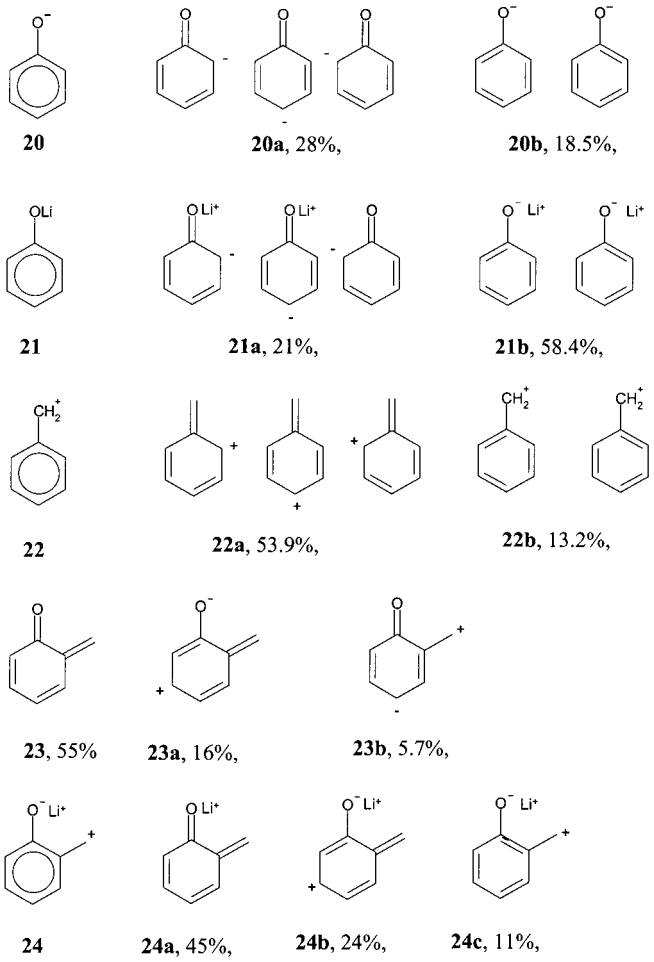
bond lengths, respectively (due to rehybridization), and large γ and δ values have the opposite effect.[21] The angular-strain-induced bond lengthening reduces the contribution of the canonic structures that have double bonds at these

positions, therefore causing relative destabilization. The strain-induced bond shortening has the opposite effect, causing a larger contribution of the canonic structures with double bonds, therefore stabilizing. The net outcome is that the "up" benzyl cation is more stable at large γ and small δ values, and the "down" cation is more stable at large δ and small γ values.

The resonance structure **19** (which is 42% of fully optimized **17**) resembles the lithiated structure of the product, and therefore raises the question whether the calculations mimic the relative products stabilities rather than the relative intermediates stabilities, and the validity of the comparison between the experimental kinetic results and the calculated model. Therefore, NRT analysis of **20**–**24** was carried out (Scheme 2). For the free phenolate anion **20**, the canonic



Scheme 2. Main canionic forms of **20**–**24**.

structures that delocalize the negative charge to the *ortho*- and *para*-positions and contain a doubly bound oxygen atom (**20a**) make 28% of the structure, and the two Kekulé structures (**20b**) are 18.5%. Adding a lithium counterion reduces somewhat the contribution of the ketonic forms **21a** to 21% and increases the contribution of the two Kekulé structures to 58.4%. Thus, the effect of lithiation of **20** is mainly in increasing the contribution of the Kekulé resonance structures. The main contributors to the structure of the benzyl cation **22** are the three resonance structures that contain a double bond between the ring and the benzylic carbon atom, 53.9% (**22a**); the two Kekulé forms contribute 13.2%. *ortho*-Quinone methide **23** is composed of 55.2% of the quinonic structure, 16% of the phenolate structure **23a**, and 5.7% of the benzyl cation structure **23b**. The lithiated form **24** (a model for **17**) consists of 45% of the quinonic form **24a**, 24% of the form **24b**, and 11% of the Kekulé structures **24c**. The respective numbers for **17** are similar: 42, 26, and 9.5%. From these numbers it can be concluded that the actual character of **17** is in-between the character of the zwitterionic form and the character of the *o*QM product. The increase of the contribution of the Kekulé structures on going from **23** to **24**, is less than on going from **20** to **21**, but the contribution of the benzylic cation forms increases considerably. Regarding **17** as an intermediate is therefore justified.[22]

