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Dark singlet oxygenation of organic substrates in single-phase and multiphase microemulsion systems

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This paper is dedicated to the memory of Professor Jean Rigaudy from the Laboratoire de Chimie Organique of the Ecole Supérieure de Physique et Chimie Industrielle de Paris

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Abstract—The disproportionation of hydrogen peroxide catalyzed by molybdate anions provides an effective non-photochemical source of singlet oxygen $^1O_2$, ($^1\Delta_g$). Microemulsions are the preferred media to carry out 'dark' singlet oxygenation of labile and hydrophobic substrates. Single-phase and multiphase microemulsion systems have been developed and improved for the last decade and their respective advantages and limitations are shortly reviewed and discussed.
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1. Introduction

'Ordinary' oxygen, $^3O_2$, is somewhat 'extraordinary' since its HOMO is degenerated and contains two electrons with parallel spins, one in each orbital. Therefore, it behaves chemically as a diradical, which reacts slowly with most organic molecules that are in the ground singlet state and very quickly with free radicals and molecules in the triplet excited states. On the contrary, its first excited state is a singlet state with both electrons into the same orbital. The so-called singlet oxygen, $^1O_2$ ($^1\Delta_g$), is therefore a highly reactive, yet selective, bielectronic oxidizer that received many applications in organic synthesis, mainly at the laboratory scale.[1] Most commonly, it is generated by photosensitization of triplet molecular oxygen, but may also be generated in high yields in a number of chemical reactions.[2] These have been employed mainly in mechanistic studies, but scarcely used in organic synthesis. The reasons are that they involve either highly oxidizing inorganic reagents (ClO^-),[3] which may cause side reactions, or polycyclic aromatic endoperoxides (anthracene and naphthalene derivatives)[4] that require previous preparation. A more serious disadvantage of endoperoxides is the fact that they are used in stoichiometric amounts and large quantities of aromatic polycyclic co-products are simultaneously generated, which encumber the isolation of the wanted oxidation product.

In 1980s, a catalytic chemical source has been discovered, in which $^1O_2$ is quantitatively generated in a mild and convenient method by the disproportionation of hydrogen peroxide induced catalytically by sodium molybdate.[2,5] The reaction proceeds efficiently in alkaline aqueous solutions[6] or in highly polar organic solvents such as methanol[7] in which hydrosoluble[8] or low-molecular-weight organic substrates[9] can be effectively oxidized on the preparative scale.

However, the intermediate peroxomolybdates generated by the H_2O_2/MoO_4^{2-} system exhibit a double reactivity, either they can release $^1O_2$ by cleavage of the Mo–O bonds or they can epoxidize labile substrates under acidic[10] or neutral conditions.[11] Two strategies have been developed to avoid the epoxidation side reaction. One uses heterogeneous molybdate-based catalysts that prevent close contact between organic substrates and peroxomolybdates.[12] The other one uses microemulsions (pems), which are stable microdispersions of water and an immiscible organic solvent. The hydrophilic reactants (H_2O_2, Na_2MoO_4) and the organic substrate are separately solubilized in the aqueous and in the organic compartments of the microemulsion, respectively.

Keywords: Microemulsion; Singlet oxygen; Multiphase media; Hydrogen peroxide.

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Singlet oxygen is chemically generated into the aqueous microdroplets and then it diffuses out, before deactivation, to the organic solvent phase where it reacts with the substrate.[13]

This article describes the successive developments and the respective advantages/drawbacks of various microemulsion systems starting from a complex and chlorinated single-phase microemulsion to simple and thermo-sensitive multi-phase systems containing an environmentally friendly microemulsion in equilibrium with an excess organic phase or/and an excess aqueous phase.

2. Available strategies for dark singlet oxygenation in microemulsion systems

Singlet oxygen, ${}^1O_2$, exhibits enhanced reactivity and selectivity compared to those of ground state oxygen, ${}^3O_2$. Singlet oxygen has found considerable synthetic utility since it can undergo selective reactions with a wide range of electron-rich molecules (olefin,[1,14] conjugated dienes,[15,16] polycyclic aromatic hydrocarbons,[4] phenols,[17] sulfides[18] and heterocycles[19]). Singlet oxygenation is usually carried out by dye-sensitized photooxidation based on molecular oxygen and visible light.[20] This method can be conducted in a large variety of nonpolar and polar solvents and a wide range of temperature (−100 to +100 °C); the low temperatures are particularly advantageous when labile oxidation products such as dioxetanes have to be prepared. However, it requires specially designed gas/liquid photo-reactors, which are seldom available in research laboratories or industrial plants. Moreover, large-scale photooxidation entails hazardous processing conditions because of the combination of light, organic solvents and dioxygen. As a result of the foregoing disadvantages, photooxidation has found little industrial applications except for the preparation of low tonnages of valuable flavours and fragrances.[21] By contrast, ‘dark’ singlet oxygenation, via catalytic disproportionation of hydrogen peroxide, provides a safe and inexpensive alternative to photooxidation that can be carried out in ordinary multi-purpose plant stirred tank reactors.[22]

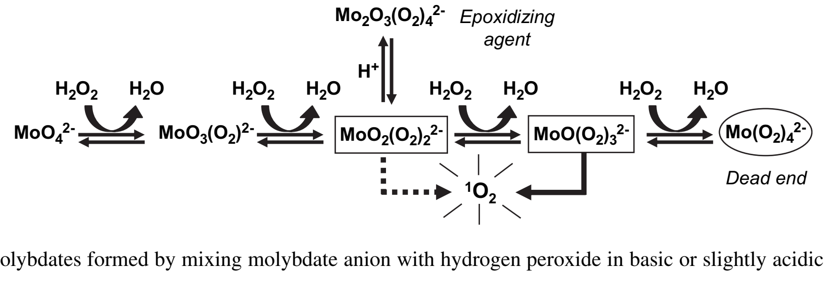
2.1. Chemical generation of singlet oxygen

