Photooxygenation in polymer matrices: *En route* to highly active antimalarial peroxides*

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Abstract: Photooxygenation involving the first excited singlet state of molecular oxygen is a versatile method for the generation of a multitude of oxy-functionalized target molecules often with high regio- and stereoselectivities. The efficiency of singlet-oxygen reactions is largely dependent on the nonradiative deactivation paths, mainly induced by the solvent and the substrate intrinsically. The intrinsic (physical) quenching properties as well as the selectivity-determining factors of the (chemical) quenching can be modified by adjusting the microenvironment of the reactive substrate. Tetraarylporphyrins or protoporphyrin IX were embedded in polystyrene (PS) beads and in polymer films or covalently linked into PS during emulsion polymerization. These polymer matrices are suitable for a broad variety of (solvent-free) photooxygenation reactions. One specific example discussed in detail is the ene reaction of singlet oxygen with chiral allylic alcohols yielding unsaturated β-hydroperoxy alcohols in (*threo*) diastereoselectivities, which depended on the polarity and hydrogen-bonding capacity of the polymer matrix. These products were applied for the synthesis of mono- and spirobicyclic 1,2,4-trioxanes, molecules that showed moderate to high antimalarial properties. Subsequent structure optimization resulted in in vitro activities that surpassed that of the naturally occurring sesquiterpene-peroxide *artemisinin*.

*Keywords*: photochemistry; oxygen; malaria; peroxide; polymers.

INTRODUCTION

The active species in type II photooxygenation reactions is molecular oxygen in its first excited singlet state, as originally postulated by Kautsky [1]. This has been proven by elegant experiments performed by Foote and coworkers where reactions of photochemically generated singlet molecular oxygen were compared with the corresponding reactions of the active oxygen formed in the hypochlorite/hydrogen peroxide system [2]. The results from these allylic oxidations with singlet molecular oxygen ($^1O_2$) are clearly different than these of autoxidative (triplet oxygen) pathways [3]. Type II photooxygenation reactions involve the $^1\Delta_g$ state of oxygen ($^1\Delta_g\text{-}O_2$), which is formed by energy transfer either from a singlet or a triplet excited sensitizer molecule or by chemical methods [4–6]; the second excited state of oxygen ($^1\Sigma_g^+$) has not yet been unambiguously described as the reactive component in an oxygen-transfer process.

In contrast to type I photooxygenation (radical type) or electron-transfer-induced photooxygenation (either involving the reaction between substrate cation radicals and triplet oxygen or the reaction
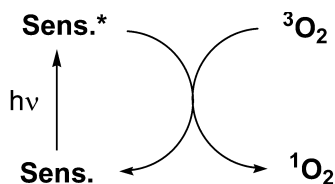
Scheme 1 Generation of $^1\Delta_g\text{-}O_2$ by energy transfer from an excited sensitizer.

of superoxide radical anion), singlet-oxygen reactions are highly selective and show all kinetic properties of pericyclic reactions [7–9]. The most important chemical reaction modes are the $[\pi^2+\pi^2+\sigma^2]$-ene reaction [10], the $[\pi^4+\pi^2]$-cycloaddition [11], and the $[\pi^2+\pi^2]$-reaction yielding 1,2-dioxetanes [12,13], as well as heteroatom oxidation (e.g., sulfide to sulfoxide [14]). The first three reaction modes represent efficient synthetic routes to a broad variety of oxy-functionalized products. For practical purposes, singlet oxygen is in the vast majority of applications generated in solution phase by photochemical triplet-triplet sensitization from appropriate dyestuffs absorbing in the visible range (Scheme 1). For all relevant solvents, a variety of sensitizers is known and well characterized concerning their chemical stability and singlet-oxygen quantum yields [15]. From the viewpoint of the principles of the green chemistry concept [16], photooxygenation appears to be *the* most promising oxidation route: the sole oxygen source is natural (triplet) oxygen, and no transition metals have to be applied for oxygen activation. The energy source for activating molecular oxygen is simply visible light, and, thus, photooxygenation is one of the archetype reactions feasible also for solar chemistry applications [17,18]. In order to use photonic energy for converting ground-state oxygen into a reactive oxygen species, long-wavelength light-absorbing dyestuffs can be used that are widely distributed in nature.

In contrast to the other popular oxygen source, hydrogen peroxide (with a maximum atom efficiency of 47 % [19]), complete atom economy can be reached and both oxygen atoms incorporated in the final products. This is obviously so for the three reaction modes depicted in Scheme 2, but also for the reduction products derived from the [2+2]- and [4+2]-adducts.
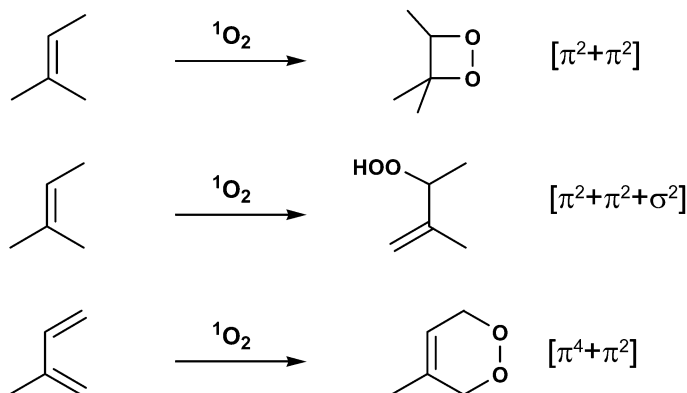
Scheme 2 Reaction modes of $^1\Delta_g\text{-}O_2$ in solution with alkenes and dienes.