Conclusions

It was experimentally proven that the regioselectivity of the "up" and "down" *ortho*-quinone methide formation in the oxidation of α-tocopherol and related compounds is simply a function of angular strain, but not of the annulated ring size, and a theoretical explanation according to the SIBL principle, which fully sustained the experimental findings, has been provided. This combination of experimental and theoretical facts finally allowed us to conclusively address the open question of regioselectivity in oxidations of vitamin E type antioxidants. It is worth mentioning that in the case discussed here, the Mills–Nixon postulation, which started from the wrong premises, yields (qualitatively) the same result as the SIBL treatment presented here. However, the specific agreement between Mills–Nixon effect and SIBL should not be taken as a general rule, since it has been shown that in other cases the Mills–Nixon postulation contradicts SIBL and yields the wrong structural predictions.[23]

As an additional benefit, an important mechanistic insight into the oxidation of the physiologically important vitamin E system was obtained. Thus, the good correlation between the experimental and the theoretical results suggests that the highest energy intermediate in the oxidation of vitamin E is the phenolate–benzyl cation. A further study of the mechanism of the discussed oxidation is currently being carried out.

Experimental Section

General: Unless otherwise stated ^{1}H NMR spectra were recorded at 300.13 MHz, ^{13}C NMR spectra at 75.47 MHz with $CDCl_3$ as the solvent and TMS as the internal standard. Data are given in ppm units through-

out. ^{13}C peaks were assigned by means of APT, HMQC, and HMBC experiments. Nomenclature and numbering of the carbon atoms in chromans and tocopherols as proposed by the IUPAC[24,25] have been used throughout. The abbreviation "d.i." denotes peaks from two equivalent carbons. Elemental analyses were performed at the microanalytical laboratory of the Institute of Physical Chemistry at the University of Vienna (Austria). All chemicals used were of reagent grade, all solvents were of HPLC grade. Solvents were dried according to standard procedures; *n*-hexane was dried over sodium metal. All molecular weight (M) data are given in $g\,mol^{-1}$, density data (ρ) in $g\,mL^{-1}$.

Synthesis of test compounds: Compound **12** was available from commercial sources. The preparation of **6** and **10** is described in a previous work.[26]

***trans*-1,3,4-Trimethyl-5a,6,7,8,9,9a-hexahydrodibenzofuran-2-ol (4) and *cis*-1,3,4-trimethyl-5a,6,7,8,9,9a-hexahydrodibenzofuran-2-ol (5)**: A solution of trimethylhydroquinone ($M=152.19$, 1.52 g, 10.00 mmol) and *trans*-1,2-dibromocyclohexane ($M=241.95$, 2.42 g, 10.00 mmol) in 1,2-dichlorobenzene (50 mL) was quickly added to refluxing 1,2-dichlorobenzene (200 mL) containing aluminum chloride ($M=133.34$, 3.0 g, 22.5 mmol). The solution was refluxed for as little as 1 min and poured into ice-cold 1 M NaOH (250 mL) containing sodium sulfite (0.2 g). The mixture was stirred under argon. After dissolution of the precipitate, which occurred within about 3 min, the phases were separated, and the organic phase was extracted with NaOH (100 mL; 2 M). The organic layer was discarded, and the combined aqueous phases were extracted once with toluene (30 mL), which was also discarded. After acidification of the aqueous layer with H_2SO_4, (5 M) the solution was stirred for 2 h at room temperature and extracted three times with chloroform (50 mL). The organic extracts were dried over Na_2SO_4 and evaporated to dryness. The residue was subjected to chromatography on silica gel (*n*-hexane/chloroform 4 : 1, v/v) affording **5** ($M=232.33$, 0.564 g, 2.43 mmol, 24.3 %) and **4** ($M=232.33$, 0.265 g, 1.14 mmol, 11.4 %), as well as 3,5,6-trimethyl-8-oxatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-4-ol (**13**, 3.4 %) and unchanged starting material (trimethylhydroquinone, 0.189 g, 1.24 mmol, 12.4 %). The synthesis was repeated several times to obtain sufficient amounts of products.

