Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Molecular Catalysis A: Chemical 251 (2006) 41–48
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Type II photooxygenation in polymer matrices for the synthesis of new antimalarial peroxides

Axel G. Griesbeck *, Anna Bartoschek, Tamer T. El-Idreesy, O. Höinck, Claus Miara

Institute of Organic Chemistry, University of Cologne, Greinstr. 4, D-50939 Köln, Germany

Available online 6 March 2006

Abstract

Type II photooxygenation involves the photochemical activation of dioxygen into its first excited singlet state and the application of this reactive species in oxy-functionalization of organic molecules. A broad variety of reactions and substrates can be applied in type II processes. The efficiency is determined by the lifetime of the $^1\Delta_g$-dioxygen and the physical as well as the chemical quenching rates by the substrate. The singlet oxygen ene reaction with allylic alcohols was developed as a route to mono- and spirobicyclic 1,2,4-trioxanes, molecules which showed moderate to high antimalarial properties similar to the naturally occurring sesquiterpene-peroxide *artemisinin*. As sensitizing materials tetraarylporphyrins embedded in polystyrene (PS) beads or in polymer films were used. Alternatively, the sensitizers were covalently linked to polystyrene during emulsion polymerization. The diastereoselectivity of the ene reaction with chiral allylic alcohols served as a probe for the microenvironment in the polymer matrices. Applications of this technique for the synthesis of a multitude of peroxides are described.

Keywords: Photooxygenation; Singlet oxygen; Allylic hydroperoxides; Trioxanes; Stereoselectivity

1. Introduction

The reactive oxygen species in Type II photooxygenation reactions is the first excited singlet state of molecular oxygen as originally postulated by Kautsky et al. [1] and subsequently proven by elegant experiments performed by Foote [2]. The results from oxidations with singlet molecular oxygen ($^1O_2$) are clearly different to autoxidative (triplet oxygen) pathways [3]. Type II reactions involve the $^1\Delta_g$ state of oxygen ($^1\Delta_g$-O_2), which is formed by energy transfer either from a singlet or a triplet excited sensitizer molecule or by chemical methods [4–7]; the second excited state of oxygen ($^1\Sigma_g{}^+$) is extremely short-lived and thus can not be applied as reactive component in oxygen-transfer processes.

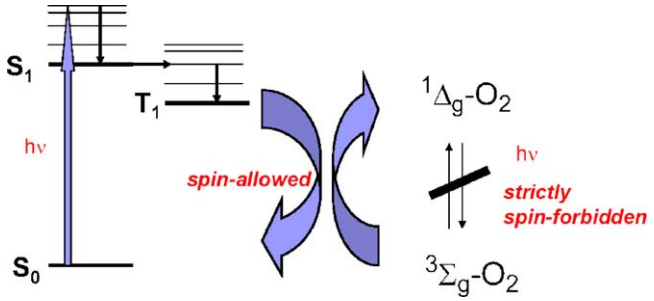
In contrast to Type I photooxygenation (radical type) or electron transfer induced photooxygenation (either involving the reaction between substrate cation radicals and triplet oxygen or the reaction of the superoxide radical anion), singlet oxygen reactions are highly selective and often are typical for pericyclic processes [8,9]. The most important examples are the $[\pi^2+\pi^2+\sigma^2]$-ene reaction resulting in allylic hydroperoxides [10], the $[\pi^4+\pi^2]$-cycloaddition yielding endoperoxides (1,2-dioxenes) [11] and the $[\pi^2+\pi^2]$-reaction to 1,2-dioxetanes [12,13]. Furthermore, the oxidation of heteroatoms (e.g. sulfide to sulfoxide [14]) is a prominent side-reaction. For practical purposes, singlet oxygen is generated in solution phase by photochemical triplet–triplet sensitization from appropriate dyestuffs absorbing in the visible range (Scheme 1). A great deal of sensitizers are known and characterized concerning their stability and singlet oxygen quantum yields [15]. When considering the principles of "green chemistry" [16], photooxygenation is the most promising route: the oxygen source is triplet dioxygen and no transition metals have to be applied for oxygen activation. The energy source is simply visible light and thus, photooxygenation is the archetype reaction feasible for solar applications [17,18]. In order to use photonic energy for converting ground-state oxygen into a reactive oxygen species, long-wavelength light absorbing dyes are used which are widely distributed in nature.

In contrast to hydrogen peroxide (maximum atom efficiency of 47% [19]), complete atom economy can be reached with singlet oxygen 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.

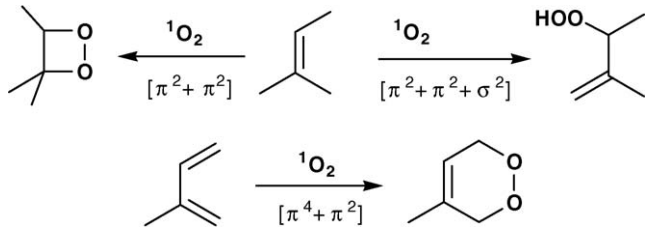
The ene reaction is the most prominent path for activation of C–C double bonds in the presence of allylic hydrogen atoms.

