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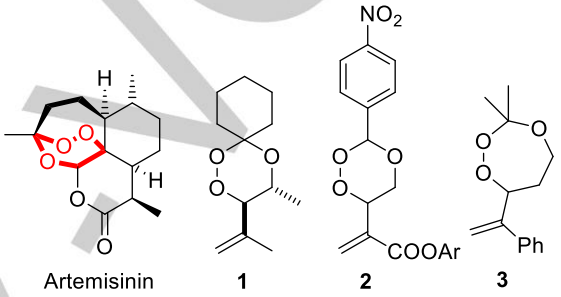
Spirofused and annulated 1,2,4-trioxepane-, 1,2,4-trioxocane-, and 1,2,4-trioxonane-cyclohexadienones: Cyclic peroxides with unusual ring conformation dynamics

Angelika Eske, Sabrina Ecker, Carolina Fendinger, Bernd Goldfuss, Matthis Jonen, Jens Lefarth, Jörg.-M. Neudörfl, Matthias Spilles, and Axel G. Griesbeck*

Abstract: C-3 or C-4-hydroxyalkyated phenols are highly reactive towards peroxidation by Oxone and result in the formation of tertiary C-3 hydroperoxides. This reaction can also be performed with photochemically generated singlet oxygen. Other characteristic singlet oxygen reactions do however not proceed with caroate. The initial formed hydroperoxides are cyclized under Lewis-acid catalysis with boron-, indium- or iron-based catalysts to give spiroannulated peroxides **6**, **9** which exhibit restricted ring inversion processes whereas the larger nine-membered ring peroxides **12** are less stable thermally and show –possibly correlated – also higher ring flexibility (by NMR analysis).

Cyclic organic peroxides are Janus-faced compounds: some of them show uncontrollable and violent behavior, some of them remarkable strong pharmacological effects.[1] The disreputable *triacetone triperoxide* (TATP) is a dangerous and uncontrollable explosive and an example for the first properties.[2] *Artemisinin* is the most popular example for the beneficial properties of cyclic peroxides.[3] The 2015 Nobel prize in physiology and medicine for the Chinese scientist Youyou Tu for “discoveries concerning a novel therapy against Malaria” honored her groundbreaking work in structure elucidation and investigations of antimalarial activities of this natural lactone peroxide.[4] The central compound in this research is the unusual peroxide *artemisinin*, a structurally complex tetracyclic sesquiterpene lactone with an endoperoxide substructure that can be isolated from the leaves of *artemisia annua*.[5] Due to its very high antimalarial activities, artemisinin, its derivatives, and numerous analogs have become important as antimalarial drugs against multidrug-resistant forms of the *plasmodium falciparum* parasite.[6] Recently, several reports also report on antitumor[7] and ß-cell reactivation relevant in diabetes therapy of these compounds.[8] This high pharmacological potential combined with its synthetically challenging structure have prompted synthetic chemists to design total or partial synthesis routes to this compound and derivatives thereof[9] as well as the design of artemisinin dimers, conjugates and dyads.[10] Recently, also flow photochemistry has been applied in order to produce larger amounts of artemisinin involving an oxygenation key step.[11]



Scheme 1. The natural sesquiterpene peroxide artemisinin and three pharmaactive 1,2,4-trioxane (**1**,**2**) and 1,2,4-trioxepane (**3**) derivatives.