*Data for compound **4***: ^1H NMR: $\delta=1.39$–1.62 (m, 6H; $^{2b}CH_2$, $^{3a}CH_2$, $^{3b}CH_2$), 1.90 (m, 1H; $^{2a}CH_2$), 2.02 (m, 1H; $^{2a}CH_2$), 2.03 (s, 3H; $^{6a}CH_3$), 2.08 (s, 3H; $^{4a}CH_3$), 2.12 (s, 3H; $^{7b}CH_3$), 3.05 (m, $^3J=4.7$, 2.4, 7.5 Hz, 1H; ^3CH), 4.62 (dt, $^3J=4.7$, 2.2, 2.2 Hz, 1H; ^2CH), 5.11 ppm (s, 1H; OH); ^{13}C NMR: $\delta=12.0$ (^{7b}C), 12.2 (^{6a}C), 12.4 (^{4a}C), 25.2 (^{2b}C); 26.4 (^{3b}C); 27.3 (^{3a}C); 29.2 (^{2a}C), 47.8 (^3C), 93.5 (^2C), 116.0; 120.6; 121.5; 126.8; 147.6; 149.0 ppm (^{Ar}C); elemental analysis calcd (%) for $C_{15}H_{20}O_2$ (232.32): C 77.55, H 8.68; found: C 77.72, H 8.83.

*Data for compound **5***: ^1H NMR: $\delta=1.42$–1.61 (m, 6H; $^{2b}CH_2$, $^{3a}CH_2$, $^{3b}CH_2$), 1.92 (m, 1H; $^{2a}CH_2$), 2.04 (m, 1H; $^{2a}CH_2$), 2.05 (s, 3H; $^{6a}CH_3$), 2.08 (s, 3H; $^{4a}CH_3$), 2.13 (s, 3H; $^{7b}CH_3$), 3.08 (td, $^3J=7.3$, 2.4, 2.4 Hz, 1H; ^3CH), 4.20 (s, 1H; OH), 4.56 ppm (m, $^3J=7.3$, 6.3, 6.3 Hz, 1H; ^2CH); ^{13}C NMR: $\delta=12.1$ (^{7b}C), 12.2 (^{6a}C), 12.5 (^{4a}C), 21.8 (^{2b}C); 26.6 (^{3b}C); 27.8 (^{3a}C); 28.0 (^{2a}C), 44.4 (^3C), 88.4 (^2C), 115.8; 120.3; 121.2; 126.2; 147.0; 148.4 ppm (^{Ar}C); elemental analysis calcd (%) for $C_{15}H_{20}O_2$ (232.32): C 77.55, H 8.68; found: C 77.61, H 8.69.