* Corresponding author. Tel.: +49 221 4703083; fax: +49 221 4705057.
E-mail address: griesbeck@uni-koeln.de (A.G. Griesbeck).

1381-1169/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2006.02.004



Scheme 1. Generation of $^1\Delta_g$-O_2 by energy transfer from an excited sensitizer.



Scheme 2. Pericyclic reaction modes of $^1\Delta_g$-O_2 in solution.

The reaction was first described in 1943 by 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 and simultaneous allylic shift of the double bond. As the result of this reaction, allylic hydroperoxides are formed. The former products can be transformed into epoxyalcohols by a titanium(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].

2. Results and discussion

It has been realized for a long time that in spite of the favorable reactivity pattern of $^1O_2$, condensed phase photooxygenation conditions suffer from several drawbacks: (a) the sensitizer has to be soluble in the respective solvent, thus limiting the available dye-solvent combinations; (b) removal of the dye from the product after the reaction either by chromatography or distillation is sometimes an elaborate process; (c) singlet oxygen has its optimal lifetimes 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 (e.g. by decomposition of chlorinated hydrocarbons to HCl or induced by $^1O_2$ itself) or other oxygenated reactive intermediates, especially when long reaction times are necessary (higher photostability was observed with perfluoroalkyl- and dichlorophenyl-substituted porphyrine photosensitizers [24,25]); (e) solution purging with pure oxygen is highly problematic for industrial applications and sometimes also for small scale laboratory syntheses. A global 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 $^1O_2$ is strongly dependent on the media and ranges from 3.1 μs in H_2O (60 μs in D_2O) to 59,000 μs in CCl_4. 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 [26–28]. Thus, the non-radiative 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 circa 700 by exchanging CH with CF. This already demonstrates a serious application problem especially for polar substrates with low solubility in protic solvents. 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.

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 microsized molecular containers (micelles, vesicles) for photochemical transformations has also been recently explored for photooxygenations [36]. The ultimate goal for singlet oxygen reactions is high enantioselectivity which has been recently realized in organocatalytic reactions of ketones and aldehydes [37,38] using soluble porphyrins in DMF or DMSO solutions.

In contrast to these approaches, polymer-bound sensitizers such as the commercially available polystyrene-bound rose bengal [39] were developed quite early. Recently, numerous variations have been reported, e.g. ionic porphyrins immobilized on cationically functionalized polystyrene (PS), [40] pyrylium salts immobilized on merrifield resins as electron-transfer sensitizers [41], polystyrene-bound benzophenones as immobilized triplet photosensitizers [42], photosensitizers ionically bound at polymeric ion exchanging resins [43], polymer-bound ruthenium(II) complexes [44], and polyethylene glycol supported tetra(hydroxyphenyl)-substituted porphyrins [45]. The combination of a microreactor system as the reaction medium and visible light as reagent offers a new and convenient approach towards 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

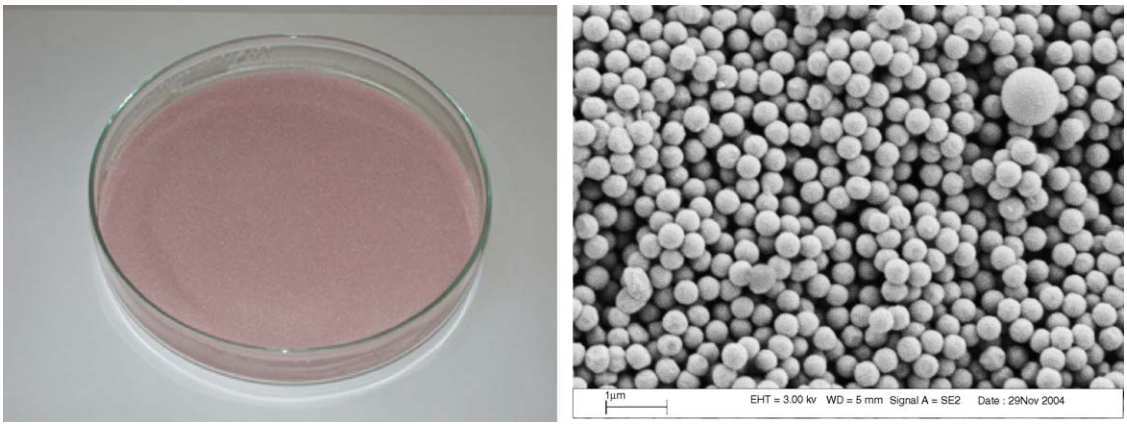


Fig. 1. Commercial polystyrene (PS) beads treated with TPP (in a petri dish) and polystyrene beads (SEM picture) covalently linked to protoporphyrin IX, average diameter 300 nm.