For the allylic activation of C–C double bonds in the presence of allylic hydrogen atoms, the ene reaction is the most prominent path. The reaction was first described in 1943 by G. O. Schenck [20]. In the course of this reaction, $^1O_2$ attacks one center of a C–C double bond with abstraction of an allylic hydrogen atom or an allylic silyl group (bound to oxygen) and simultaneous allylic shift of the double bond. As the result of this reaction, allylic hydroperoxides are formed or O-silylated α-hydroperoxy carbonyl compounds. The former products can be transformed into epoxyalcohols by a tita-

nium(IV)-catalyzed intermolecular oxygen-transfer reaction (analogous to the Sharpless reaction) [21], or into 1,2,3-triols by an osmium(VIII)-catalyzed *vic*-bishydroxylation [22]. It is remarkable to note that all oxygen atoms that are incorporated in the alkene originate from air and water and no further oxidants are needed (Scheme 3).
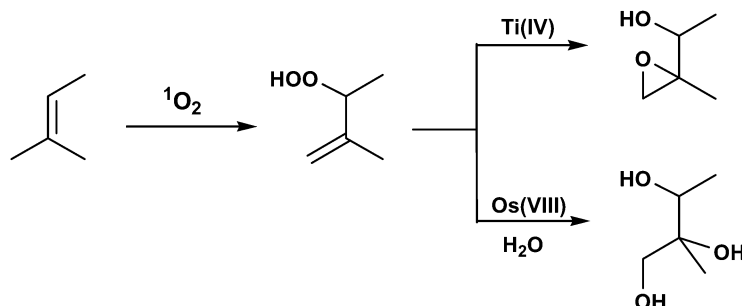
Scheme 3 Complete dioxygen transfer in the ene reaction mode and follow-up reactions.

PROBLEM DESCRIPTION

It has been recognized in recent years that in spite of the favorable reactivity pattern of $^1O_2$, condensed-phase photooxygenation conditions suffer from at least five major drawbacks: (a) the sensitizer dye must be soluble in the respective solvent, thus limiting the dye-solvent combinations that can be used; (b) removal of the dye from the product after the reaction either by chromatography or distillation is often an elaborate process; (c) singlet oxygen has its longest lifetime in environmentally problematic solvents such as halogenated hydrocarbons (tetrachloromethane, freons, etc. [23]); (d) photobleaching of the dye is often observed in halogenated solvents due to the formation of acid or is induced by $^1O_2$ itself or other oxygenated reactive intermediates, especially when long reaction times are necessary (higher photostability was observed with perfluoroalkyl- [24] and dichlorophenyl- [25] substituted porphyrine photosensitizers); and (e) solution purging with pure oxygen is highly problematic for industrial applications and sometimes also for small-scale laboratory syntheses. A general solution to all these problems is desirable in order to make photooxygenation a real green chemical process. Another challenge for the singlet-oxygen community is to make "chiral singlet oxygen", i.e., to modify the reaction environment in such a way that matrix effects might imprint stereochemical information in type II reactions.

The lifetimes of singlet oxygen ($^1\Delta_g$) in commonly used solvents are given in Table 1. The mechanism of singlet-oxygen quenching by solvent molecules has been intensively discussed in the recent decades, and different pathways were postulated. As a common ground, the relevance of electronic to vibrational (e-v) energy transfer is recognized, recognizable from the effect of exchanging CH by CD or CF bonds in a common solvent molecule. Thus, the nonradiative lifetime of singlet oxygen is increased in a deuterated solvent by a factor of about 20 compared to the protonated compound and by a factor of ca. 700 by exchanging CH with CF. This already demonstrates a serious application problem especially for polar substrates with low solubility in protic solvents.

Table 1 Lifetimes of $^1\Delta_g$-O_2 (μs) in protic and aprotic solvents and in dry air[a]: effects of deuterium and fluorine incorporation.

H_2O	CH_3OH	C_6H_6	$(CH_3)_2CO$	$CHCl_3$
3.1	9.1	30	51	229
D_2O	CD_3OD	C_6D_6	$(CD_3)_2CO$	$CDCl_3$
68	270 [27]	681	992	7.000
$C_6H_5CH_3$	C_6F_6	CCl_4	C_6F_{14}	air
29 [28]	21.000	59.000	68.000	86.000

[a]From ref. [26].

PROBLEM SOLUTIONS

In order to meet the requirements of green chemistry applications and to make type II photooxygenation, a highly regio- and diastereoselective process, several solutions have been considered. A common theme is the use of constrained media in order to control selectivity properties of singlet oxygen and avoid unfavorable solvent conditions.

It has been reported that triplet oxygen can be directly activated during zeolite irradiation in the presence of adsorbed alkenes [29], presumably through low-energy oxygen-alkene CT complexes [30]. The regioselectivity of singlet-oxygen ene reactions can be modified in the supercages of NaY zeolites [31], a phenomenon which has been widely explored in the last years [32]. Photooxygenation of an alkene in the presence of ephedrine as chiral inductor was performed in a NaY zeolite, yielding hydroperoxides with low enantioselectivities [33]. In these cases, the singlet-oxygen sensitizers are simply co-adsorbed in the zeolite supercages. Sensitizer molecules can also be incorporated into nafion membranes [34,35], an approach which enables the spatial separation of dye and substrate. The use of micro-sized molecular containers (micelles, vesicles) for photochemical transformations has also been recently explored for photooxygenations [36].