2,2,3,3,4,6,7-Heptamethyl-2,3-dihydrobenzofuran-5-ol (7): A solution of $TiCl_4$ ($M=189.71$, $\rho=1.73$, 1.3 mL, 12.0 mmol) in dry dioxane (10 mL) was added dropwise to a refluxing solution of trimethylhydroquinone ($M=152.19$, 1.52 g, 10.00 mmol) and pinacolon ($M=100.16$, $\rho=0.801$, 1.3 mL, 10.40 mmol) in dioxane (60 mL) under an inert atmosphere. The solution was stirred at 80 °C for 1 h, refluxed for 3 h, poured into 100 mL of ice-cold HCl (2 M), and stirred for approximately 10 min. Chloroform (100 mL) was added, and the organic phase was separated, quickly washed with concentrated $NaHCO_3$ solution and twice with water (50 mL), dried over Na_2SO_4, and evaporated to dryness. The solid residue was recrystallized from *n*-hexane and twice from glacial acetic acid to afford **7** as white, glittery crystals ($M=234.34$, 1.502 g, 6.41 mmol, 64.1 %). ^1H NMR: $\delta=0.96$ (s, 6H; $^{3a}CH_3$), 1.13 (s, 6H; $^{2a}CH_3$), 1.97 (s, 3H; $^{6a}CH_3$), 2.04 (s, 3H; $^{4a}CH_3$), 2.18 (s, 3H; $^{7b}CH_3$), 5.45 ppm (s, 1H; OH); ^{13}C NMR: $\delta=11.8$ (^{7b}C), 12.1 (^{6a}C), 12.6 (^{4a}C), 18.1 (d.i., ^{2a}C), 21.8 (^{3a}C), 44.3 (^3C), 82.5 (^2C), 115.6, 120.6, 122.4, 137.4, 147.6, 148.8 ppm (^{Ar}C); elemental analysis calcd (%) for $C_{15}H_{22}O_2$ (234.34): C 76.88, H 9.46; found: C 76.94, H 9.53.

2,2,4,6,7-Pentamethyl-2,3-dihydrobenzo[d][1,2]-oxasilol-5-ol (8): A solution of 5,7,8-trimethyl-4*H*-benzo[1,3]dioxin-6-ol (3-oxa-5,7,8-trimethylchroman-6-ol,[27] $M=194.23$, 1.94 g, 10.00 mmol) in concentrated aqueous HBr (50 mL) was stirred for 30 min at room temperature. The mixture was diluted with water (100 mL) and extracted twice with chloroform, and the extract was washed with water, dilute $NaHCO_3$ solution, and again with water. After drying over Na_2SO_4 the solvent was removed in vacuo. The residue was taken up in dry THF (20 mL), and dichlorodimethylsilane ($M=129.06$, $\rho=1.064$, 2.4 mL, 19.7 mmol) was added. Powdered magnesium (1.00 g, 42.1 mmol) was added to this mixture, and the mixture was sonicated in an inert atmosphere for 2 h, adding charges of magnesium (0.2 g) every 30 min. Et_2O (100 mL) was added, and the mixture was filtered slowly through a glass frit. The filtrate was stirred together with HCl (2 M, 100 mL) for 2 h, and the aqueous phase was discarded. The organic phase was washed with water and dried over Na_2SO_4. Evaporation of the solvent and chromatography on silica gel provided **8** ($M=222.36$, 1.42 g, 6.39 mmol, 63.9 %) as white powder (m.p. 97–98 °C). ^1H NMR: $\delta=0.38$ (s, 6H; $^{2a}CH_3$), 1.74 (dd, $J=12.3$ Hz, 2H; $^3CH_2$), 2.08 (s, 6H; $^{4a}CH_3$, $^{6a}CH_3$), 2.14 (s, 3H; $^{7b}CH_3$), 4.05 ppm (s, 1H; OH); ^{13}C NMR: $\delta=-2.2$ (d.i., ^{2a}C), 12.2 (^{4a}C), 12.3 (^{6a}C), 12.9 (^{7b}C), 21.6 ($^3CH_2$), 118.3, 119.1, 121.0, 122.8, 146.1, 147.8 ppm (^{Ar}C); elemental analysis calcd (%) for $C_{12}H_{18}O_2Si$ (222.36): C 64.82, H 8.16; found: C 64.58, H 8.26.

