Strategies for cleaner oxidations using photochemically generated singlet oxygen in supercritical carbon dioxide

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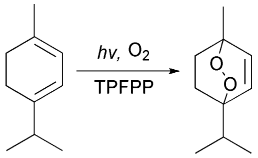
Photochemically generated singlet oxygen, $^1O_2$, has been reacted with four different substrates in supercritical carbon dioxide. By using fluorous surfactants and a co-solvent to solubilise more polar photosensitisers and reactants respectively, the applicability of the system is greatly enhanced.

Introduction

Photochemistry is a somewhat neglected tool in the green chemistry area[1] even though the environmental importance of photochemistry has a long history.[2,3] The photochemical reactions of singlet oxygen, $^1O_2$, are particularly appealing in this context since they combine the green aspect of photochemistry with the high E-factor of $^1O_2$ addition reactions. $^1O_2$ is widely used in contemporary organic synthesis.[4] It can be generated chemically using sodium hypochlorite and hydrogen peroxide[5] or Ph_3PO_3;[6] however by far the most convenient, and cleanest route, is *via* photosensitisation using low energy visible light and an appropriate catalytic photosensitiser such as rose bengal.[4] $^1O_2$ reacts with 1,3-dienes to form endoperoxides or with alkene substrates to produce allylic hydroperoxides which can also be easily reduced to the corresponding allylic alcohol.[7] Although at least one photochemical $^1O_2$ reaction is carried out industrially, there are significant problems associated with the production and use of $^1O_2$ particularly in a large scale since such reactions are commonly performed in chlorinated solvents such as $CHCl_3$ or CCl_4 which are not industrially viable and significantly detract from the environmental sustainability of any process using $^1O_2$.[8] Chlorinated solvents are utilised since they are non-flammable and the lifetime of $^1O_2$ in these solvents is long compared to other conventional solvents.[9–11]

Supercritical carbon dioxide ($scCO_2$) is fully oxidised and hence non-flammable and non-toxic. It is completely miscible with permanent gases such as O_2 and possesses lower viscosity and higher diffusivity than more conventional solvents. This can enable reactions to proceed without the mass transport limitations often found in typical multi-phase reaction systems.[12] Metal catalysed oxidation reactions using O_2 and metal catalysts[13–16] have been successfully performed in $scCO_2$ and demonstrated these advantages. Photophysical experiments[17–19] have shown that $^1O_2$ can be generated in $scCO_2$ with an extended lifetime compared to many conventional solvents.

We have recently reported the rapid and quantitative conversion of α-terpinene to ascaridole in $scCO_2$ using a CO_2-soluble photosensitiser, 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (TPFPP), Scheme 1.[20] Our studies showed that under single phase conditions, between 120 and 200 bar, complete conversion of 30 μL of α-terpinene could be achieved in 160 s with zero-order kinetics at a constant turnover frequency (TOF) over this pressure range.



Scheme 1 Photo-oxidation of α-terpinene to ascaridole.

Following the initial batch studies, an efficient LED illuminated sapphire tube reactor has been developed for continuous operation with a significantly enhanced space-time yield when compared to conventional $^1O_2$ reactor systems.[21]

TPFPP is a fluorinated analogue of *meso*-tetraphenylporphyrin (TPP), a common $^1O_2$ photosensitiser, Scheme 2. It was chosen for these systems because of its high solubility in $scCO_2$ due to the fluorinated phenyl-substituted groups. Thus both the reagents and the photosensitiser were soluble in the $scCO_2$. However, there are many oxidation reactions of $^1O_2$ where one or more components may not be sufficiently soluble in $scCO_2$. This limitation needs to be addressed if the use of $scCO_2$ as a solvent for $^1O_2$ is to become widespread.

This paper initially focuses on expanding the scope of reactions that can be performed with photochemically generated $^1O_2$ in $scCO_2$. Then the use of a co-solvent and surfactants in $scCO_2$ to solubilise reactants and alternative photosensitisers respectively are described.