and constrained media which 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 [46]. The solubility of the favorable singlet oxygen sensitizers of the *meso*-tetraarylporphyrin-type (e.g. $\Phi_{\Delta} = 0.89$ for TPP in benzene [47]) 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, tetrarylporphyrins and haematoporphyrins are known also to physically quench singlet oxygen [48,49], 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 dissolved in the polystyrene matrix and irradiated in the presence of air and (2) the use of polymer-bound tetrarylporphyrin-sensitizers with a substrate likewise dissolved in the matrix and irradiated.

A simple and useful approach to solvent-free photooxygenation is the use of polystyrene matrices with an adsorbed singlet oxygen sensitizer: the reaction is performed with the organic substrate embedded in commercially available polystyrene beads which are crosslinked with divinylbenzene (100–200 mesh, 74–149 μm diameter unswelled). The non-polar sensitzer (*para*-substituted *meso*-tetraarylporphyrins or the parent *meso*-tetraphenylporphyrin, TPP) for the generation of singlet oxygen was transferred in catalytic amounts into the polystyrene 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 polystyrene beads change their space structures while swelling with a non-polar solvent [50]. After swelling with ethyl acetate, an average bead diameter of 130 ± 25 μm was determined by optical microscopy (Fig. 1). In the polystyrene 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.

The substrate was subsequently transferred into the polymer beads by the same procedure. Depending on the polarity and the volatility of the substrate, the beads can be loaded with 50–100 wt.% of substrate. 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 (Fig. 2). The loading, photolysis and the unloading process were repeated five times with citronellol (**1**) without noticeable sensitizer bleaching or decreasing of the efficiency.

Citronellol (**1**) gave a mixture of regioisomeric hydroperoxides **9** in 95–98% yields in the same regio- and stereoisomeric composition as in non-polar solvents Scheme 3 without need for purification. Under solvent-free conditions the degree of conversion was comparable to the solution photooxygenation in tetrachloromethane. Likewise, the ene and [4 + 2]-cycloaddition reactions of the substrates shown in Scheme 4 were performed with high conversions (based on recovered material) and excellent product purities.

This reaction represents an important industrial application of a singlet oxygen ene reaction as the first step of the route to the fragrant chemical speciality *rose oxide* [51,52], 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. The best results were obtained with polymer beads from polyhydroxybutyric acid (PHB).

A more elaborate approach is the use of polymer matrices with covalently linked singlet oxygen sensitizers. In order to crosspolymerize the dyestuff, tetrakis-(4-ethenylphenyl) porphyrin (tetrastyrylporphyrin, TSP [53]) was copolymerized

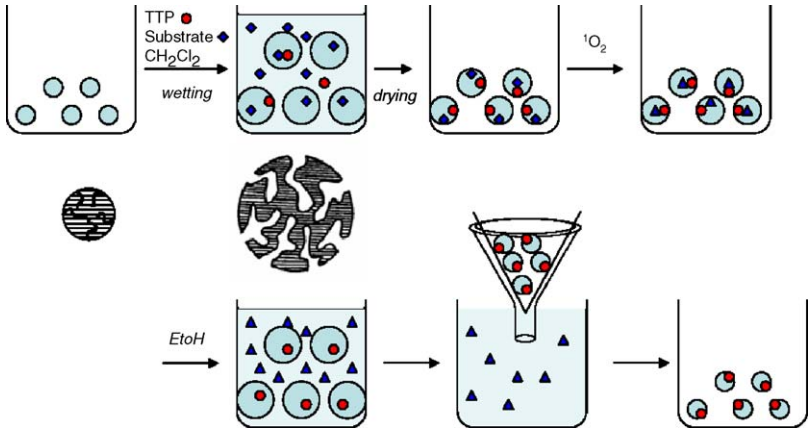
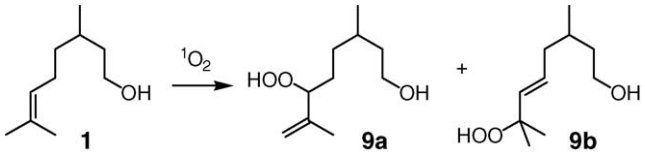