Chemical sources of ${}^1O_2$ belongs to a special type of reaction able to produce molecules in an electronically excited state through a chemiexcitation pathway. Such reactions are uncommon and, most often, the excited species is generated in poor yield except in the particular case of ${}^1O_2$. Several chemical processes are known to release ${}^1O_2$ in high yields.[2,23] This remarkable behaviour results from two specific features of ${}^1O_2$: (i) the low excitation energy of ${}^1O_2$ (94 kJ) is easily attainable by many chemical reactions; (ii) the chemical formation of a molecule in the triplet state such as ${}^3O_2$ from singlet state reactants is unfavourable with regard to Wigner’s rule. Reagents are typically in a singlet state and when the release of O_2 occurs through *a heterolytic or a concerted mechanism*, Wigner’s rule foresees the conservation of the total spin and thus the formation of oxygen in the singlet state. A historical example of this type of reaction is the oxidation of H_2O_2 by ClO^- that provides Cl^-, H_2O and ${}^1O_2$ in 100% yield.[24] Since the discovery, in 1963, of the formation of ${}^1O_2$ by the system H_2O_2/ClO^-, there has been a surge of interest in quest of other chemical sources of ${}^1O_2$. In particular, a systematic screening of the whole periodic classification has been conducted in 1985 searching for ${}^1O_2$ in the decomposition of aqueous basic H_2O_2 induced by mineral oxides, hydroxides or oxoanions. Singlet oxygen was detected by specific trapping with a water-soluble rubrene derivative. About 30 new chemical sources of ${}^1O_2$ were thus identified such as alkaline earths hydroxides, lanthanides and actinide oxides, oxoanions of transition metals in d^0 configuration and the strong oxidizers Au^{3+}, IO_3^- and IO_4^-. Most of the active mineral compounds were not acting as ClO^- through oxidation of H_2O_2 but rather as catalysts for the disproportionation of H_2O_2.[2]

Among them, the MoO_4^{2-}/H_2O_2 system has been investigated in detail because the reaction efficiently generates ${}^1O_2$ in homogeneous phase. It was shown that decomposition proceeds only in basic solutions and is catalytic with respect to molybdate. It was found that all the oxygen released by the disproportionation of H_2O_2 is in the singlet state (Eq. 1).

$$2H_2O_2 \xrightarrow[\text{pH } 9-12]{MoO_4^{2-}} 2H_2O + {}^1O_2\ (100\%) \qquad (1)$$

The reaction is first order with respect to molybdate but a much more complex rate law was observed for H_2O_2. The reaction is second order at low concentration of H_2O_2 (<0.1 M), zero order at higher concentration (0.1–0.2 M) and then the rate decreases with further increase of H_2O_2 concentration.[5] These results were rationalized by identifying and quantifying the intermediate peroxometallates by ${}^{95}Mo$ NMR and UV–vis spectroscopy.[6] At natural pH, four peroxomolybdates $MoO_{4-n}(O_2)_n^{2-}$, namely the mono-, di-, tri- and tetra- peroxomolybdates, are successively formed by increasing the H_2O_2 concentration. Comparison of these results with kinetic studies, performed under similar conditions, leads to the conclusion that the triperoxomolybdate, $MoO(O_2)_3^{2-}$, is the main precursor of ${}^1O_2$. ${}^{95}Mo$ NMR also reveals that in neutral and slightly acidic media, a dimeric form of the protonated diperoxoanion $HMoO_2(O_2)_2^{2-}$ is the main peroxo compound present in the solution. Since all these peroxo species are in slow equilibrium (Scheme 1), it is



Scheme 1. Different peroxomolybdates formed by mixing molybdate anion with hydrogen peroxide in basic or slightly acidic aqueous solutions.

of utmost importance to maintain the pH value between 9 and 12 and the concentration of uncomplexed H_2O_2 (0.1–0.5 mol L^{-1}) within the optimal conditions to maximize the rate of $^1O_2$ generation and to limit the epoxidizing action of peroxomolybdates.

From the ^{95}Mo NMR experiments, equilibrium constants between all the peroxo compounds have been calculated. They allowed us to build a predominance diagram showing the prevalent peroxo complexes as a function of pH and H_2O_2 concentration on a logarithmic scale (Fig. 1).[10] The best conditions for $^1O_2$ generation coincide with the shaded area corresponding to the prevalence of triperoxomolybdate $MoO(O_2)_3^{2-}$.

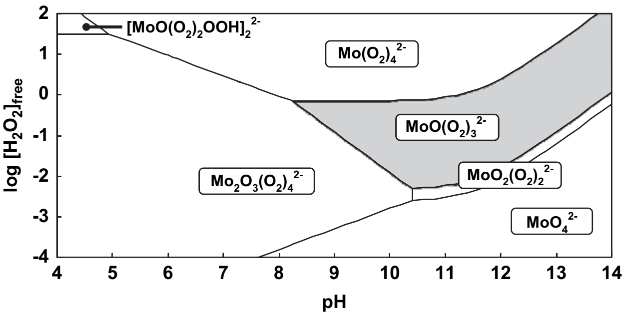
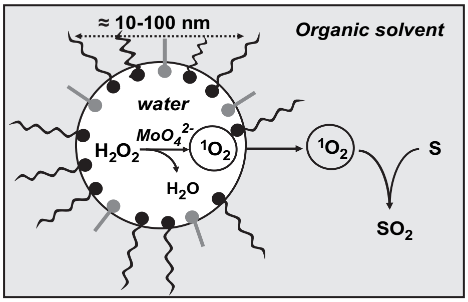


Figure 1. Predominance diagram of the MoO_4^{2-}/H_2O_2 system as a function of pH and H_2O_2 concentration. The shaded area corresponds to the optimum conditions for $^1O_2$ generation.