In the last decade, we have developed a synthetic protocol to a series of 1,2,4-trioxanes with antimalarial properties similar to the natural products, e.g. the 1,2,4-trioxane **1**.[12] Furthermore, dyads (additional to hybrids or dimeric structures)[13] composed of natural artemisinine derivatives and synthetic trioxanes were realized.[14] In extension to these compound families, we synthesized a series of ester-substituted 1,2,4-trioxanes (e.g. **2**) that showed remarkable strong glutathione-transferase (GST) inhibition.[15] The (homo)allylic alcohol / singlet oxygen approach to allylic hydroperoxides that was used for these processes limits the reaction to 1,2,4-trioxanes[12] and seven-membered analogs like compound **3**.[16] Another way to allylic hydroperoxides is the caroate oxidation of phenols that are substituted at C4[17] a method that was also used for the synthesis of new spiroannulated 1,2,4-trioxanes.[18] The process uses as reagent Oxone®, a triple salt composed of $2KHSO_5$, $KHSO_4$, and K_2SO_4, a remarkably powerful oxidant with the potassium salt of Caro´s acid (caroate) as the reactive component.[19] The caroate reaction of phenols occurs at moderate basic conditions (pH = 8) in aqueous medium. Singlet oxygen was postulated as the reactive oxygen species in this specific application.[17] This assumption appears plausible because singlet oxygen $^1O_2$ was already described as a decomposition product from Caro´s acid either uncatalyzed or ketone-catalyzed.[20] Thus, this non-photochemical approach to singlet oxygen products appears to be of general relevance for the synthesis of 1,n-hydroxy hydroperoxides from 4-hydroxyalkyl phenols. We first investigated if this caroate approach really follows a singlet oxygen path and therefore compared the reactivity of probe molecules from $^1O_2$. As model substrate, commercial 4-hydroxyethylphenol **4** was applied.

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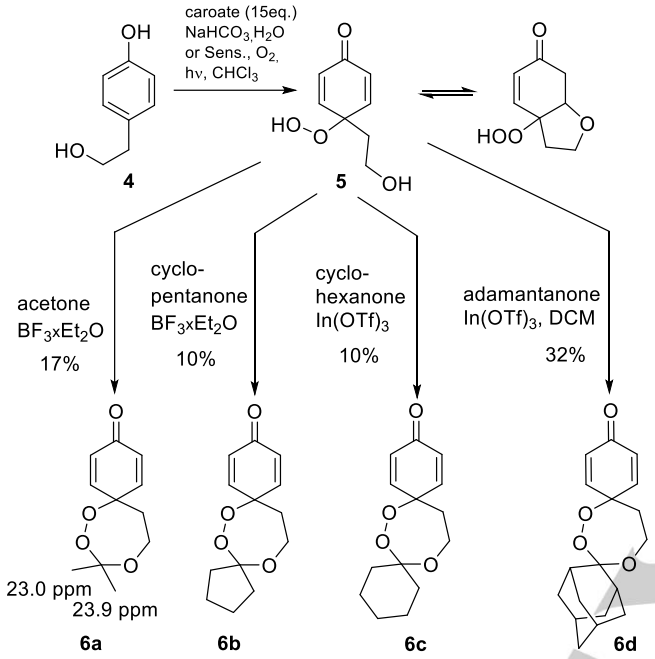
The caroate decomposition in aqueous media at pH = 10.5 leads to the formation of the hydroperoxide **5** in yields between 56 and 76% (in the presence of the lactol as side-product).[21] The corresponding reaction with photogenerated $^1O_2$ (Sens. = tetraphenylporphyrin) also resulted in **5**. No other typical singlet oxygen substrates (e.g. limonene, 2,3-dimethyl-2-butene) did however resulted in the expected $^1O_2$ products under caroate conditions, making the phenolate (at the given pH) reactivity a very special case.



Scheme 2. Caroate-induced hydroperoxidation of 4-hydroxyethylphenol **4** and subsequent peroxyacetalization under Lewis-acid catalysis.