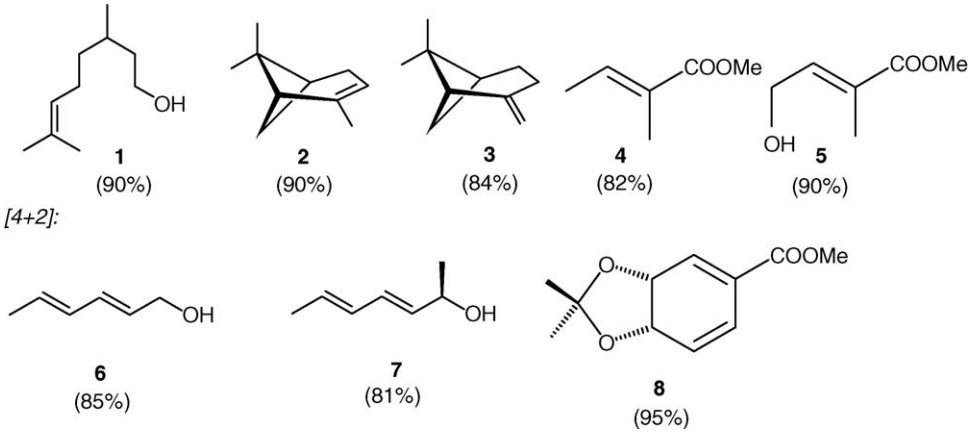
Fig. 2. Wetting–drying-photooxygenation protocol for unpolar substrates.



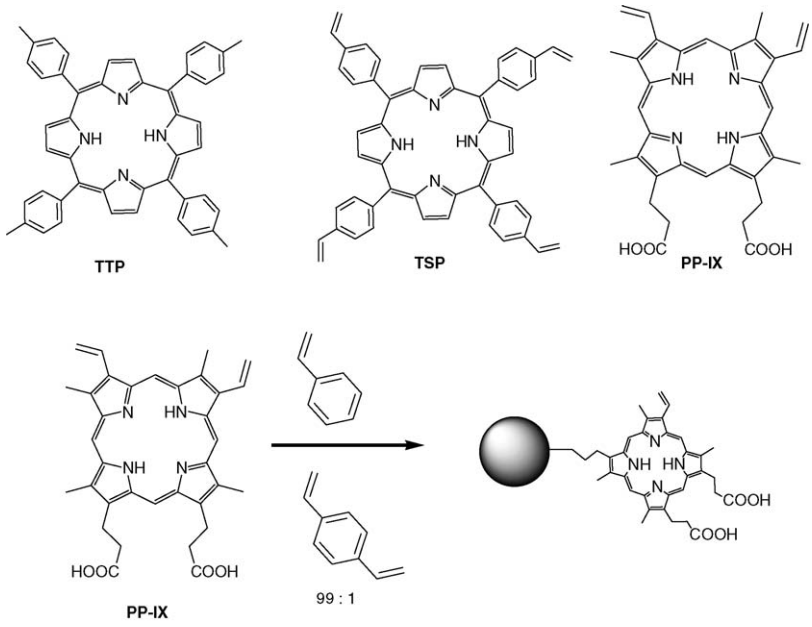
Scheme 3. Singlet oxygen ene reaction with citronellol: an efficiency monitor.

via emulsifier-free emulsion polymerization with styrene and divinylbenzene. 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 polystyrene 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 [54]) which can be crosspolymerized into a polystyrene matrix (Fig. 1, Scheme 5). 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 polystyrene resin with non-covalently bound sensitizer (Scheme 4).

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 **1**. From the comparison of the degrees of conversion in both experiments, a loading degree of 0.1% TSP in the polystyrene 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.



Scheme 4. Substrates applied in polymer-supported photooxygenations [46].

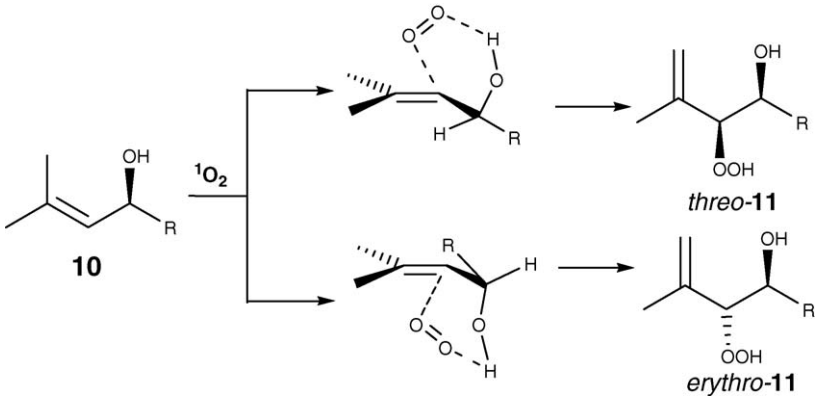


Scheme 5. Porphyrine sensitizers for non-covalent (TTP) and covalent (TSP, PP-IX) polymer modification; synthesis of polystyrene-supported protoporphyrin IX.

2.1. Stereoselectivity of the $^1O_2$ ene reaction with chiral allylic alcohols

The stereoselectivity of the singlet-oxygen ene reaction has been investigated in detail in the last decade [55,56]. The singlet oxygen attacks in a suprafacial process (hydrogen abstraction occurs from the same π face of the olefinic double bond) [57]. 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) [58,59]. 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.