2.2. Reaction media compatible with the source of $^1O_2$ based on the MoO_4^{2-}/H_2O_2 system

The MoO_4^{2-}/H_2O_2 system is able to quantitatively convert an inexpensive, environmentally friendly and storable source of oxygen, i.e., H_2O_2, into a valuable short-live oxidizing species, i.e., $^1O_2$, according to reaction 1. High flux of $^1O_2$ can be efficiently produced at room temperature in water and may be used to perform singlet oxygenation of water-soluble substrates at the preparative level. For moderately hydrophobic substrates, polar solvents such as methanol or DMF may be used instead of water since they can dissolve all the reactants and may sustain the formation of $^1O_2$, with lower yield and slower rate than in water. Those media are not suitable for highly hydrophobic substrates nor for organic substrates such as allylic alcohols, which suffer competitive side reactions with peroxomolybdates.[11]

In order to overcome those problems, two-phase systems, water/organic solvent, have been tested. Hydrophilic reactants (H_2O_2, Na_2MoO_4) lie in the aqueous phase whereas the hydrophobic substrate is localized in the immiscible organic solvent phase. The chemical generation of $^1O_2$ takes place in the aqueous layer but this short-live species is not able to reach the organic phase before deactivation since the mean travel distance of $^1O_2$ in water ($\approx$200 nm) is much smaller than the diameter of the droplets ($\approx 10^6$ nm) formed under vigorous stirring of the biphasic system. Therefore most of the available $^1O_2$ is wasted through deactivation by water molecules and a large excess of H_2O_2 is thus required to bring about appreciable conversion of the substrate. By contrast, microemulsions are suitable for the chemical formation of $^1O_2$ and the oxidation of highly hydrophobic or fragile substrates on the preparative scale with a minimum loss of $^1O_2$. These macroscopically homogeneous mixtures consist of a microscopically heterogeneous dispersion of an oil and water submicrodomains stabilized by an interfacial monolayer of surface-active molecules (Scheme 2). Although more complex in composition than traditional reaction media, microemulsions present definite advantages: (i) they dissolve large amounts of hydrophilic compounds, which are confined in the aqueous microdroplets, as well as nonpolar organic molecules, which are localized in the organic microdomains; (ii) they protect substrates and products sensitive to H_2O_2 or to peroxomolybdates or to alkaline conditions. In addition, the typical size of the microdroplets ($\approx$10–100 nm) is much smaller than the mean travel distance of $^1O_2$ in water. Hence, in spite of its short lifetime in H_2O ($\tau_\Delta \approx 4$ μs), $^1O_2$ can diffuse freely, before deactivation, from the aqueous droplets to the organic phase, where it can react with the substrate.



Scheme 2. Schematic representation of a W/O microemulsion used to oxidize hydrophobic or fragile organic substrates S with $^1O_2$ chemically generated by the system H_2O_2/MoO_4^{2-}.

2.3. Designing single-phase and multiphase microemulsion systems

How can microemulsions be thermodynamically stable? A rough picture for describing microemulsion formation is to consider a subdivision of the dispersed phase into very small droplets with a radius r. Then the entropy change, ΔS, can be approximately expressed as a function of the number of droplets of dispersed phase n, the Boltzmann constant k and the dispersed phase volume fraction Φ (Eq. 2).

$$\Delta S = -nk[\ln \Phi + \{(1-\Phi)/\Phi\}\ln(1-\Phi)] \quad (2)$$

So, the entropy of mixing is of the order of nk. The associated free energy change is the sum of the enthalpy for increasing the O/W interface ($\Delta A \gamma_{O/W}$) and of the entropy change (Eq. 3).

$$\Delta G = \Delta A \gamma_{O/W} - T\Delta S \quad (3)$$

where ΔA is the change in interfacial area A ($=n4\pi r^2$) and $\gamma_{O/W}$ is the interfacial tension between oil (O) and water (W). Therefore, the spontaneous microemulsification is thermodynamically favoured (ΔG=0) if the surfactant can reduce the interfacial tension to a sufficiently low value (Eq. 4).[25]

$$\gamma_{O/W} \approx kT/4\pi r^2 \quad (4)$$

At room temperature, $kT \approx 4 \times 10^{-18}$ mJ and if $r \approx 10$ nm is assumed in a rough calculation, it follows from Eq. 4 that very low interfacial tensions ($\gamma_{O/W} \approx 0.01$ mN m^{-1}) between oil and water would be required to attain a stable droplet radius. A few surfactants (some double chain ionics and some non-ionics) can produce extremely low interfacial tensions, typically 10^{-2} to 10^{-4} mN m^{-1}, but in most cases, such low values cannot be achieved by a single surfactant.

The addition of a co-surfactant (medium-chain alcohol) is an effective way to further decrease $\gamma_{O/W}$. It also confers to the interfacial film the flexibility required to avoid the formation of liquid crystalline phases. Moreover, addition of salts is often necessary to reduce the electrostatic repulsion between head groups of ionic surfactants.