3,5,6,9-Tetramethyl-8-oxa-tricyclo[7.1.1.$0^{2,7}$]undeca-2,4,6-trien-4-ol (9): A solution of 1,1,3,3-tetramethoxycyclobutane ($M=176.21$, 3.52 g, 20.00 mmol) was added dropwise to a solution of trimethylhydroquinone ($M=152.19$, 1.52 g, 10.00 mmol) in trifluoroacetic acid (30 mL), glacial acetic acid (55 mL), and acetic anhydride (15 mL). The mixture was stirred for 24 h, and the solvent was removed under reduced pressure. The semisolid residue was dissolved in ethanol (20 mL). Water (20 mL), concentrated HCl (2 mL), and powdered zinc ($M=65.37$, 0.30 g, 4.59 mmol) were added to the solution. After 2 h, the addition of zinc (0.30 g, 4.59 mmol) was repeated. After the metal had completely dissolved, the mixture was filtered through a glass frit and extracted three timed with diethyl ether (50 mL). The combined extracts were dried over Na_2SO_4, and the solvent was thoroughly evaporated in vacuo. After re-dissolution in Et_2O (50 mL), a solution of methylmagnesium bromide (3.0 M solution in Et_2O, 20 mL, 60 mmol) was added dropwise. The solution was stirred for 30 min, and then refluxed for 3 h. After slow addition of a saturated NH_4Cl solution (ca. 50 mL) under stirring, the organic phase was washed with HCl (2 M) and water, dried over Na_2SO_4, and filtered through a layer of silica gel. The mixture was concentrated to a volume of about 10 mL and was left standing in the refrigerator overnight. The precipitate which was formed was collected by filtration. A second fraction was collected from the concentrated filtrate. Recrystallization of the combined precipitates from acetic acid afforded **9** ($M=218.30$, 0.51 g, 2.34 mmol, 23.4 %) as white, glittery plates, m.p. 84–86 °C. ^1H NMR: $\delta=1.41$ (s, 3H; $^{2a}CH_3$), 2.08 (s, 3H; $^{7a}CH_3$), 2.12 (s, 3H; $^{8b}CH_3$), 2.18 (s, 3H; $^{5a}CH_3$), 3.28 (dd, $J=5.5$, 7.2 Hz, 2H; $^3CH_2$, $^{3'}CH_2$), 3.38 (dd, $J=5.5$, 7.2 Hz, 2H; $^3CH_2$, $^{3'}CH_2$), 3.62 (quint, $J=5.5$ Hz, 1H; ^4CH), 4.85 ppm (s, 1H; OH); ^{13}C NMR: $\delta=12.0$ (^{8b}C), 12.1 (^{7a}C), 12.4 (^{5a}C), 21.8 (^{2a}C), 29.9 (^4CH), 36.1 (d.i., ^3C, $^{3'}C$), 80.1 (^2C), 117.7, 118.5, 121.2, 128.9, 144.4, 144.9 ppm (^{Ar}C); elemental analysis calcd (%) for $C_{14}H_{18}O_2$ (218.30): C 77.03, H 8.31; found: C 76.91, H 8.29.

2,2,5,7,8-Pentamethyl-3,4-dihydro-2*H*-benzo[e][1,2]oxasilin-6-ol (11): A solution of 2-(2-bromoethyl)-1,4-dihydroxy-3,5,6-trimethylhydroquinone ($M=259.14$, 2.6 g, 10.03 mmol) and dichlorodimethylsilane ($M=129.06$, $\rho=1.064$, 2.4 mL, 19.7 mmol) in dry THF (20 mL) was charged with powdered magnesium (1.00 g, 42.1 mmol), and the mixture was sonicated under an inert atmosphere for 2 h. Et_2O (100 mL) was added, and the mixture was filtered through a glass frit. The filtrate was stirred together with HCl (2 M, 30 mL) for 1 h, and the aqueous phase was discarded. The organic phase was washed with water and dried over Na_2SO_4. Evaporation of the solvent provided a yellow, waxy solid, which was recrystallized from acetic acid to give **11** as a white powder ($M=236.39$, 0.97 g, 4.10 mmol, 41.0 %), m.p. 124–126 °C. ^1H NMR: $\delta=0.23$ (s, 6H; $^{2a}CH_3$),