The diastereoselectivity of the ene reaction of $^1O_2$ was investigated by using the chiral allylic alcohol **10**. Both the polymer-bound as well the free sensitizer system (vide supra) gave similar diastereoselectivities (with the polymer-bound sensitizer somewhat higher), however *considerably lower* than in non-polar solvents (photooxygenation of **10** in CCl_4 proceeds with a *threo*-diastereoselectivity of 93%). We have initially found that the diastereoselectivities subside under solvent-free conditions (Table 1); 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 **10** 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



Scheme 6. Singlet oxygen ene reactions with chiral allylic alcohols: stereo electronic control.

Table 1
Photooxygenation[a] of the allylic alcohol **10** in solvents and different polymeric matrices[b]

CCl_4	10:1
PS	3.4:1
PLA	3:1
CA	2.3:1
PHB	1.8:1
PEG	1.8:1
PVAA	1.7:1
EtOH	1.5:1

[a] >80% conversions, solvent concentration: 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).

Table 2
Photooxygenation of the chiral allylic alcohol **10** 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 **10** g^{-1} PS.
[b] Diastereoselectivities given as *threo*:*erythro* ratios.
[c] Initial concentration: 0.1 mmol **10** g^{-1} PS.

either in the sensitizer-bound or free sensitizer PS-DVB matrices [60].

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 which leads to reduced hydrogen-bonding capacity towards the singlet oxygen molecule. This effect is expressed in the effect of loading degree as well as of conversion percentage on the diastereoselectivity (Table 2). Especially the latter effect is noteworthy, implying that the products of the ene reaction (**11**) are better hydrogen bond acceptors and thus reduce the π-facial directing effect continuously during the progress of the reaction.

2.2. Application of solvent-free photooxygenation for the synthesis of new antimalarials

The quest for new antimalaria-active substances has been recognized as an important 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 resistances exist already in many places with this most aggressive pathogen of the *plasmodium falciparum* species [63], including the "gold standard", chloroquine. There are numerous potential drugs and derivatives, some of them are shown in Fig. 3. 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 artemisinine has been recognized as the triggering process from studies of its redox behaviour [74], as well as from studies on secondary products and also on adducts to cell components. Recent studies by Krishna and co workers [75] 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 a radical-induced parasite damage. Remarkably active antimalarial 1,2,4-trioxolanes (*sec*-ozonides) have been reported by the Vennerström group [76].

A straightforward approach to the basic structure (pharmacophore) of artemisinine and derivatives is the peroxyacetalization of β-hydroperoxy alcohols such as the ene products **11** described above (Scheme 6) [77,78]. The substrates **12** 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 [79] (Scheme 7).

From the work by Jefford [80] 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

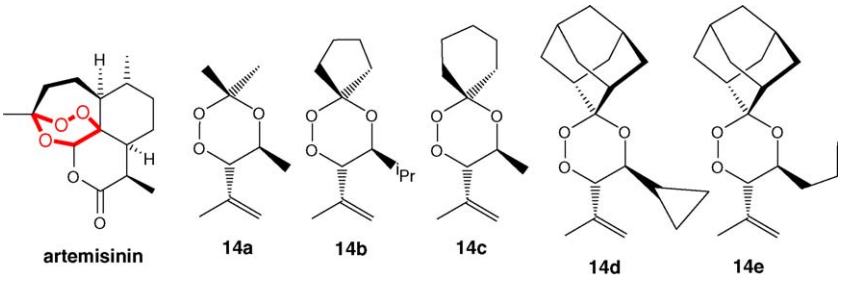
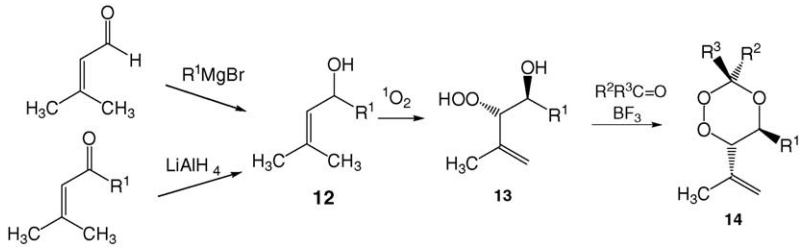


Fig. 3. Selected examples of antimalarial 1,2,4-trioxanes.



Scheme 7. Singlet oxygen ene reactions with chiral allylic alcohols **12**.