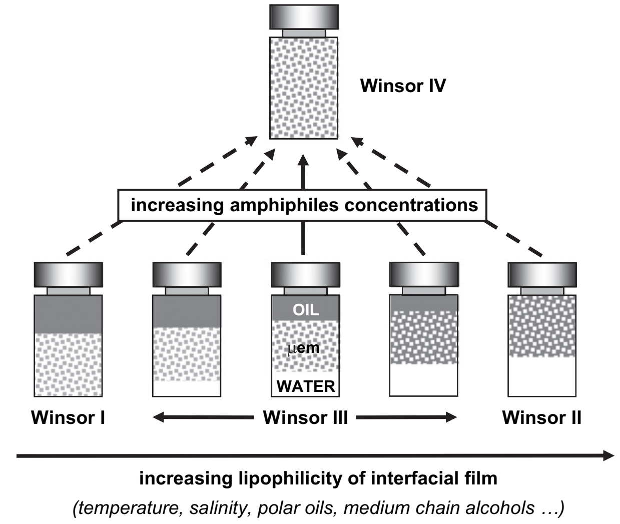
To get the required low interfacial tension, the affinity of the interfacial monolayer of surface-active molecules (surfactant plus co-surfactant) must be high for both the aqueous phase and the organic phase. Depending on the surfactant concentration and on the relative affinities for W and O, different types of microemulsions can be obtained according to Winsor's classification:[26]

- W I systems: the surfactant is preferentially soluble in water and O/W microemulsions form in equilibrium with an excess oil phase;
- W II systems: the surfactant lies mainly in the oil phase and W/O microemulsions form with an excess aqueous phase;
- W III systems: a three-phase system where a bicontinuous microemulsion coexists with both excess aqueous and oil surfactant-poor phases;
- W IV systems: a single phase that forms upon addition of a sufficient quantity of amphiphiles (surfactant plus co-surfactant).

According to the aimed application it may be desirable to tune the formulation in order to get the wanted type of Winsor system. Many physicochemical formulation parameters are able to modify the relative affinity of the amphiphiles for O and W. All the variables that increase the lipophilicity of the interfacial monolayer will shift the system from W I to W III and finally to W II and vice versa (Scheme 3 and Table 1). In this formulation scan, the W III systems play a central role since they correspond to well-balanced interfacial films.[27]

2.4. Single-phase W/O microemulsions for singlet oxygenation

2.4.1. Single-phase W/O microemulsions based on chlorinated hydrocarbon as the oil phase. The first microemulsion designed to sustain singlet oxygenation with a chemical source of $^1O_2$ was based on sodium dodecyl sulfate (SDS) as the surfactant.[13] This highly hydrophilic surfactant does not provide microemulsion alone and it spontaneously gives direct micelles in water instead of the reverse micelles that are required to obtain the wanted W/O microemulsion. So, all the parameters that decrease $\gamma_{O/W}$ and that increase both the flexibility and the lipophilicity of the interfacial film (see Table 1) have to be favoured in order to compensate for the excessive hydrophilicity of SDS. A satisfactory W/O microemulsion was prepared by mixing SDS with *n*-butanol as the hydrophobic co-surfactant, methylene chloride as a rather polar solvent and sodium molybdate as electrolyte and catalyst. This optically isotropic, fluid and transparent liquid meets all the requirements in order to be a preparatively useful medium: (i) no phase separation during storage and during the oxidation process; (ii) high solubility of the reactants; (iii) chemical inertness of the microemulsion components towards H_2O_2, Na_2MoO_4 or the intermediates derived thereof ($^1O_2$ and peroxomolybdates); (iv) relatively high lifetime of $^1O_2$ ($\tau_\Delta \approx 40$ μs). Various typical organic substrates (polycyclic aromatic hydrocarbons, heterocycles, conjugated dienes, olefins, sulfides) were successfully oxidized on the preparative scale by the MoO_4^{2-}/H_2O_2 system in order to illustrate four standard types of $^1O_2$ reactions, namely, the ene reaction, the [2+2] cycloaddition, the [4+2] cycloaddition and the sulfide oxidation. More recently, this



Scheme 3. Modification of the Winsor type of microemulsion systems by scanning one of the formulation variables or by increasing surfactant concentration. The system shown is based on a non-ionic surfactant and has equal volumes of water and oil, μem corresponds to microemulsion phase.

Table 1. Qualitative effect of formulation variables on the lipophilicity of amphiphilic interfacial film between O and W

Formulation variables	Lipophilicity of interfacial film
Surfactant molecular structure	
Lipophilic chain length	↗↗
Lipophilic chain branching	↘
Ethylene oxide polyether chain length	↘↘↘
Surfactant concentration	No influence
Temperature increase	
Non-ionic surfactant	↗↗↗
Ionic surfactant	↘
Aqueous phase salinity	
Non-ionic surfactant	↗
Ionic surfactant	↗↗↗
Oil phase molecular structure	
Hydrocarbon chain length	↘
Hydrocarbon chain branching or cyclisation	↗
Polarity of the oil	↗↗
Alcohol (co-surfactant)	
Short-chain alcohol concentration (C_2 or C_3)	Slight influence
Medium-chain alcohol concentration (C_4 to C_6)	↗↗

method was applied to the selective oxidation of labile chiral allylic alcohols into allylic hydroperoxides. High chemoselectivity (up to 97%) and diastereoselectivity (up to 92% *threo* preference) can be achieved in proper W/O microemulsion whereas the unwanted epoxides were the major products (93% in water and 61% in MeOH) when the reaction was conducted in homogeneous solvents (Scheme 4).[11]

2.4.2. Single-phase environmentally friendly W/O microemulsions. Despite its demonstrated synthetic usefulness, industrial use of this SDS/*n*-BuOH/CH_2Cl_2-based microemulsion is hampered for several reasons: (i) environmental legislation aims at reducing the use of chlorinated solvents; (ii) a large amount of SDS relative to the substrate is required in order to obtain a stable microemulsion; (iii) notably for substrates that are only moderately reactive towards $^1O_2$, space time yields are low because a large excess of aqueous H_2O_2 has to be added in order to compensate for the loss of $^1O_2$, most of which being deactivated before reaction.