Subsequent peroxyacetalization with BF_3 or $In(OTf)_3$ as Lewis-acid catalysts (Lewis acid optimization see SI) delivered the 1,2,4-trioxepanes **6a**-**6d** in moderate to low yields (Scheme 2). We were initially surprised by the complexity of the NMR spectra of these compounds: in the ^1H NMR all cyclohexadienone H´s appeared with different chemical shifts and also the formally enantiotopic methyl groups appear at 1.3 and 1.6 ppm (Figure 1). Analogously, ^{13}C NMR signals for all carbon atoms were different (Figure 2). Temperature-dependent NMR measurements were possible only until 50°C because of the instability of the cyclic peroxides and no coalescence effects could be determined. Thus, we speculated that the actual chemical structures of the products deviate from the expected 1,2,4-trioxepane ring. Two products could be crystallized and revealed that also this assumption was incorrect (Figure 3).[22]

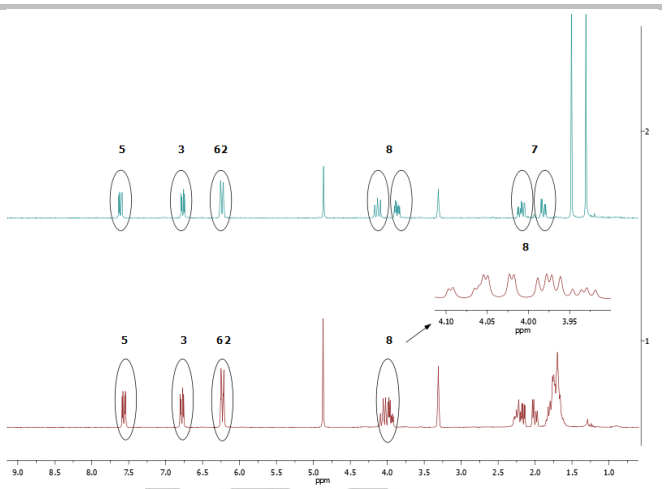


Figure 1. ^1H-NMR spectra of **6a** and **6b** in $CDCl_3$.

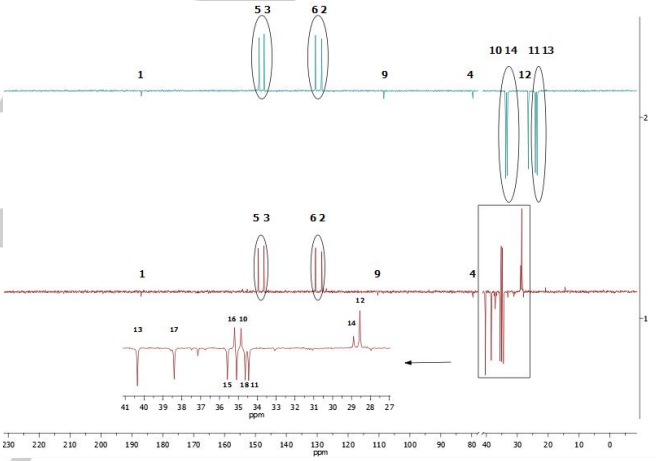


Figure 2. ^{13}C-NMR spectra of **6c** and **6d** in $CDCl_3$

Thus, the expected cyclic ring peroxide structures **6** are actually the products of the peroxacetalization. The anisochronicity effects in the NMR spectra are obviously a consequence of slow peroxide ring inversion, an unusual property that we have not yet observed in the six-membered 1,2,4-trioxane series.

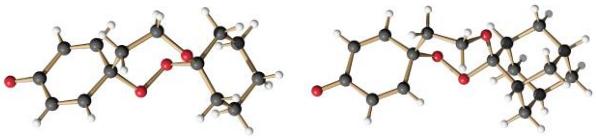


Figure 3. Structures of spiro-1,2,4-trioxepanes **6c** and **6d** in the crystal.