Table 3
Activity profile of 1,2,4-trioxanes **14**: in vitro activities[a]

Chloroquine	200
Artemisinin	2.8
14a	1309
14b	10.6
14c	3.1
14d	1.9
14e	1.8

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

have applied this concept for the syntheses of compounds **14**. The acetone adduct **14a** showed comparatively low activities against *Plasmodium falciparum* of approximately the same order of magnitude as for chloroquine (Table 3). The spiroanellation of cyclopentane rings to different β-hydroxy hydroperoxides **13** resulted in noticeable more active compounds (e.g. **14b**). 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 (**14c**). These considerations suggested the need to investigate the spiroadamantane connection.

The products **14d** and **14e** (in yields of 15–25% from the corresponding β-hydroxy hydroperoxides **13** by treatment with adamantanone in the presence of catalytic amounts of BF_3) showed consistently excellent activities against *plasmodium 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 [81]. Further progress in activities is expected from the application of terpenoid allylic alcohols as substrates.

3. Conclusions

A variety of polymer matrices are suitable for (solvent-free) photooxygenation reactions. The ene reaction of singlet oxygen with chiral allylic alcohols is a reaction probe providing informations on the polarity and hydrogen-bonding capacity in the polymer framework. 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*.

Acknowledgements

The authors are thankful to the University of Cologne for an interdisciplinary medicine-chemistry project funding, the Deutsche Forschungsgemeinschaft (project Gr 881/12), the Fonds der Chemischen Industrie, the Swiss Tropical Institute, Basel (Prof. R. Brun) and the Institute of Parasitology, University Bonn (Prof. A. Hörauf, Dr. M. Saeftel) for plasmodium activity testing.

References

[1] H. Kautsky, H. de Bruijn, R. Neuwirth, W. Baumeister, Chem. Ber. 66 (1933) 1588.
[2] C.S. Foote, Acc. Chem. Res. 1 (1968) 104.
[3] G.O. Schenck, K. Gollnick, G. Buchwald, S. Schroeter, G. Ohloff, Liebigs Ann. Chem. 674 (1964) 93.
[4] A.A. Frimer, Singlet Oxygen, CRC Press, Boca Raton, FL, 1985.
[5] H.H. Wasserman, R.W. Murray, Organic Chemistry Singlet Oxygen, 40, Academic Press, New York, 1979.
[6] B. Rånby, J.F. Rabeck, Singlet Oxygen Reactions with Organic Compounds and Polymers, Wiley, Chichester, New York, 1978.
[7] C. Pierlot, J. Poprawski, J. Marko, J.-M. Aubry, Tetrahedron Lett. 41 (2000) 5063;
F.M. van Laar, D.E. De Vos, P. Grobet, J.-M. Aubry, L. Fiermansc, P.A. Jacobs, Stud. Surf. Sci. Catal. 135 (2001) 135.
[8] J.-M. Aubry, B. Mandard-Cazin, M. Rougee, R.V. Benasson, J. Am. Chem. Soc. 117 (1995) 9159;
A.G. Griesbeck, M. Fiege, M.S. Gudipati, R. Wagner, Eur. J. Org. Chem. (1998) 2833.
[9] A.G. Griesbeck, W. Adam, A. Bartoschek, T.T. El-Idreesy, Photochem. Photobiol. Sci. 2 (2003) 877.
[10] A.G. Griesbeck, T.T. El-Idreesy, W. Adam, O. Krebs, in: W.M. Horspool, F. Lenci (Eds.), CRC Handbook of Organic Photochemistry and Photobiology, CRC Press, Boca Raton, 2004, pp. 1–20 (chapter 8).
[11] W. Adam, S. Bosio, A. Bartoschek, A.G. Griesbeck, in: W.M. Horspool, F. Lenci (Eds.), CRC Handbook of Organic Photochemistry and Photobiology, CRC Press, Boca Raton, 2004, pp. 1–19 (chapter 25).
[12] W. Adam, M. Heil, T. Mosandl, C.R. Saha-Möller, in: W. Ando (Ed.), Organic Peroxides, Wiley, 1992, p. 221.
[13] A.L. Baumstark, A. Rodriguez, in: W.M. Horspool, P.S. Song (Eds.), Handbook of Organic Photochemistry and Photobiology, CRC Press, Boca Raton, 1995, p. 335.
[14] E.L. Clennan, Acc. Chem. Res. 34 (2001) 875.
[15] F. Wilkinson, W.P. Helman, A.B. Ross, J. Phys. Chem. Ref. Data 24 (1995) 663.
[16] P.T. Anastas, J.C. Warner, Green Chemistry, Theory and Practice, Oxford University Press, Oxford, 1998.
[17] P. Esser, B. Pohlmann, H.-D. Scharf, Angew. Chem. Int. Ed. Engl. 33 (1994) 2009.
[18] K.-H. Funken, J. Ortner, Z. Phys. Chem. 213 (1999) 99.
[19] R. Noyori, M. Aoki, K. Sato, Chem. Commun. (2003) 1977.