In contrast to these approaches, polymer-bound sensitizers such as the commercially available polystyrene (PS)-bound rose bengal [37] were developed quite early. Recently, numerous variations have been reported, e.g., ionic porphyrins immobilized on cationically functionalized PS [38], pyrylium salts immobilized on merrifield resins as electron-transfer sensitizers [39], PS-bound benzophenones as immobilized triplet photosensitizers [40], photosensitizers ionically bound at polymeric ion-exchanging resins [41], polymer-bound ruthenium(II) complexes [42], and polyethylene glycol-supported tetra(hydroxyphenyl)-substituted porphyrins [43]. The combination of a microreactor system as the reaction medium and visible light as reagent offers a new and convenient approach to green photochemistry. Not only is the production of side products retarded as a result of the enhanced selectivity, but also the amount of environmentally problematic and expensive solvents is reduced. The term "microcontainer" refers to organized and constrained media that provide microcavities and/or surfaces to accommodate the substrates and allows the reaction to take place.

Our first approach to this problem was the use of tetraarylporphyrin sensitizers embedded in a commercially available polystyrene-divinylbenzene (PS-DVB) copolymer as a reaction medium for photooxygenation reactions [44]. The solubility of the favorable singlet-oxygen sensitizers of the *meso*-tetraarylporphyrin-type (e.g., ϕ_Δ = 0.89 for tetraphenylporphyrin, TPP, in benzene [45]) is low in aprotic polar solvents and even lower in protic solvents. Therefore, the best way for product isolation from the crude reaction mixture is extraction with a protic solvent such as ethanol or methanol. On the other hand, tetraarylporphyrins and haematoporphyrins are known also to physically quench singlet oxygen [46,48], and thus must not be applied in high concentrations in solution where they tend to form dimers and increased singlet-oxygen quenching. Two solutions were developed by us to circumvent these problems in reaction processing: (1) the microcontainer approach where substrate and sensitizer are dis-

solved in the PS matrix and irradiated in the presence of air, and (2) the use of polymer-bound tetraaryl-porphyrin-sensitizers with a substrate likewise dissolved in the matrix and irradiated.

A simple, albeit highly useful, approach to solvent-free photooxygenation is the use of PS matrices with an adsorbed singlet-oxygen sensitizer: the reaction is performed with the organic substrate embedded in commercially available PS beads, which are cross-linked with DVB (100–200 mesh, 74–149 µm diameter unswelled). The nonpolar sensitizer (*para*-substituted *meso*-tetraarylporphyrins or the parent *meso*-TPP) for the generation of singlet oxygen was transferred in catalytic amounts into the PS network by swelling the resin with a solution of the sensitizer in dichloromethane (or in secondary cycles also with ethyl acetate) and subsequent evaporation of the solvent. As investigated in detail, the PS beads change their space structures while swelling with a nonpolar solvent [48]. After swelling with ethyl acetate, an average bead diameter of 130 ± 25 µm was determined by optical microscopy (Fig. 1). In the PS matrix, the sensitizer-to-substrate molar ratio was typically 1:1000, but also ratios as low as 1:20.000 were still effective for quantitative conversions of reactive substrates.
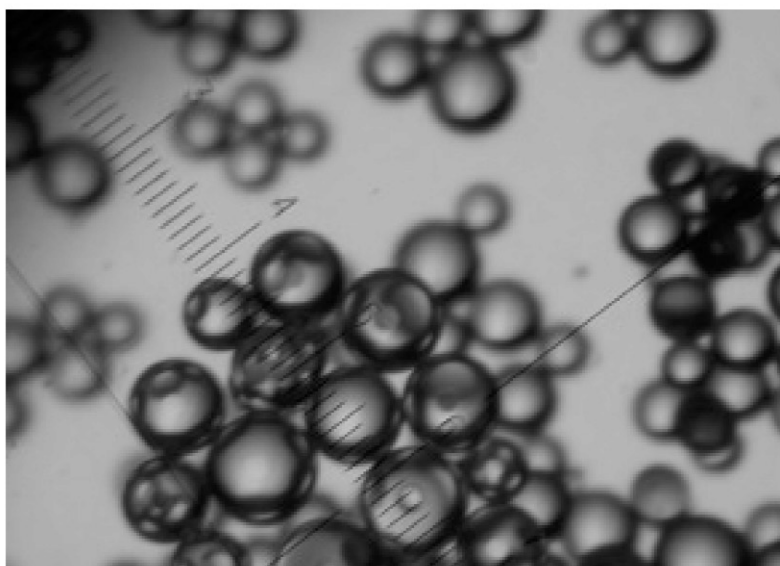
Fig. 1 PS beads (optical microscopy) loaded with tetratolylporphyrine, average diameter 110 µm.

The substrate was subsequently transferred into the polymer beads by the same procedure. Depending on the polarity and the volatility of the substrate, they can be loaded in 50–100 wt %, resulting in single polymer beads containing, after evaporation of the excess solvent, substrate volumes of ca. 0.5–1 nl. Irradiation is performed in a petri dish by means of a sodium street lamp or a halogen bulb lamp without external cooling or additional purging with oxygen. After complete conversion, the product was extracted from the polymer beads by repeated washing with ethanol. Due to the extreme low solubility of *meso*-tetraarylporphyrins in more polar solvents, the sensitizer stayed nearly completely in the solid support and the substrate loading process could be repeated. The loading, photolysis, and the unloading process were repeated five times with citronellol (**1**) without noticeable sensitizer bleaching or decreasing of the efficiency. Citronellol gave the hydroperoxide mixture **2a:2b** in 95–98 % yields in the same regio- and stereoisomeric composition as in nonpolar solvents (Scheme 4) without need for purification. Under solvent-free conditions, the degree of conversion was comparable to the solution photooxygenation in tetrachloromethane (pseudo-first-order conditions).
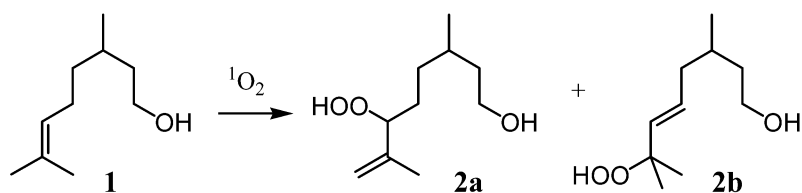
Scheme 4 Singlet-oxygen ene reaction with citronellol: an efficiency monitor.