In order to explore if this structural behavior also occurs for larger ring systems, we have applied homologous substrates: the C_3-linked phenol **7**[23] is converted into the hydroperoxide **8** in 36% yield and peroxyacetalization with acetone delivers the 1,2,4-trioxocane **9a** in low yields (6-21%). Again, the two methyl groups

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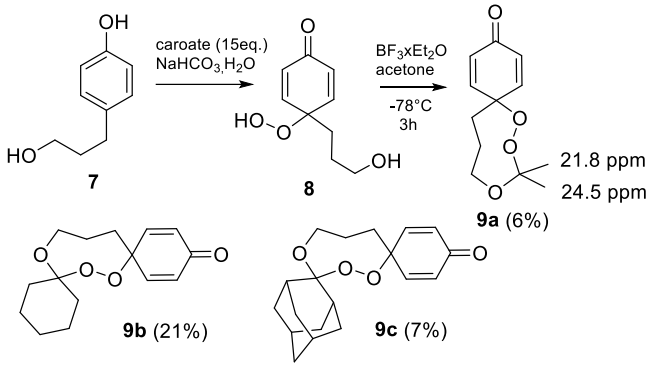
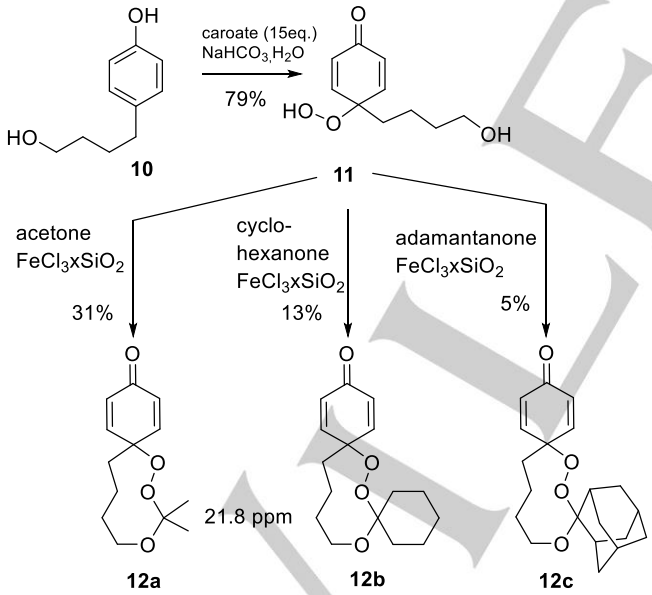
appear with different chemical shift (Scheme 3) and also other derivatives show the anisochronicity effects analogous to the seven-membered ring peroxides **6a**-**d**. Using $In(OTf)_3$ as Lewis acid, the corresponding eight-membered peroxides **9b** and **9c** were also available.



Scheme 3. Caroate-induced hydroperoxidation of 4-hydroxypropylphenol **7** and subsequent peroxyacetalization under Lewis-acid catalysis.

Motivated from the ring structure of the highly unstable triacetone triperoxide, we envisaged the synthesis also of nine-membered peroxides, the 1,2,4-trioxononanes: the C_4-linked phenol **10**[24] is converted with caroate into the hydroperoxide **11** in 79% yield. The ferric chloride catalyzed[25] peroxyacetalization with three ketones delivered the 1,2,4-trioxocanes **12a**-**12c** in low yields (Scheme 4). From these products, no anisochronicity NMR effects were detected, e.g. the NMR of the 3,3-dimethyl derivative **12a** showed only one methyl signal in ^1H and ^{13}C NMR (Figure 4).



Scheme 4. Caroate-induced hydroperoxidation of 4-hydroxybutylphenol **10** and subsequent peroxyacetalization under Lewis-acid ($FeCl_3$) catalysis.