[20] G.O. Schenck, H. Eggert, W. Denk, Liebigs Ann. Chem. 584 (1953) 177.
[21] W. Adam, M. Braun, A.G. Griesbeck, V. Lucchini, E. Staab, B. Will, J. Am. Chem. Soc. 111 (1989) 203.
[22] A.G. Griesbeck, T.T. El-Idreesy, unpublished results.
[23] http://allen.rad.nd.edu/compilations/SingOx/table1/t1.htm (lifetime data).
[24] S.G. DiMagno, P. Dussault, J.A. Schultz, J. Am. Chem. Soc. 118 (1996) 5312.
[25] H. Quast, T. Dietz, A. Witzel, Liebigs Ann. (1995) 1495.
[26] C. Schweitzer, R. Schmidt, Chem. Rev. 103 (2003) 1685.
[27] C. Tournaire, S. Croux, M.-T. Maurette, I. Beck, M. Hocquaux, A.M. Braun, E. Oliveros, J. Photochem. Photobiol. B 19 (1993) 205.
[28] P.R. Ogilby, M. Kristiansen, R.L. Clough, Macromolecules 23 (1990) 2698.
[29] F. Blatter, H. Sun, S. Vasenkov, H. Frei, Catal. Today 41 (1998) 297.
[30] S. Vasenkov, H. Frei, J. Phys. Chem. B 101 (1997) 4539.
[31] J. Shailaja, J. Sivaguru, R.J. Robbins, V. Ramamurthy, R.B. Sunoj, J. Chandrasekhar, Tetrahedron 56 (2000) 6927.
[32] E.L. Clennan, in: V. Ramamurthy, K.S. Schanze (Eds.) Mol. Supramol. Photochem. 9 (2003) 275.
[33] A. Joy, R.J. Robbins, K. Pitchumani, V. Ramamurthy, Tetrahedron Lett. 38 (1997) 8825.
[34] C.-H. Tung, J.-Q. Guan, J. Am. Chem. Soc. 120 (1998) 11874.
[35] D. Zhang, L.-Z. Wu, Q.-Z. Yang, X.-H. Li, L.-P. Zhang, C.-H. Tung, Org. Lett. 5 (2003) 3221.
[36] C.-H. Tung, L.-Z. Wu, L.-P. Zhang, H.-R. Li, X.-Y. Yi, K. Song, M. Xu, Z.-Y. Yuan, J.-Q. Guan, H.-W. Wang, Y.-M. Ying, X.-H. Xu, Pure Appl. Chem. 71 (2000) 2289.
[37] H. Sundén, M. Engqvist, J. Casas, I. Ibrahem, A. Córdova, Angew. Chem. Int. Ed. 43 (2004) 6532.
[38] A. Córdova, H. Sundén, M. Engqvist, I. Ibrahem, J. Casas, J. Am. Chem. Soc. 126 (2004) 8914.
[39] A.P. Schaap, A.L. Thayer, E.C. Blossey, D.C. Neckers, J. Am. Chem. Soc. 97 (1975) 3741.
[40] J.J. Inbaraj, M.V. Vinodu, R. Gandhidsan, R. Murugesan, M. Padmanabhan, J. Appl. Polymer Sci. 89 (2003) 3925.
[41] J. Mattay, M. Vondenhof, R. Denig, Chem. Ber. 122 (1989) 951.
[42] J.L. Bourdelande, J. Font, F. Sachez-Ferrando, Can. J. Chem. 61 (1983) 1007.
[43] R. Gerdes, O. Bartels, G. Schneider, D. Wöhrle, G. Schulz-Ekloff, Polym. Adv. Technol. 12 (2001) 152.
[44] M. Suzuki, O. Bartels, R. Gerdes, G. Schneider, D. Wöhrle, G. Schulz-Ekloff, M. Kimura, K. Hanabusa, H. Shirai, Phys. Chem. Chem. Phys. 2 (2000) 109.
[45] M. Benaglia, T. Danelli, F. Fabris, D. Sperandio, G. Pozzi, Org. Lett. 4 (2002) 4229.
[46] A.G. Griesbeck, A. Bartoschek, Chem. Commun. (2002) 1594;
A. Bartoschek, T.T. El-Idreesy, A.G. Griesbeck, L.-O. Höinck, C. Miara, J.M. Neudörfl, Synthesis (2005) 2433.
[47] C. Tanielian, L. Golder, C. Wolff, J. Photochem. 25 (1984) 117.
[48] R. Schmidt, H.-D. Brauer, J. Am. Chem. Soc. 109 (1987) 6976.
[49] C. Tanielian, G. Heinrich, A. Entezami, J. Chem. Soc. Chem. Commun. (1988) 1197.
[50] D.C. Sherrington, Chem. Commun. (1998) 2275.
[51] G. Ohloff, E. Klein, G.O. Schenck, Angew. Chem. 73 (1961) 578.