The development of microemulsion media that meet all the demands from a preparative and industrial point of view is not straightforward. In particular, a major challenge is finding a substitute for CH_2Cl_2, in which $^1O_2$ has a relatively long lifetime, thus reducing the required amount of aqueous H_2O_2 and the risk of phase separation. The formulation of microemulsions based on polar solvents is critical because polar molecules are likely to interact with the interfacial film impeding a straightforward formation of the microdispersed medium. The composition of the microemulsion was optimized by resorting to the experimental design methodology (simplex). Therefore, suitable compositions for stable microemulsions based on ethyl acetate as organic solvent in the highly complex seven components system (organic solvent, H_2O, SDS, BuOH, substrate, Na_2MoO_4 and H_2O_2) have been found that allow 'dark' singlet oxygenation of lipophilic substrates.[28]

In a further step, solvent-free microemulsion conditions were developed by replacing the organic solvent by the liquid substrates themselves, i.e., α-terpinene and β-citronellol. This latter substrate is particularly relevant as a model since this substrate is industrially photooxidized with $^1O_2$ during the first step of the preparation of rose oxide, an important perfumery ingredient (Scheme 5).[28]

2.4.3. One phase W/O microemulsions combined with a dewatering process. Monophasic microemulsions are particularly suitable for the peroxidation of labile or highly hydrophobic compounds. However, they present two major drawbacks:

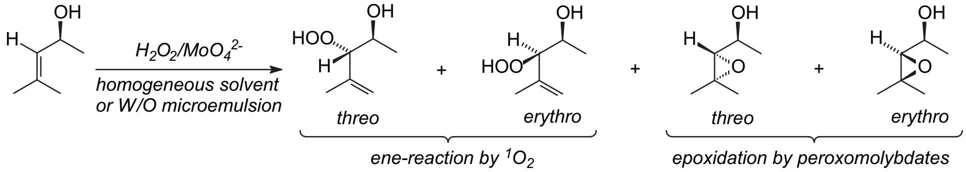
Firstly, the addition of hydrogen peroxide during the reaction results in an increase of the water proportion, which modifies the composition of the microemulsion. In particular, high substrate concentrations or poorly reactive organics require large amounts of H_2O_2 that generate high amounts of water and thus destabilize the system. Ultimately, demixing occurs leading to the formation of an emulsion that is inappropriate for efficient singlet oxygenation. Such a drawback limits the use of one-phase microemulsions either to highly reactive substrates or to relatively low concentrations of substrate.

Secondly, the use of reaction mixtures containing high concentration of amphiphiles hampers facile recovery of the desired products. Moreover, at the end of the oxidation process, the reaction medium is relatively complex, since it is made up of more than six constituents, namely water, oil, surfactant, co-surfactant, catalyst and oxidation product(s). Hence, isolation of the products requires a tedious treatment of the microemulsion.

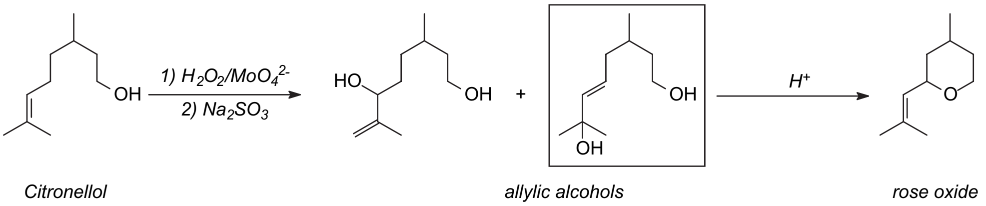
To avoid composition alterations after the addition of H_2O_2 during the peroxidation, a pervaporation membrane process was combined with the oxidizing microemulsion. A semibatch oxidation process in which water is continuously and selectively removed from the system to maintain the initial composition of the microemulsion was developed. The efficiency of such a process was illustrated with the peroxidation of a poorly reactive substrate, namely, β-pinene.[29]

2.5. Multiphase microemulsions for singlet oxygenation

Obtaining single-phase microemulsions requires considerable amounts of surfactant and often some co-surfactant as well, typically 15–25%. This makes recovery of the reaction products from these complex media somewhat problematic. To overcome work-up problems, two- or three-phase systems can be prepared by decreasing the amount of surfactant required to obtain single-phase microemulsions (Scheme 3).



Scheme 4. Chemical oxidation of mesitylol by the MoO_4^{2-}/H_2O_2 system in homogeneous solvents (water or methanol) or in W/O microemulsions.



Scheme 5. Chemical oxidation of citronellol by singlet oxygen and conversion of one of the hydroperoxide into rose oxide.

In these multiphase systems, namely W I, W II and W III systems, the microemulsion phase coexists, respectively, with oil, water or both, depending on the relative affinity of the interfacial film for oil and water, respectively.