Results and discussion

Oxidation of 2,3-dimethyl-2-butene

We have examined the $scCO_2$ reaction of $^1O_2$ with an alkene substrate to demonstrate the applicability of $scCO_2$ to a Schenk "ene" type [2 + 2] reaction. This is a common reaction of

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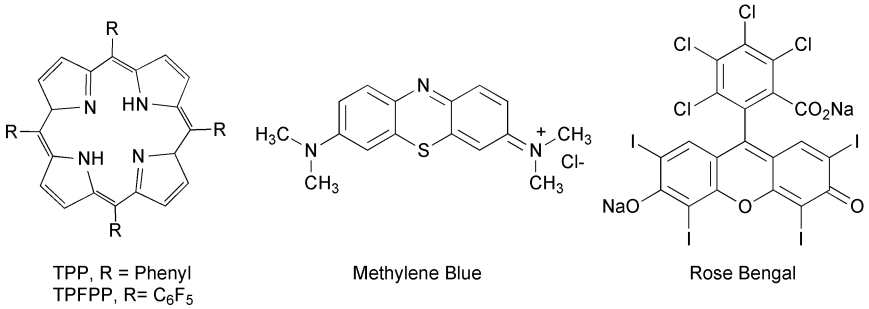


Scheme 2 Structures of photosensitisers investigated in these studies.

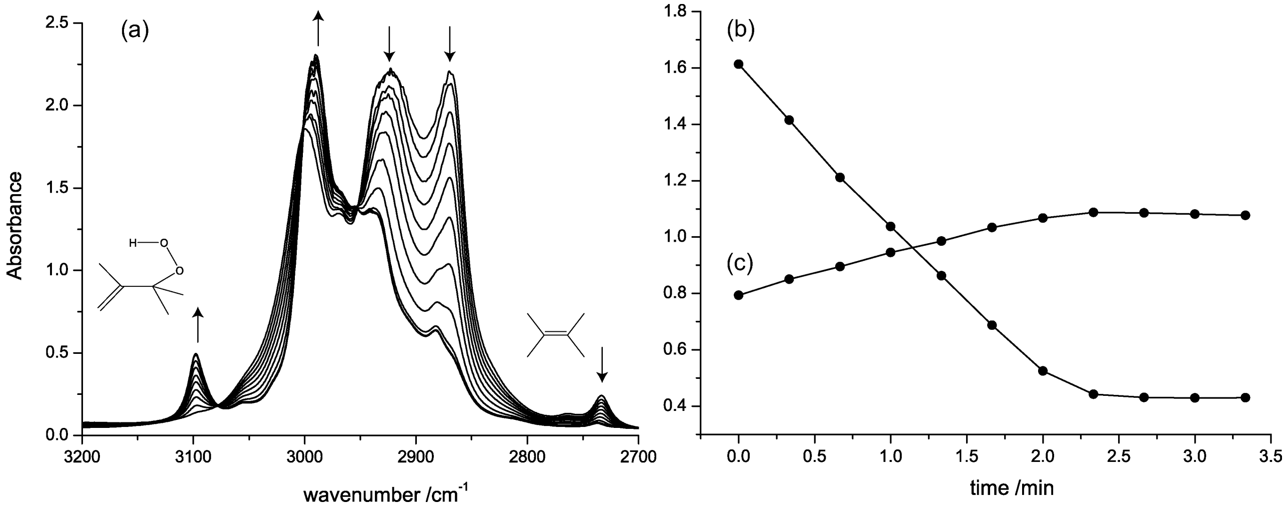
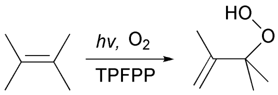


Fig. 1 (a) FTIR monitoring of the reaction of 2,3-dimethyl-2-butene with O_2 in $scCO_2$ using TPFPP at 40 °C during irradiation (300 W xenon lamp with a filter to cut out UV irradiation). Spectra were recorded at 20 s intervals showing (b) loss of starting material (2737 cm^{-1}) and (c) formation of peroxide (3098 cm^{-1}).