This reaction represents an important industrial application of a singlet-oxygen ene reaction as the first step of the route to the fragrant chemical specialty *rose oxide* [49,50], and was used by us as the model process for evaluating the efficiency of singlet-oxygen reactions in polymeric matrices. Beside PS beads, we investigated several polymer films/beads with different degrees of polymer weight distribution, oxygen diffusion properties, and internal polarity and observed pronounced differences in substrate conversion (Table 2). The best results were obtained with polymer beads from polyhydroxy-butyric acid (PHB).

Table 2 Photooxygenation[a] of citronellol (**1**) in different polymeric matrices[b].

PS	PLA	CA	PHB	PEG	PVAA
79	68	40	100	5	44

[a]Yield in %, 5 h irradiation, 3.2 mmol of **1**, 1:4 (weight) substrate:polymer.
[b]Polystyrene (PS), polylactic acid (PLA), cellulose acetate (CA), polyhydroxybutyric acid (PHB), polyethylene glycol (PEG), poly-*N*-vinylacetamid (PVAA).

Additional examples of ene- and [4+2]-cycloadditions (Scheme 5) revealed that the reactivity and selectivity behavior is often comparable to solution photochemistry: the highly reactive α-pinene **3** gave the allylic hydroperoxide **4** in excellent yield (90 %), and the singlet oxygen [4+2]-cycloaddition with sorbinol (**7**) [51] or the chiral diene **9** proceeded with high yields (85 %, 81 %) and negligible substrate (or sensitizer) loss in the PS matrix. Even less reactive substrates like β-pinene (**5**) were transformed into the corresponding allylic hydroperoxides with complete conversion.
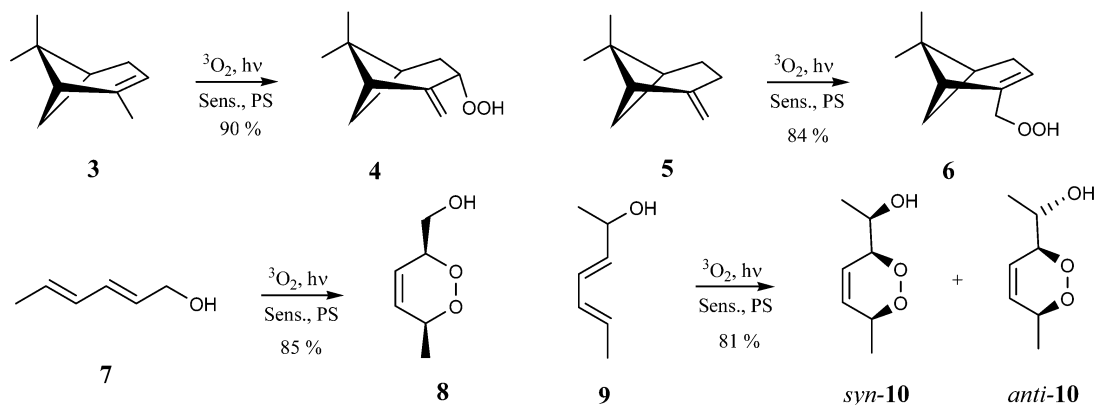
Scheme 5 Singlet-oxygen reactions in PS matrices: ene and [4+2]-cycloadditions.

A more elaborate approach is the use of polymer matrices with covalently linked singlet-oxygen sensitizers (Fig. 2). In order to cross-polymerize the dyestuff, tetrakis-(4-ethenylphenyl)porphyrin (tetrastyrylporphyrin, TSP [52]) was copolymerized via emulsifier-free emulsion polymerization with styrene and DVB. This technique allows the synthesis of resin particles with high particle size reproducibility. The TSP-PS-DVB resin beads are translucent nanoparticles (size range 150 300 nm). The polymer beads show high mechanical stability and (like the commercial PS resins) high loading capacity due to the large surface area, and behave as inexpensive, highly efficient, and resistant sensitizers. They are also easily and efficiently recycled with photooxygenation turnover number up to 3000 without any sensitizer bleaching or bleeding. It is especially noteworthy to mention that the polymer matrix was stable even against the potential oxidants produced during the photooxygenation (hydroperoxides or endoperoxides). Another readily available singlet-oxygen sensitizer for application in aqueous media is protoporphyrin IX ($\Phi_\Delta = 0.14$ in water [53]) which can be cross-polymerized into a PS matrix. The solvent-free photooxygenation procedure using the polymer-bound sensitizer follows the same protocol as with the adsorbed sensitizer systems. In order to explore the potential of the new TSP-PS-DVB solvent-free photooxygenation procedure and identify its influence on the chemo-, regio-, and stereoselectivity pattern in the type II photooxygenation reaction, the same substrates for both ene and [4+2]-cycloaddition reactions with singlet oxygen have been investigated as described above for the PS resin with noncovalently bound sensitizer.
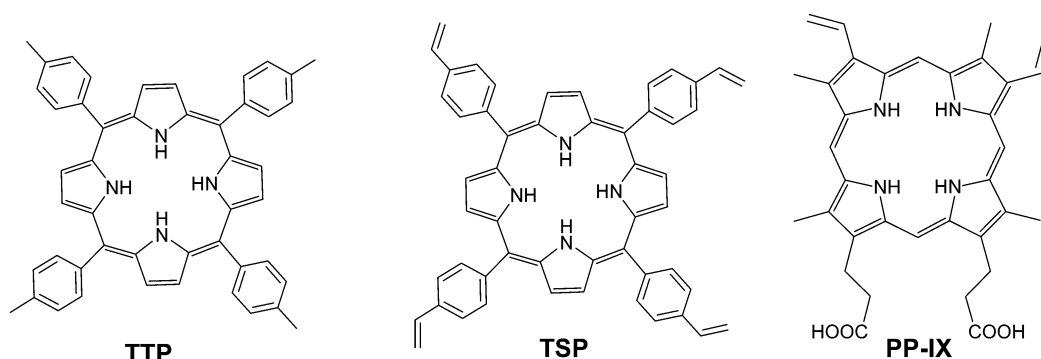