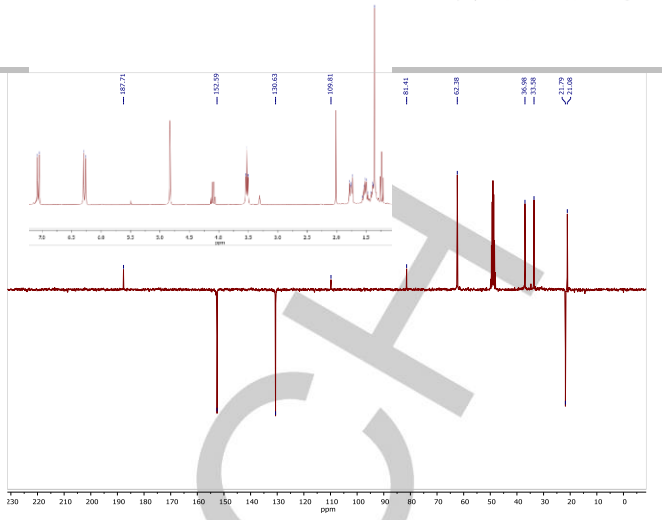
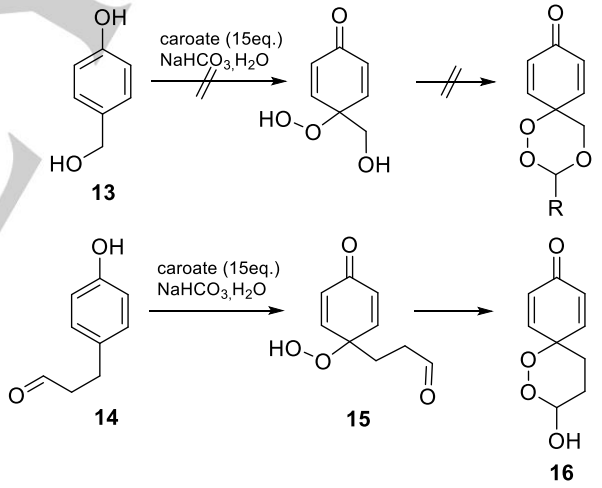


Figure 4. ^1H-NMR and ^{13}C-NMR spectra of the 1,2,4-trioxononane **12a** in $CDCl_3$ (negative signals CH and CH_3).

This synthetic protocol could not be applied for the generation of spiro-fused 1,2,4-trioxanes, i.e. the hydroperoxide from the oxone conversion of 4-hydroxymethylphenol **13** was not formed and consequently could not be transformed into 1,2,4-trioxanes. An analogous six-membered peroxide **16** was synthesized via the uncatalyzed intramolecular peracetal formation from the aldehyde **14** (Scheme 5).



Scheme 5. Caroate-induced hydroperoxidation of aldehyde **14** and intramolecular 1,2-dioxane (**16**) formation.

Alternatively to spirofused cyclic peroxides, this approach also allows the synthesis of annulated peroxides, e.g. the 3-hydroxymethylated phenol **17**[26] was successfully converted into a seven-membered cyclic peroxide **19** via the corresponding hydroperoxide **18** (Scheme 6) in 41% overall yield.

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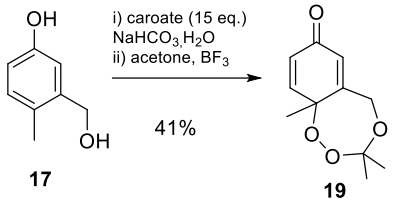


Scheme 6. Caroate-induced hydroperoxidation / acetone peroxyacetalization of 4-methyl-3-hydroxymethylphenol **17**.

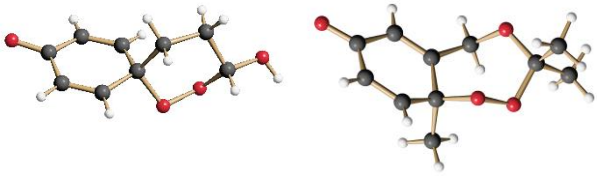
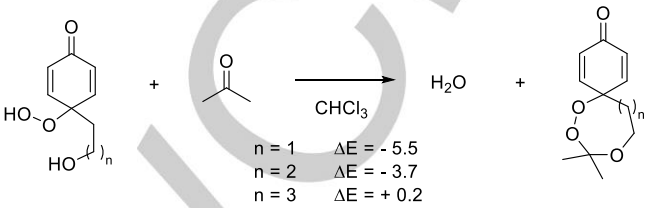


Figure 5. Structures of the cyclic peroxides **16** and **19** in the crystal.