$^1O_2$ which has been widely used for the synthesis of allylic hydroperoxides and related compounds such as reduction to allylic alcohols.[7] Fig. 1 shows that quantitative conversion of 2,3-dimethyl-2-butene to 3-hydroperoxy-2,3-dimethylbut-1-ene (Scheme 3) can be achieved using TPFPP as photosensitiser with 2.63 mol% O_2 in $scCO_2$ within 250 s. The yield was confirmed by ^{1}H-NMR spectroscopy. The reaction was monitored using FTIR spectroscopy and the reaction kinetics were followed using the intensity of the 2737 cm^{-1} and 3098 cm^{-1} bands, Fig. 1(b) and 1(c). The reaction was found to proceed with zero-order kinetics under these conditions. The TOF of this reaction, 14 s^{-1} is of similar magnitude to that for the TPFPP photo-catalysed oxidation of α-terpinene, suggesting that the key rate-determining step is the photo-generation of $^1O_2$ rather than the reaction with the organic substrate.

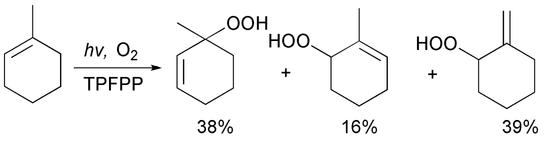


Scheme 3 The Schenk "ene" addition of $^1O_2$ to 2,3-dimethyl-2-butene to form 3-hydroperoxy-2,3-dimethylbut-1-ene.

Photo-oxidation of 1-methyl-cyclohexene

The product distribution following photo-oxidation of 1-methyl-cyclohexene (MCH) has been reported to be highly dependant upon the nature of the solvent.[22] Therefore it is an excellent reaction with which to evaluate $scCO_2$ as a solvent. We have examined the photo-oxidation of MCH in $scCO_2$ using TPFPP as the photosensitiser with 2.63 mol% O_2 in $scCO_2$ at 140 bar. Monitoring of the reaction was again by FTIR and plotting of the band maxima at 3081 cm^{-1}, 3047 cm^{-1} and 3034 cm^{-1} *versus* irradiation time, Fig. 2, again showed zero-order kinetics reaction with complete conversion after 400 s with a TOF of 9 s^{-1}.

The reaction of 1-methyl-cyclohexene with $^1O_2$ results in the production of both secondary and tertiary allylic hydroperoxides, see Scheme 4. The yield of each product was calculated from ^{1}H-NMR spectra and is shown in Scheme 4. The reaction in $scCO_2$ shows similar regioselectivity to reactions that have been previously performed in non-polar *n*-alkane solutions.[22] This is consistent with other areas of supercritical chemistry which have concluded that $scCO_2$ often behaves similarly to *n*-hexane.[23]



Scheme 4 Photo-oxidation of 1-methyl-cyclohexene to yield (from left to right) 3-hydroperoxy-3-methylcyclohex-1-ene, 6-hydroperoxy-1-methylcyclohex-1-ene and 1-hydroperoxy-2-methylenecyclohexane.