Fig. 2 Porphyrine sensitizers for noncovalent (**TTP**) and covalent (**TSP**, **PP-IX**) polymer modification.

In order to estimate the percentage of TSP covalently bound in the TSP-PS-DVB resin, two parallel photooxygenation reactions were run using identical amounts of the synthesized TSP-PS-DVB resin and the commercially available PS-DVB copolymer (loaded with a given amount of the sensitizer). Both reactions were carried out under identical reaction conditions using identical amounts of **9**. From the comparison of the degrees of conversion in both experiments, a loading degree of 0.1 % TSP in the PS resin was determined. For both reaction setup (adsorbed porphyrins as well as covalently linked dyestuff), an average loading degree of 1–2 µmol g^{-1} is adjusted.

## STEREOSELECTIVITY OF THE $^1O_2$ ENE REACTION AS A POLARITY SENSOR

The stereoselectivity of the singlet-oxygen ene reaction was investigated in detail in the last decade [54,55]. The singlet oxygen attacks in a suprafacial process (hydrogen abstraction occurs from the same π-face of the olefinic double bond) [56]. In view of the small size of the reactive molecule singlet oxygen, steric interactions are expected to be less important in directing the facial approach. Thus, stereoelectronic control is decisive in all cases where an orthogonal alignment of the reactive CH bond (involved in the hydrogen-transfer step) is accompanied by a π-face directing effect. Remarkable steering effects of the diastereoselectivity for the ene reaction were discovered with chiral allylic alcohols

(Scheme 6) [57,58]. The hydroxy group is conformationally aligned by 1,3-allylic strain, and hydrogen-bonding coordinates the incoming enophile with preferential formation of the *threo*-configured ene product. As shown in Scheme 6, hydrogen-bond interaction dictates also the regioselectivity of the reaction.
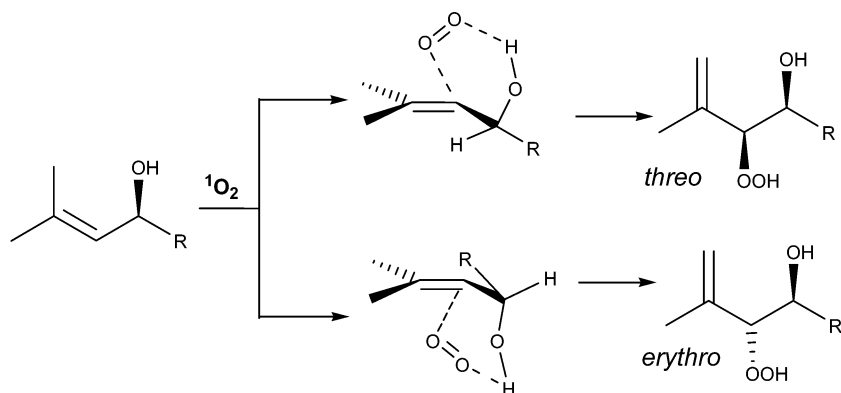
Scheme 6 Singlet-oxygen ene reactions with chiral allylic alcohols: stereoelectronic control.

The diastereoselectivity of the ene reaction of $^1O_2$ was investigated using chiral allylic alcohols **11a–d** (Scheme 7). Both the polymer-bound as well as the free sensitizer system (vide supra) gave similar diastereoselectivity (with the polymer-bound sensitizer somewhat higher), however *considerably lower* than in nonpolar solvents (photooxygenation of **11a** in CCl$_4$ proceeds with a *threo*-diastereoselectivity of 93 %). We have initially found that the diastereoselectivities subside under solvent-free conditions (Table 3); this effect is accounted for by increased intermolecular hydrogen-bonding between the (highly concentrated) substrates molecules in both microcontainer PS systems; this assumption was further supported by the fact that photooxygenation of **11a** in rose bengal/cellulose acetate film resulted in an even lower diastereoselectivity, indicating additional intermolecular hydrogen-bonding between the matrix and the substrates in comparison with the photooxygenation carried out either in the sensitizer-bound or free sensitizer PS-DVB matrices [59].
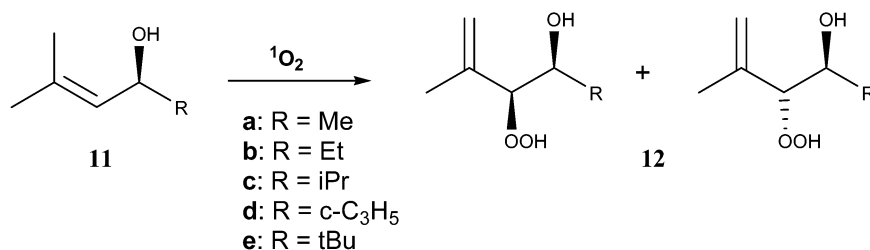
Scheme 7 Singlet-oxygen ene reactions with chiral allylic alcohols **11a–d**.