Comparing the peroxide-containing ring families described in this communication, it became clear that slow ring conformational interconversion exists for seven- and eight-membered rings whereas the nine-membered cyclic peroxides undergo faster ring movements. This effect does qualitatively also match the stability features: whereas compounds **6** and **9** (and **19**) were stable in solution (and in solid state for **6c** and **6d**), the larger ring systems **12** slowly decompose also in solution even when stored at -20°C. Stabilizing stereoelectronic effects were described by Alabugin and colleagues to explain the unusual stability of *bis*-peroxides (1,2,4,5-tetroxanes).[27] The key stabilizing feature that was identified by quantum chemical calculation was a hyperconjugative $n_{O(O)} \rightarrow \sigma^*_{CO}$ interaction which is also relevant for the stabilization of 1,2,4-trioxanes. Density functional theory (DFT) calculations of the three model compounds **6a**, **9a**, and **12a** resulted in all cases in a complex pattern of minimum conformations with similar energies. The ring inversion barriers could thus not determined unam-biguously. Concerning the stability of the cyclic peroxides, comparison of the homologous hydroperoxides **5**, **8**, and **11** with the Gibbs free energies of the lowest energy conformers of the peroxides **6a**, **9a**, and **12a** resulted in reaction energies that serve as measures for the relative stabilization of the different ring sizes (Scheme 7, see also SI). It is safe to assume that the differences in ΔΔG arise predominately from changes in the peracetal structure of the products and thus indicate a 5.7 kcal/mol (in chloroform) stabilization of the seven-membered trioxepane in comparison to the nine-membered ring. The relative stabilization difference between seven- and eight-membered peroxides is only 1.8 kcal/mol (in chloroform). The conformational stabilization for the seven- and eight-membered peroxides originate from a per-anomeric effect as described as a central peroxide-stability determining effect also for numerous cyclic peroxides, e.g. artemisinin and ozonides.[27,28] Even higher stabilization energies for n_O-σ^*_{CO}-interaction was determined by natural bond orbital (NBO) methods that seem however to be counterbalanced by increasing ring-strain in the nine-membered peroxides.[29]

In summary, the gain in stabilization, as determined from Gibbs energy difference between starting materials and products decreases with increasing ring size. This overall effect is composed of stabilizing NBO interactions (per-anomeric effect. dominates for 6-8 membered peroxides) and destabilizing ring strain that prevail for the nine-membered peroxides **12**. These opposing effects explain unusual thermal stabilities of medium-sized peroxides (e.g. the artemisinin derivatives) and the instability of the nine-membered 1,2,4-trioxononanes (e.g. TATP).



	lpO(O)→σ*CO(C)	lpO(C)→σ*CO(O)
6a (n = 1)	13.6	8.8 kcal/Mol
9a (n = 2)	12.8	15.3 kcal/Mol
12a (n = 3)	14.5	19.4 kcal/Mol

Scheme 7. M062X/6-311++G**-GD3 (PCM, in $CHCl_3$) // B3LYP/6-31G*-GD3BJ calculated free reaction energies of hydroperoxides to cyclic peroxides and NBO-calculated (per)anomeric interaction energies..

Keywords: Peroxides • photochemistry • oxygenation • heterocycles • structures

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Spirofused and annulated 1,2,4-trioxepane-, trioxocane-, and trioxononane cyclohexadienones: Cyclic peroxides with unusual ring conformation dynamics

New spirofused and ring-annulated peroxides with unusual conformational behaviour are available from Oxone-induced peroxidation and peracetalization of 3- and 4-functionalized phenols. The stability properties enlighten the dichotomy of cyclic peroxides between medicinal and energetic properties.