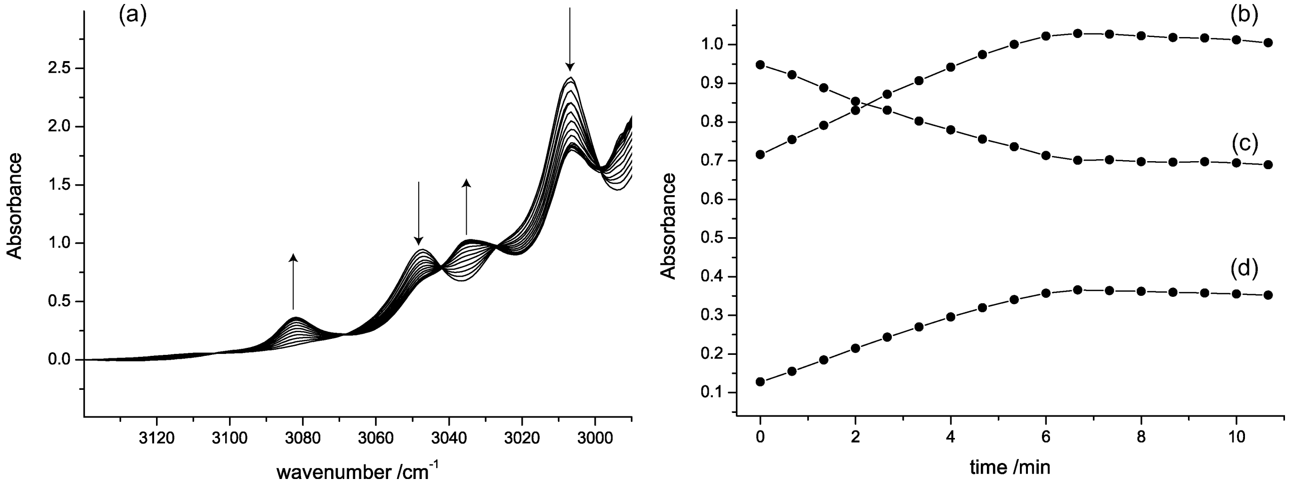
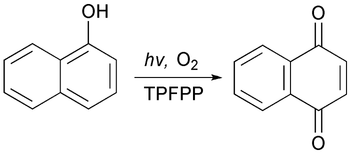


Fig. 2 (a) FTIR monitoring the reaction of MCH with O_2 in $scCO_2$ at 40 °C using TPFPP at 140 bar during irradiation (300 W xenon lamp with a filter to cut out UV irradiation), (Table 1, entry 11). Spectra were recorded at 40 s intervals. The kinetic traces show changes in intensity with time at band maxima at (b) 3034 cm^{-1}, (c) 3047 cm^{-1} and (d) 3081 cm^{-1}. All three traces follow zero-order kinetics.

Oxidation of 1-naphthol with dimethyl carbonate co-solvent

The use of $scCO_2$ is often hampered by the poor solubility of organic compounds with a polar protic character. The solubility of polar materials can often be dramatically increased by use of a co-solvent.[24] We have tried using a co-solvent in $scCO_2$ for oxidation using $^1O_2$ of 1-naphthol to naphthalene-1,4-dione (see Scheme 5). This reaction is of particular interest because of the biological activity possessed by the quinonoid class of natural products,[25] which are derivatives of Juglone (5-hydroxy-1,4-naphthoquinone) formed by the photo-oxidation of 1,5-dihydroxynaphthalene.[26]



Scheme 5 Photo-oxidation of 1-naphthol to form naphthalene-1,4-dione.

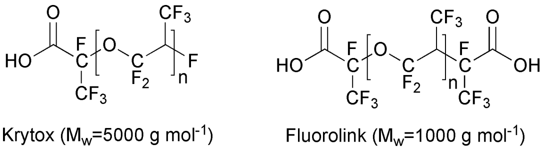
We have previously demonstrated that dimethyl carbonate can be used as a co-solvent to enhance the solubility of TPFPP in citronellol in continuous photo-oxidation, allowing the substrate and photosensitiser to be pumped continually.[21]

Thus, photo-oxidation of 1-naphthol was performed with dimethyl carbonate as a co-solvent to liquefy the substrate and to enhance the solubility of the substrate in $scCO_2$. The volume of the batch reactor was increased by changing the path length to 15 mm to enable 500 μL of a solution consisting of dimethyl carbonate containing 7 mg of 1-naphthol and 0.2 mg of TPFPP to be injected into the cell and pressurised to 160 bar with a mixture of O_2 and $scCO_2$ (1.31 mol% O_2 in CO_2).

The yield was calculated using gas chromatography because absorptions of the dimethyl carbonate co-solvent swamp the FTIR spectrum and the reaction reached completion within 1 h. The TOF was much lower than for the reactions performed previously, probably due to the higher dilution used and quenching effects caused by dimethyl carbonate. Future studies will investigate the effect of co-solvents and the potential use of gas expanded liquids (GXLs[27]) to optimise these reaction systems further.