Table 3 Photooxygenation[a] of the chiral allylic alcohol **11a** in solvents and different polymeric matrices[b].

CCl$_4$	PS	PLA	CA	PHB	PEG	PVAA	EtOH
10:1	3.4:1	3:1	2.3:1	1.8:1	1.8:1	1.7:1	1.5:1

[a]>80 % conversions, solvent conc.: 0.03 M, 1:10 (weight) substrate:polymer, diastereoselectivities given as *threo:erythro* ratios.
[b]Polystyrene (PS), polylactic acid (PLA), cellulose acetate (CA), polyhydroxybutyric acid (PHB), polyethylene glycol (PEG), poly-*N*-vinylacetamid (PVAA).

The relative (*threo*) configuration of the major diastereoisomers has been derived from several chemical modifications of the β-hydroperoxy alcohols, among them also the peroxyacetalization described later. The first unambiguous proof was achieved for compound **12e**, which could be crystallized (Fig. 3) [60].
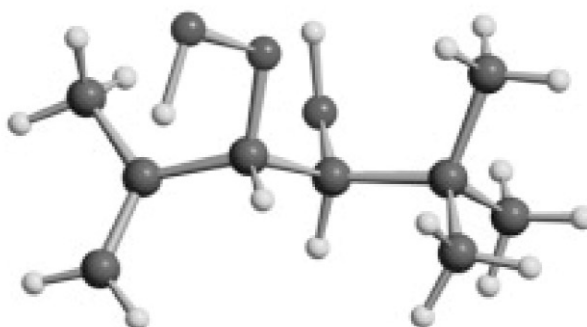
Fig. 3 Structure of the β-hydroperoxy alcohol *threo*-**12e** in the crystal.

The diastereoselectivity apparently serves as a sensor for the polarity and the hydrogen-bonding capacity of the microenvironment. In the solvent-free approach, there is substrate aggregation that leads to reduced hydrogen-bonding capacity toward the singlet-oxygen molecule. This effect is expressed in the effect of loading degree as well as of conversion percentage on the diastereoselectivity (Table 4). The latter effect is especially noteworthy, implying that the product of the ene reaction (**12b**) is a better hydrogen-bond acceptor and thus reduces the π-facial directing effect continuously during the progress of the reaction.

Table 4 Photooxygenation of the chiral allylic alcohol **11a** in PS at different degrees of loading and conversion dependency.

Loading[a]	0.1	1.0	4.0		
d. r.[b]	6.1:1	3.4:1	3.0:1		
% Conversion[c]	10	30	50	80	100
d. r.[b]	8.5:1	8.3:1	7.2:1	6.6:1	6.0:1

[a]In mmol **11a** / g PS.
[b]Diastereoselectivities given as *threo:erythro* ratios.
[c]Initial concentration: 0.1 mmol **11a** / g PS.

APPLICATION OF SOLVENT-FREE PHOTOOXYGENATION FOR THE SYNTHESIS OF NEW ANTIMALARIALS

The eager demand for new antimalaria-active substances has been recognized as a pressing challenge in recent years [61,62]. Of special interest is the search for efficient and less-toxic compounds exhibiting high activity against *malaria tropica* because multidrug resistance exists already in many places with this most aggressive pathogen of the *Plasmodium falciparum* species [63], including also the "gold standard", chloroquine. There are numerous potential drugs and derivatives, some of them are shown in Fig. 4. Besides the well-established quinoline derivatives, compounds that are currently tested as pharmaceutical leads include those that interact with different locations of infected erythrocytes. A class of compounds having in common the structural motif of cyclic peroxides play a special role both because of their structures and the possible mode of action. Many of these compounds are structurally derived from the naturally occurring sesquiterpene lactone *artemisinin* (*qinghaosu*), a compound with a 1,2,4-trioxane core structure [64,65]. But also 1,2-dioxanes as occurring in *yingzhaosu A* and *C* show high antimalarial activities [66]. Extensive work has been published on the total synthesis of artemisinin [67], the preparation of derivatives [68] as well as on the elucidation of the peroxide-specific mode of action [69]. Semisynthetic derivatives have been reported from several research groups as well as fully synthetic spirobicyclic peroxides and "dual systems", with 1,2,4-trioxanes linked to quinolines [70–73]. The heme iron(II)-initiated dissociative one-electron reduction of artemisinin has been recognized as the triggering process from studies of its redox behavior [12,74], as well as from studies on secondary products and also on adducts to cell components. Recent studies by Krishna et al. have shown that artemisinin acts as a strong inhibitor of the calcium-transport enzyme PfATP6 and thus might act more selectively than expected from the notion of radical-induced parasite damage [75].
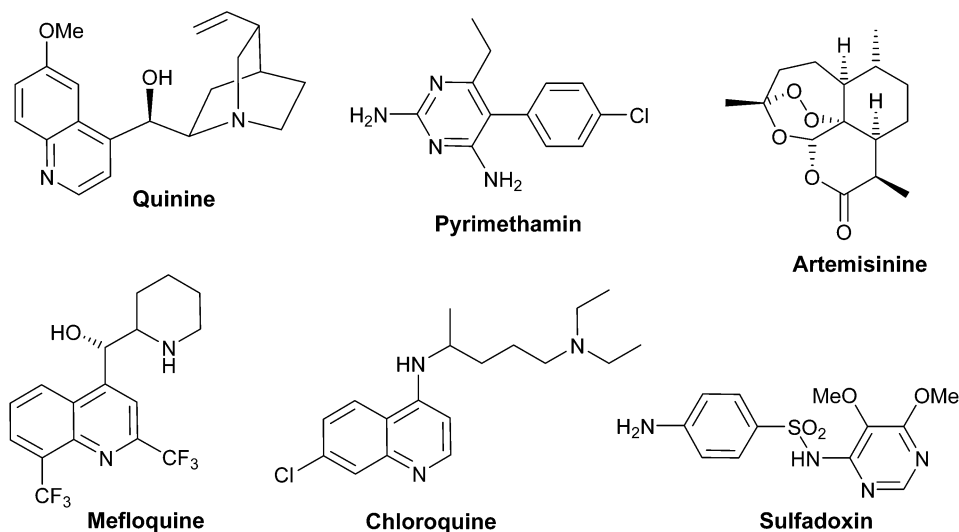