0.82 (m, 2H; $^{3}CH_2$), 2.06 (s, 3H; $^{7a}CH_3$), 2.09 (s, 3H; $^{5a}CH_3$), 2.13 (s, 3H; $^{8b}CH_3$), 2.74 (m, 2H; $^{4}CH_2$), 6.12 ppm (s, 1H; OH); ^{13}C NMR: $\delta = -2.5$ (d.i., ^{2a}C), 12.2 (^{7a}C), 12.3 (^{5a}C), 12.4 (^{8b}C), 14.0 ($^{3}CH_2$), 21.4 ($^{4}CH_2$), 117.7, 118.8, 121.5, 124.9, 144.0, 146.1 (^{Ar}C); elemental analysis calcd (%) for $C_{13}H_{20}O_2Si$ (236.39): C 66.05, H 8.53; found: C 66.19, H 8.66.

3,5,6-Trimethyl-8-oxatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-4-ol (13): A solution of trimethylhydroquinone ($M = 152.19$, 1.52 g, 10.00 mmol) and 1,3-dibromocyclohexane ($M = 241.95$, 2.42 g, 10.00 mmol) in 1,2-dichlorobenzene (150 mL) was added quickly to refluxing 1,2-dichlorobenzene (100 mL) containing aluminum chloride ($M = 133.34$, 3.0 g, 22.5 mmol). The solution was refluxed for 30 min and poured into ice-cold NaOH (1 M, 250 mL) containing sodium sulfite (0.2 g). The mixture was stirred under argon for 30 min. The organic phase was extracted with NaOH (2 M, 100 mL). The organic layer was discarded, and the combined aqueous phases were extracted once with toluene (30 mL), which was also discarded. After acidification of the aqueous layer with H_2SO_4 (5 M), the solution was stirred for 1 h at room temperature and extracted three times with chloroform (50 mL). The organic extracts were dried over Na_2SO_4 and evaporated to dryness. The semisolid residue was recrystallized from acetic acid to give **13** as slightly yellow crystals ($M = 232.33$, 1.682 g, 7.24 mmol, 72.4%). ^{1}H NMR: $\delta = 1.30$ (m, 1H; $^{3}CH_2$), 1.49–1.93 (m, 6H; $^{2a}CH_2$, $^{3a}CH_2$, $^{4b}CH_2$), 1.93 (m, 6H; $^{2a}CH_2$, 2.02 (m, 1H; $^{3}CH_2$), 2.02 (m, 1H; $^{2a}CH_2$), 2.05 (s, 3H; $^{7a}CH_3$), 2.08 (s, 3H; $^{5a}CH_3$), 2.12 (s, 3H; $^{8b}CH_3$), 2.94 (m, 1H; ^{4}CH), 4.22 (tt, $^{3}J = 9.0$, 2.5 Hz, 1H; ^{2}CH), 4.86 ppm (s, 1H; OH). ^{13}C NMR: $\delta = 12.1$ (^{8b}C), 12.2 (^{7a}C), 12.6 (^{5a}C), 22.6 (^{3a}C), 29.4 (^{2a}C), 34.3 (^{4b}C), 36.8 (^{4}C), 37.8 (^{3}C), 84.3 (^{2}C), 119.3, 121.6, 122.0, 123.4, 144.6, 144.7 ppm (^{Ar}C); elemental analysis calcd (%) for $C_{15}H_{20}O_2$ (232.32): C 77.55, H 8.68; found: C 77.70, H 8.63. Compound **13** was also obtained as a byproduct of the synthesis of compounds **4** and **5**.