Use of fluorous surfactants to solubilise photosensitisers

Porphyrin-based molecules are some of the most widely used $^1O_2$ photosensitisers. Although it is possible to dissolve the perfluorinated TPFPP in pure $scCO_2$, TPFPP is not ideal, particularly since its cost may be prohibitive for widespread application. TPFPP has not been as widely used for $^1O_2$ reactions as the more common photosensitisers, methylene blue, rose bengal and TPP, Scheme 2, but these are insoluble in $scCO_2$. However, there are a variety of strategies for enhancing solubility in $scCO_2$ including the use of co-solvents (as above). An alternative approach is to use fluorinated surfactants, which has been previously used for polymer synthesis,[28,29] nanoparticle formation,[30] biocatalysis,[31] Lewis acid catalysis,[32] and cobalt catalysed oxidation.[33] Here we investigate two highly fluorinated surfactants, Krytox and Fluorolink (see Scheme 6) for solubilising $scCO_2$-phobic photosensitisers to promote $^1O_2$ reactions in $scCO_2$.



Scheme 6 Molecular formulae of the fluorinated surfactants.

Fig. 3 shows the UV/visible spectra of a reaction mixture of α-terpinene, TPP, and O_2 in $scCO_2$ with and without the addition of Krytox. In the absence of the surfactant, TPP was essentially insoluble in $scCO_2$ and the characteristic UV/visible bands of TPP were not observed. The addition of 3.2 wt% of Krytox into the reaction system resulted in both the Soret band and Q bands of TPP becoming quite intense.

The kinetics of the reaction of α-terpinene were monitored by FTIR using TPP with surfactants or TPFPP. Both surfactant

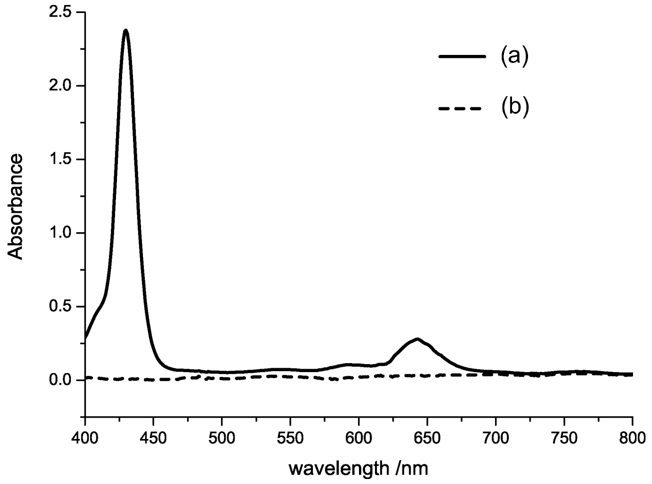


Fig. 3 UV spectra of the reaction system composed of α-terpinene, TPP, and O_2 in $scCO_2$ (Table 1, entry 2), with (a) and without (b) the addition of Krytox surfactant.

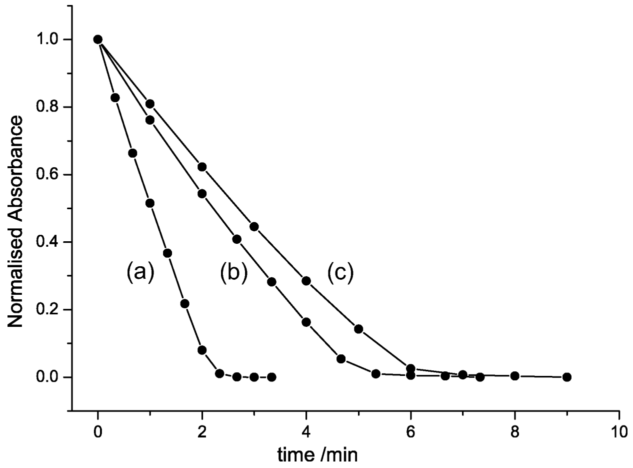


Fig. 4 Kinetic traces showing the zero-order kinetics of the reaction of α-terpinene with O_2, in $scCO_2$ at 40 °C during irradiation (300 W xenon lamp with a filter to cut out UV irradiation) with (a) TPFPP, (b) TPP plus Fluorolink surfactant and (c) TPP plus Krytox surfactant by plotting the normalised absorbance at 3042 cm^{-1}. See Table 1 for full experimental details.