Fig. 4 Structures of classical antimalarials.

A straightforward approach to the basic structure (pharmacophore) of this compound and derivatives is the peroxyacetalization of β-hydroperoxy alcohols such as the ene products **12** described above (Scheme 8) [76,77]. The substrates are easily accessible via reduction of unsaturated ketones or Grignard addition to the corresponding aldehydes. A multitude of these compounds was generated via the polymer photooxygenation protocol described above and subsequent acetalization with carbonyl compounds catalyzed by boron trifluoride [78]. Several of these compounds were crystallized, and X-ray structures were determined (e.g., for compounds **13f,g**, see Fig. 5).
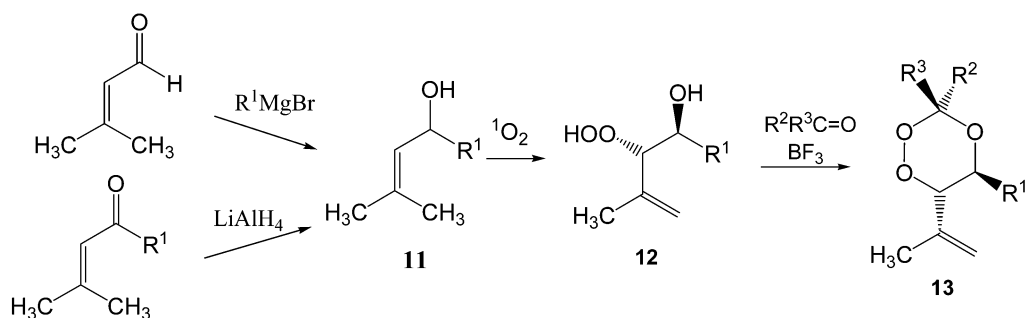
Scheme 8 Singlet-oxygen ene reactions with chiral allylic alcohols **11a–d**.
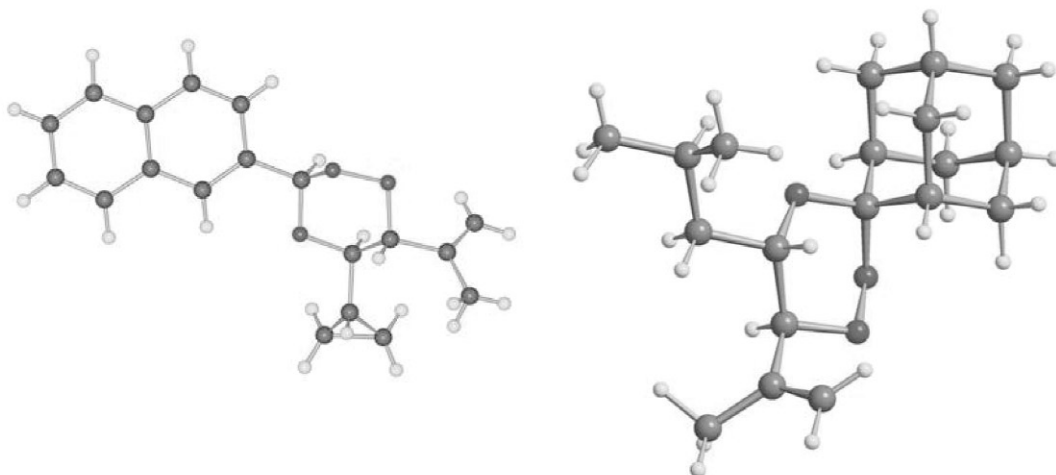
Fig. 5 Structure of the 1,2,4-trioxanes **13f** and **13g** in the crystal.