W III system is a yardstick in the formulation of micro- and macro-emulsions since it corresponds to a 'balanced state' for the interfacial film separating the aqueous and the organic microdomains. It is obtained under well-defined physicochemical conditions of salinity, temperature or hydrophilic–lipophilic balance of the surfactant. In this case, both interfacial tensions between the microemulsion phase on one side and the oil phase or the aqueous phase on the other side are ultralow (10^{-4}–10^{-2} mN m^{-1}). A yet more important aspect is that the phase separation of a well-balanced W III system is also extremely rapid (a few minutes) after stirring making these systems ideal for easy recovery of the products.[30] Most of the surfactant lies in the microemulsion phase whereas organic product partitions between the microemulsion and the oil phases. Hence, the product can be recovered easily from the microemulsion by several extractions with fresh solvent while the surfactant and the catalyst, which are in the microemulsion phase, can be reused. Two multiphase systems have already been investigated, the first one is formulated with an anionic surfactant[31] whereas the second one, based on a non-ionic one, has never been reported before and will be discussed in Section 3.

2.5.1. Multiphase microemulsions based on an anionic surfactant plus a medium-chain alcohol as co-surfactant.

Five components were mixed, namely, water, sodium molybdate, sodium dodecyl sulfate (SDS), *n*-propanol and toluene to prepare multiphase microemulsion systems. Representing the whole phase diagram for this system would require a prohibitive number of experiments. Binary diagrams showing the percentage of amphiphiles as a function of a scan variable, known as 'optimization diagrams', are usually preferred to investigate the influence of one parameter on the phase behaviour. Formulation scans can be achieved at fixed SDS/PrOH (=1/1) and W/O (=1/1) ratios by changing one of the formulation variables (Table 2) namely, salinity.[32] Addition of sodium molybdate actually induces W I → W III → W II transitions (Fig. 2) since this electrolyte decreases the repulsion between the surfactant polar heads, leading to a curvature inversion of the interfacial film.

In order to decrease the amount of amphiphilic molecules, which are responsible for work-up problems, two- or three-phase systems B, C and D were prepared with very low amounts of surfactant and co-surfactant (6%), as indicated in Figure 2. In addition, the presence of an excess oil phase as in the case of W I or W III systems allows an easier recovery of the oxidation product as it partitions between the organic and the microemulsion phases. The single-phase microemulsion A has also been prepared for comparison. To investigate the influence of the microemulsion type on the peroxidation yield, i.e., to determine if globular (W/O or O/W) or bicontinuous microstructures are preferable for the reaction of $^1O_2$ with organic compounds, α-terpinene was chosen as a model substrate (Table 2). Hydrogen peroxide was added to the media A–D in a lower amount than required by stoichiometry (Eq. 1) in order to obtain a partial peroxidation of the substrate (Scheme 6).

Table 2. Dependence of the substrate conversion on the microemulsion type and composition

Entry	Winsor type	Composition		α-Terpinene conversion (%)	
		$Na_2MoO_4 \cdot 2H_2O$ (mol kg^{-1})	SDS+ *n*-PrOH (% w/w)	Without modification	Excess water phase removed
A	IV	0.15	25	78	—
B	I	0.45	6	65	—
C	III	0.54		36	75 (C*)
D	II	0.64		20	74 (D*)

Toluene/(water+catalyst)=1:1 (w/w); SDS/*n*-PrOH=1:1 (w/w); α-terpinene=0.1 mol kg^{-1}; H_2O_2=0.15 mol kg^{-1}.

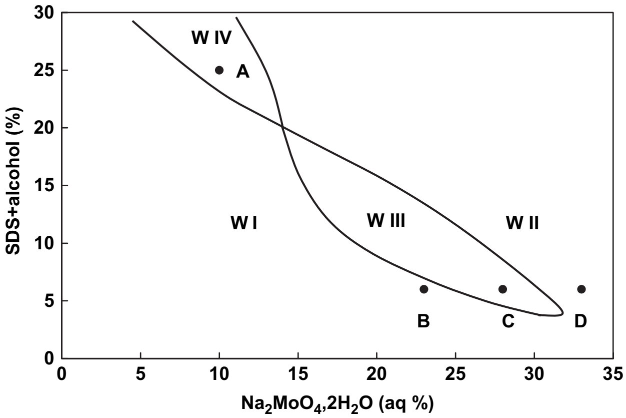
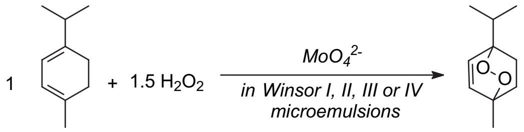


Figure 2. Optimization diagrams for toluene/water/SDS/aPrOH/Na_2MoO_4 system at 25 °C. (SDS/PrOH=1:1 (w/w); toluene/(water+catalyst)=1:1 (w/w); abscissa=% catalyst/(water+catalyst) (w/w)). For dots A–D, see Table 2.



Scheme 6. Dark singlet oxygenation of α-terpinene in single-phase and multiphase microemulsion systems.

The four types of microemulsion systems (entries A–D) are rather different with regard to substrate conversion. Performances decrease in the order W IV>W I≫W III>W II (Table 2). The dramatic decrease of substrate conversion observed for W III and W II systems can be ascribed to the presence of an excess aqueous phase. Indeed, under stirring, the catalyst and hydrogen peroxide equally partition between the aqueous microdomains (10–100 nm) of the microemulsion and the macrodroplets (10–100 μm) of the excess aqueous phase. Unfortunately, all the molecules of $^1O_2$ generated in the macrodroplets are wasted through physical deactivation by water before reaching the organic phase since the droplets radius is much larger than the mean travel distance of $^1O_2$ in water (≈200 nm). The elimination of the water excess phase in W III and W II systems (entries C* and D* in Table 2) induces an increase in the substrate conversion, in agreement with our previous explanation.