2,2,6,8,9-Pentamethyl-2,3,4,5-tetrahydrobenzo[b]oxepin-7-ol (14): 6-Benzyloxy-2,2,5,7,8-pentamethylchroman-4-one[28] ($M = 342.42$, 0.85 g, 2.48 mmol) and *N*-methyl-*N*-nitrosotoluenesulfonamide ($M = 214.24$, 0.65 g, 3.03 mmol) were dissolved in aqueous EtOH (50 mL, EtOH/H_2O = 4:1, v/v). The mixture was cooled to 0 °C in an ice bath, and an aqueous solution of KOH (0.1 g in 5 mL of water) was added dropwise. After stirring for 10 min, the mixture was allowed to reach room temperature and was stirred for additional 30 min. HCl (2 M) was added until a pH of 5 was reached. The mixture was stirred for additional 10 min, and extracted twice with CH_2Cl_2 (50 mL). The solvent was evaporated, and the residue was re-dissolved in ethanol (50 mL). Water (20 mL), concentrated HCl (2 mL), and powdered zinc ($M = 65.37$, 0.30 g, 4.59 mmol) were added. After 10 min, the addition of zinc (0.30 g, 4.59 mmol) was repeated. After the metal had completely dissolved, the mixture was filtered through a glass frit and stored at −10 °C. After three days the crystalline precipitate was collected by filtration under inert gas and recrystallized from acetic acid to give **14** ($M = 234.34$, 0.325 g, 1.386 mmol, 55.9%) as a white, crystalline mass, m.p. 67 °C. ^{1}H NMR: $\delta = 0.86$ (m, 2H; $^{3}CH_2$,), 1.22 (s, 6H; $^{2a}CH_3$), 1.83 (m, 2H; $^{4}CH_2$), 2.04 (s, 6H; $^{8a}CH_3$), 2.16 (s, 6H; $^{8a}CH_3$, $^{9b}CH_3$), 2.99 (m, 2H; $^{5}CH_2$), 4.12 ppm (s, 1H; OH); ^{13}C NMR: $\delta = 12.5$ (^{6a}C), 12.8 (^{8a}C), 12.9 (^{9b}C), 18.8 (^{4}C), 27.5 (d.i., ^{2a}C), 28.4 (^{5}C), 36.5 (^{3}C), 72.5 (^{2}C), 114.9, 120.6, 120.8, 125.1, 144.4, 145.0 ppm (^{Ar}C); elemental analysis calcd (%) for $C_{15}H_{22}O_2$ (234.34): C 76.88, H 9.46; found: C 76.87, H 9.73.

Preparation of silver oxide used in the oxidation experiments: NaOH (1 M) was added to a solution of silver nitrate in aqueous ethanol (v/v = 1:1) under vigorous stirring until no more precipitate occurred, keeping the pH at 12 or lower. The solids were removed by filtration, washed with boiling water until base-free, then with ethanol and diethyl ether. The remaining solid was suspended diethyl ether, and stirred vigorously for 2 h. Filtration of the solids and removal of solvent in vacuo produced an active Ag_2O, which was stored under oxygen in the dark.

General oxidation procedure and trapping of the resulting ortho-quinone methides: The respective phenol (**4**–**14**, 1 mmol) was dissolved in MeCN (2 mL), and freshly distilled ethyl vinyl ether (10 mL) was added. The mixture was brought to reaction temperature and kept under stirring at this temperature throughout. Freshly precipitated and pulverized Ag_2O (10 mmol, 2.32 g) was added in one portion. For kinetic studies, a 0.2 mL sample of the solution was taken, filtered through a 0.45 μm syringe filter into MeCN (3 mL), and further analyzed. The oxidation was complete after 10 min in all cases.

Oxidation of the compounds **4**–**14** was performed at four different temperatures: −78 °C, 0 °C, room temperature (25 °C), and 70 °C. All reported values are averaged values from triple runs, deviations were in no case larger than 1.2%.

For preparative separation of the oxidation products the mixture was evaporated to dryness in vacuo, followed by extraction and column chromatographic separation.[29]

Theoretical calculations: The structures of **4**–**18** were optimized at B3LYP/6–31G* theoretical level, and underwent analytical frequencies calculation to assure real minima ($N_{imag} = 0$). ΔE cited in Table 2 are relative to the optimized structure of **17**. The energies for the γ and δ deformed systems were obtained by using potential-energy scan (PES) procedure.

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[29] Detailed analytical data of the trapping products will be reported in due course.

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