It attracted our attention that during the course of the BF_3-catalyzed peroxyacetalization unexpectedly additional peroxidic products were formed. In this contribution, we now report on the synthetic potential of this side reaction and structural modifications of 1,2,4-trioxanes that led to a substantial increase in activities. We observed the formation of 1,2,4-trioxanes, in some cases also in the absence of external carbonyl components. This phenomenon was recognized the first time during the photooxygenation of prenol, sensitized by 9,10-dicyanoanthracene (9,10-DCA) [78]. This was initially interpreted as a result of an electron-transfer-initiated photooxygenation involving the radical cation of the allylic alcohol. The transformation of the independently synthesized β-hydroxy hydroperoxide **12** with boron trifluoride, however, resulted also in the formation of 1,2,4-trioxanes in the absence of carbonyl components (Scheme 9). Obviously, a slow cleavage of **12**, catalyzed by the Lewis acid, leads to the corresponding carbonyl fragments, which subsequently react with the excess β-hydroxy hydroperoxide to give the mixed trioxanes **14** and **15**, respectively. In case of the formation of volatile aldehydes (e.g., from **12a**) during this cleavage process, only **15** was formed when the former component was removed from the reaction mixture with a continuous stream of nitrogen gas.
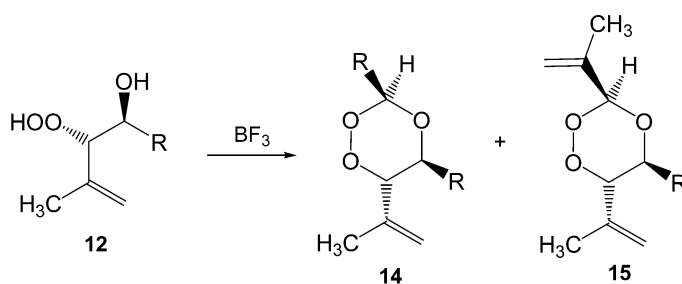
Scheme 9 Lewis-acid-catalyzed cleavage and (cross) peroxyacetalization of **12**.

In all other cases, the 2-alkylated 1,2,4-trioxanes **14b–f** were formed as the major components (Table 5) with high diastereoselectivities; the relative configuration with respect to C3 and C4 (*threo*) results from the diastereoselective ene reaction of $^1O_2$ with chiral allylic alcohols. The formation of the internal 1,2,4-trioxanes **14** and **15**, respectively, was diminished with increase of the external carbonyl component.

Table 5 Chemoselectivity of the BF_3-catalyzed cleavage and peroxyacetalization of β-hydroxy hydroperoxides **12a–f**.

	R =	**14**:**15**[a]	Yield[b]
a	CH_3	0:100	62 %
b	CH_2CH_3	63:37	41 %
c	$CH(CH_3)_2$	94:6	50 %
d	$CH_2CH(CH_3)_2$	87:13	59 %
e	$CH_2CH=CH_2$	90:10	60 %
f	cyclo-C_3H_5	61:39	33 %

[a]By ^1H NMR on the peroxidic mixture.
[b]Mixture of peroxides.

From the work by Jefford et al. [79], it was known that spiroanellation of a cyclopentane ring at the C3 position of the trioxane structure results in a considerable activity increase. Thus, we have applied this concept for the syntheses of compounds **13** (Fig. 6). The acetone adduct **13a** showed comparatively low activities against *P. falciparum* of approximately the same order of magnitude as for chloroquine (Table 6). The spiroanellation of cyclopentane rings to different β-hydroxy hydroperoxides **12** resulted in noticeably more active compounds (e.g., **13b**). This structure/activity correlation was originally interpreted in the literature as evidence for the formation of reactive C-radicals following the primary mesolytic cleavage of the peroxy bond. Spiroanellation of cyclohexane rings gave a further increase in activity by a factor of 10 (**13c**). These considerations suggested the need to investigate the spiroadamantane connection [76].

Table 6 Activity profile of 1,2,4-trioxanes: in vitro activities.[a]

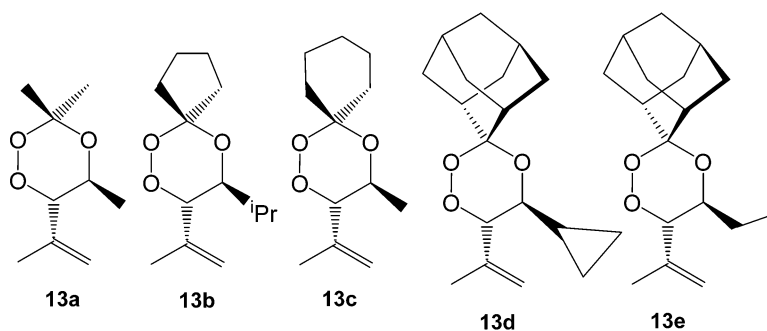| Chloroquine	Artemisinin	**13a**	**13b**	**13c**	**13d**	**13e**
200	2.8	1309	10.6	3.1	1.9	1.8

[a]IC_{50} in nM, K1-strain.

Fig. 6 Selected examples of antimalarial 1,2,4-trioxanes.

The products **13d** and **13e** (in yields of 15–40 % from the corresponding β-hydroxy hydroperoxides by treatment with adamantanone in the presence of catalytic amounts of BF_3) showed consistently excellent activities against *P. falciparum* in the range of the natural artemisinin accompanied by low cytotoxicity. The selectivity index (IC_{50} for the mammalian cell line L-6/IC_{50} for *P. falciparum*) reaches a highly promising factor of 1000 for the highly active compounds. Further progress in activities is expected from the application of terpenoid allylic alcohols as substrates.

CONCLUSIONS

Diverse polymer matrices are suitable for a broad variety of (solvent-free) photooxygenation reactions. The ene reaction of singlet oxygen with chiral allylic alcohols was shown to constitute a suitable model reaction providing information on the polarity and hydrogen-bonding capacity of the polymer matrix. The products from this singlet-oxygen reaction, β-hydroperoxy alcohols, were applied for the synthesis of mono- and spirobicyclic 1,2,4-trioxanes, molecules which showed moderate to high antimalarial properties. Subsequent structure optimization resulted in in vitro activities that surpassed that of the naturally occurring sesquiterpene-peroxide *artemisinin*.

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