These results show that multiphase systems can be used for the chemical oxidation of hydrophobic substrates provided that $^1O_2$ is exclusively generated in aqueous microdomains (∅<200 nm), which implies that no water excess phase exists or is formed as hydrogen peroxide is added. Winsor I systems consisting in an O/W microemulsion with an excess oil phase are thus suitable to oxidize fairly reactive substrates. They are, however, inappropriate to oxidize poorly reactive compounds since the large amount of H_2O_2 needed over-dilutes the O/W microemulsion and the mean distance between the aqueous microdroplets becomes much larger than 200 nm.

3. Results and discussion

3.1. Multiphase microemulsions based on a non-ionic surfactant without co-surfactant

Single- and multi-phase microemulsion systems may also be obtained by using non-ionic surfactants instead of ionic ones. In particular, the well-known surfactants *n*-alkyl-polyglycol ether (C_iE_j) exhibit three useful features with regard to the aimed application: (i) they do not require any co-surfactant to microemulsify oil and water; (ii) they are much less sensitive to electrolyte than ionic surfactants; (iii) their hydrophilicity/lipophilicity balances can be reversibly tuned by changing temperature; (iv) they are stable over a wide range of pH unlike SDS that suffers hydrolysis under acidic conditions. Moreover, by choosing properly the chemical structure of the surfactant and of the oil, the temperature at which W III systems are observed can be fixed at any given value. In this work, $C_{10}E_4$ and *n*-octane were chosen as the surfactant and the oil, respectively, because the so-called 'fish tail' point of the optimization diagrams (Fig. 3) is localized at a convenient temperature (24.3 °C).[33]

When sodium molybdate and α-terpinene are dissolved in water and octane, respectively (Table 3), the gamma shape curve shown in Figure 3 is shifted by approximately 3 °C to lower temperatures. Such a mixture forms a single-phase microemulsion (W IV) by adding 20% of $C_{10}E_4$ whereas two-phase (W I) and three-phase (W III) systems were prepared with lower surfactant concentrations (7.5% and 5%). Those three reaction media were used to carry out the peroxidation of 0.1 mol kg^{-1} α-terpinene at 22 °C for the W III and WIV and at 15 °C for the W I in the presence of a slight excess of H_2O_2 (0.25 mol kg^{-1}). The reaction was completed in about 5 h in the W IV system whereas, at the same temperature, the W III exhibits a loss of efficiency after about 50% conversion due to a loss of $^1O_2$ in the excess aqueous phase. In that latter case, complete peroxidation of terpinene was obtained by the addition of a second batch of H_2O_2. The W I exhibits a similar efficiency for the singlet oxygenation as the Winsor IV, as already shown with anionic surfactants, the slower kinetics of the reaction being due to the lower temperature (Fig. 4). Actually, it is known that the rate determining step, i.e., the generation of $^1O_2$ from peroxomolybdates, depends strongly on the temperature[5] whereas the fast step, i.e., the competitive interaction of $^1O_2$ with the substrate and the solvent, does not.

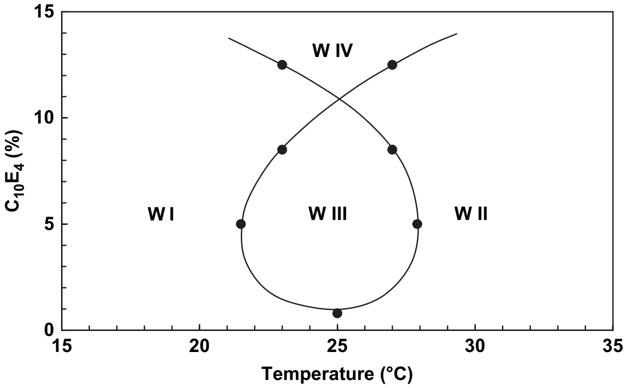


Figure 3. 'Optimization diagram' of the ternary system *n*-octane/water/$C_{10}E_4$ system as a function of temperature and surfactant concentration and at a fixed ratio octane/water=1:1 (w/w).

Table 3. Amounts of $C_{10}E_4$ and corresponding temperatures required for obtaining W I, W III and W IV microemulsion systems with the ternary system $C_{10}E_4$/water/*n*-octane

$C_{10}E_4$ (mg)	Temperature (°C)[a]		Winsor system
	Initial	Final	
400 (20%)	22	19	IV
150 (7.5%)	22	18	I
100 (5%)	15	<15	III

[a] During the reaction, the temperature must be adjusted and lowered in order to keep the same Winsor system.

Finally, in spite of apparently different kinetics behaviours, the microstructure of the microemulsion systems does not seem to have a major influence on the peroxidation reaction.

It is noteworthy that the formation of a polar oxidation product, ascaridole, during the reaction modifies the polarity of the oil resulting in a shift of the gamma shape curve to lower temperatures. Hence, the temperature must be adjusted during the reaction in order to maintain the Winsor type in which the reaction has to be conducted and also, to avoid the formation of W II systems. However, at the end of the reaction, the temperature can be decreased of approximately 5 °C for the W III and W IV, in order to obtain a W I that allows the ready recovery of ascaridole from the octane phase.