[52] W. Pickenhagen, D. Schatkowski, Dragoco Gerberding & Co. AG, Ger. Offen. DE 19645922 A1 (1998).
[53] A. Osuka, B.L. Liu, K. Maruyama, Chem. Lett. (1993) 949.
[54] C. Emiliani, M. Delmelle, Photochem. Photobiol. 37 (1983) 487.
[55] W. Adam, M. Prein, Angew. Chem. Int. Ed. Engl. 35 (1996) 477.
[56] W. Adam, T. Wirth, Acc. Chem. Res. 32 (1999) 703.
[57] M. Orfanopoulos, L.M. Stephenson, J. Am. Chem. Soc. 102 (1980) 1417.
[58] W. Adam, B. Nestler, J. Am. Chem. Soc. 115 (1993) 5041.
[59] W. Adam, H.-G. Brünker, J. Am. Chem. Soc. 117 (1995) 3976.
[60] A.G. Griesbeck, A. Bartoschek, unpublished results.
[61] J. Wiesner, R. Ortmann, H. Jomaa, M. Schlitzer, Angew. Chem. Int. Ed. 42 (2003) 5274.
[62] M. Frederich, J.-M. Dogne, L. Angenot, P. De Mol, Curr. Med. Chem. 9 (2002) 1435.
[63] D.A. Fidock, P.J. Rosenthal, S.L. Croft, R. Brun, S. Nwaka, Nat. Rev. Drug Discov. 3 (2004) 509.
[64] Y. Wu, Acc. Chem. Res. 35 (2002) 255.
[65] R.K. Haynes, S.C. Vonwiller, Acc. Chem. Res. 30 (1997) 73.
[66] C.W. Jefford, in: B. Testa, A.U. Meyer (Eds.), Advances in Drug Research, Academic Press, New York, 1997, 29 pp., Chapter 7.
[67] W.-S. Zhou, X.-X. Xu, Acc. Chem. Res. 27 (1994) 211.
[68] K.J. McCullough, M. Nojima, Curr. Org. Chem. 5 (2001) 601.
[69] G.H. Posner, P.M. O'Neill, Acc. Chem. Res. 37 (2004) 397.
[70] G.H. Posner, A.J. McRiner, I.H. Paik, S. Sur, K. Borstnik, S.J. Xie, T.A. Shapiro, A. Alagbala, B. Foster, J. Med. Chem. 47 (2004) 1299.
[71] R.K. Haynes, W.-Y. Ho, H.-W. Chan, B. Fugmann, J. Stetter, S.L. Croft, L. Vivas, W. Peters, B.L. Robinson, Angew. Chem. Int. Ed. 42 (2004) 1381.
[72] C.W. Jefford, J.-C. Rossier, W.K. Milhous, Heterocycles 52 (2000) 1345.
[73] O. Dechy-Cabaret, F. Benoit-Vical, C. Loup, A. Robert, H. Gornitzka, A. Bonhoure, H. Vial, J.-F. Magnaval, J.-P. Séguéla, B. Meunier, Chem. Eur. J. 10 (2004) 1625.
[74] W.-M. Wu, Y.-L. Wu, J. Chem. Res., Perkin 1 (2000) 4279.
[75] U. Eckstein-Ludwig, R.J. Webb, I.D.A. van Goethem, J.M. East, A.G. Lee, M. Kimura, P.M. O'Neill, P.G. Bray, S.A. Ward, S. Krishna, Nature 424 (2003) 957.
[76] Y. Dong, J. Chollet, H. Matile, S.A. Charman, F.C.K. Chiu, W.N. Charman, B. Scorneaux, H. Urwyler, J. Santo Tomas, C. Scheurer, C. Snyder, A. Dorn, X. Wang, J.M. Karle, Y. Tang, S. Wittlin, R. Brun, J.L. Vennerstrom, J. Med. Chem. 48 (2005) 4953.
[77] C. Singh, N. Gupta, S.K. Puri, Bioorg. Med. Chem. Lett. 13 (2003) 3447.
[78] C. Singh, H. Malik, S.K. Puri, Bioorg. Med. Chem. Lett. 14 (2004) 459.
[79] A.G. Griesbeck, T.T. El-Idreesy, M. Fiege, R. Brun, Org. Lett. 4 (2002) 4193.
[80] C.W. Jefford, S. Kohmoto, D. Jaggi, G. Timari, J.C. Dossier, M. Rudaz, O. Barbuzzi, D. Gerard, U. Burger, P. Kamalaprija, J. Mareda, G. Bernardinelli, I. Manzanares, C.J. Canfield, S.L. Fleck, B.L. Robinson, W. Peters, Helv. Chim. Acta 78 (1995) 647.
[81] A.G. Griesbeck, T.T. El-Idreesy, L.-O. Höinck, J. Lex, R. Brun, Bioorg. Med. Chem. Lett. 15 (2005) 595.