Contrary to ionic surfactants, the use of thermo-sensitive non-ionic C_iE_j surfactants is particularly interesting since

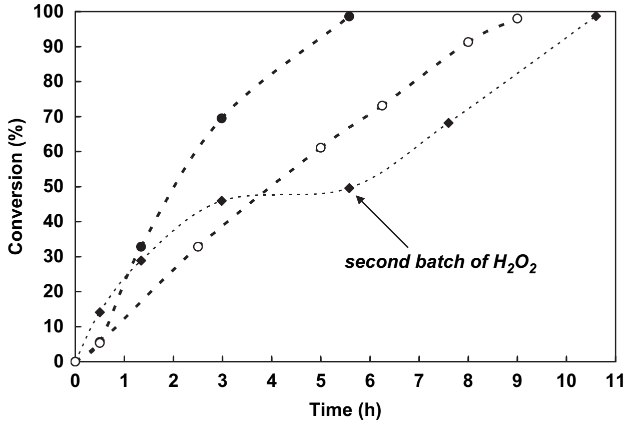


Figure 4. Conversion of α-terpinene 0.1 M in various microemulsion systems based on $C_{10}E_4$/water/octane. ● Winsor IV ($T_{initial}$=22 °C), ○ Winsor I ($T_{initial}$=15 °C), ◆ Winsor III ($T_{initial}$=22 °C).

the temperature can be used to adjust reversibly the stability region of the microemulsion and the phase separation can be induced, also reversibly, just by temperature change after the reaction process.

4. Conclusions

Single-phase or multiphase microemulsion systems are ideal media to carry out 'dark' singlet oxygenation of hydrophobic and labile substrates since they offer several benefits: (i) cosolubilization of great amounts of hydrophilic and hydrophobic compounds; (ii) compartmentalization of hydrophilic and hydrophobic species avoiding side reactions; (iii) nanometric size (10–100 nm) of the droplets. This latter feature is of utmost importance for an uncharged short-live species such as $^1O_2$ since, once generated in aqueous microdroplets, it diffuses freely through the interfacial film to the organic compartment where it reacts with the organic substrate.

Single-phase microemulsions are easy to formulate and to handle but they require large amounts of surfactants that impede recovery of oxidized products. Multiphase microemulsion systems must be prepared under well-defined physicochemical conditions of salinity, temperature or hydrophilic–lipophilic balance of the surfactant. They require much lower amounts of surfactants and they allow simple recovery of the products localized in the oil excess phase. They can sustain effective dark singlet oxygenation provided that the possible excess water phase is removed beforehand.

5. Experimental

5.1. Chemicals

Sodium molybdate dihydrate (99%), *n*-propanol (99%), sodium hydroxide (98%) and 1-isopropyl-4-methyl-1,3-cyclohexadiene (α-terpinene, 85%) were purchased from Aldrich and used without further purification. Sodium dodecyl sulfate (SDS) (98%), toluene (99%), ethyl acetate (99%), dichloromethane (99%), *n*-butanol (98.5%) and hydrogen peroxide (50%) were obtained from Prolabo. Milli-Q water (18.2 MΩ cm) was used.

5.2. Procedures

Salinity scans: samples (5 ml) were prepared in SVL tubes by mixing appropriate amounts of oil, co-surfactant, water, catalyst and surfactant. Mixtures were gently stirred and maintained at a constant temperature (25±0.1 °C) for a sufficient time in order to get thermodynamically stable systems. To further identify each phase according to Winsor label, water was coloured in blue and oil in yellow so that the microemulsion phase was green. Comparative oxidations: 40 g of μem were prepared by predissolving SDS and sodium molybdate in water+*n*-PrOH and by adding toluene to the mixture. After shaking, the systems were allowed to stabilize overnight at 25±0.1 °C. For modified W II and W III systems, greater volumes were prepared. After sufficient time to reach thermodynamic stability, the phases were separated and mixed again in the desired proportions. Finally, α-terpinene was added to the mixtures ($0.1\ \mathrm{mol\,kg^{-1}}$). Oxidations were performed at 25 °C under vigorous stirring, by adding hydrogen peroxide in two batches (1 and $0.5\ \mathrm{mol\,kg^{-1}}$ after 30 min). The substrate conversion was followed by gas chromatography and the peroxidation products were characterized by ^{1}H NMR.

A certain amount of $C_{10}E_4$ (see Table 3) is dissolved into 1 g of octane and 1 g of water containing $10^{-2}\ \mathrm{mol\,L^{-1}}$ of sodium molybdate. To this microemulsion system, placed in a thermostated bath at a given temperature, was added α-terpinene (40 μL, $0.1\ \mathrm{mol\,L^{-1}}$) followed by a batch of 30 μL H_2O_2 (50%) at zero time leading to an orange-red mixture. The reaction was monitored by HPLC. The values of x and of the temperature which define the Winsor-type system are given in Table 3.

5.3. Instrumentation

Gas chromatography (GC) analyses were performed on a Agilent 6890 N chromatograph equipped with an apolar HP-1 (60 m×0.32 mm−0.25 μm) column. ^{1}H NMR of the peroxidation products was carried out on a AC 200 Brucker spectrometer. Molybdate concentrations were determined by UV spectrometry on a Varian spectrometer at λ=204 nm.

High-performance liquid chromatography analyses were carried out with a reversed-phase column (Nova-pack C18, 4 μm, 4.6×250 mm) using a 600 controller pump from Waters, a mixture of CH_3CN/H_2O (90:10) as the eluent, and UV detection with a Waters 490E programmable multiwavelength detector.

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