systems gave quantitative conversion in <7 min with zero-order kinetics. Despite differing loadings of the various photosensitisers, the molar TOFs of the TPP–surfactant systems were similar ranging for Krytox (TOF = 9 s^{-1}), Fluorolink (TOF = 10 s^{-1}) and TPFPP (TOF = 12 s^{-1}), see Fig. 4 and Table 1, entries 1–3. A control experiment showed that the addition of Fluorolink itself had no adverse effect upon the reactivity of TPFPP with no decrease in the TOF of the reaction, see Table 1, entry 4.

These results demonstrate that even though TPP is essentially insoluble in $scCO_2$, it can still act as an efficient photosensitiser in the presence of suitable surfactants to enhance its solubility. We have also investigated our approach using Krytox and Fluorolink surfactants with two commonly used ionic photosensitisers, methylene blue and rose bengal, see Scheme 2, which are again insoluble in pure $scCO_2$.[34,35]

Solubility trials were conducted using a high pressure view cell. The solubility of methylene blue could be increased using a surfactant in $scCO_2$ as evident by the striking blue colour of the solution, shown in Fig. 5. Unfortunately, it was not possible to dissolve high concentrations of rose bengal under these conditions. However, solubility of a photosensitiser in $scCO_2$ does not in itself ensure efficient photo-oxidation reactions.

One major problem with dye-sensitised $^1O_2$ reactions is the bleaching of the dye. This is not a problem using the TPP and TPFPP photosensitisers as indicated by the zero-order kinetics. By contrast, the oxidation of α-terpinene using methylene blue in $scCO_2$ with the addition of 2.8 wt% Krytox gave incomplete conversion (Table 1, entries 7 and 8). The reason for this is demonstrated by the UV spectra in Fig. 6 which show that complete photo-bleaching of methylene blue occurs before conversion of the organic substrate was complete; hence this reaction did not follow simple zero-order kinetics.

The photo-oxidation of 2,3-dimethyl-2-butene described above, provided an additional opportunity to compare directly the TPFPP system with the TPP and surfactants system *via* FTIR monitoring of the conversion to 3-hydroperoxy-2,3-dimethylbut-1-ene. Addition of TPP and Krytox to the reaction system resulted in quantitative conversion with zero-order

Table 1 Experiments with surfactants to solubilise photosensitisers at 40 °C during irradiation[a]

Entry	Substrate	Photosensitiser	Surfactant	Oxygen concentration (mol%)	System pressure/bar	Substrate concentration/ mol L^{-1}	Photosensitiser concentration/ mol L^{-1}	TOF/s^{-1}
1	α-Terpinene	TPFPP	None	1.31	140	0.24	0.158	12
2	α-Terpinene	TPP	Krytox	1.31	140	0.24	0.079	9
3	α-Terpinene	TPP	Fluorolink	1.31	140	0.24	0.079	10
4	α-Terpinene	TPFPP	Fluorolink	1.31	140	0.24	0.158	12
5	α-Terpinene	Rose bengal	Krytox	1.31	140	0.24	0.81	0
6	α-Terpinene	Rose bengal	Fluorolink	1.31	140	0.24	0.73	0
7	α-Terpinene	Methylene blue	Krytox	1.31	140	0.24	0.82	N/A[b]
8	α-Terpinene	Methylene blue	Fluorolink	1.31	140	0.24	0.76	N/A[c]
9	DMB	TPFPP	None	2.63	140	0.32	0.079	14
10	DMB	TPP	Krytox	2.63	140	0.32	0.13	11
11	MCH	TPFPP	None	2.63	140	0.32	0.089	10
12	MCH	TPP	Krytox	2.63	140	0.32	0.13	3

[a] 300 W xenon lamp with a filter to cut out UV irradiation. [b] Due to photobleaching non zero-order kinetics observed. Reaction yield = 56%. [c] Due to photobleaching non zero-order kinetics observed. Reaction yield = 77%.

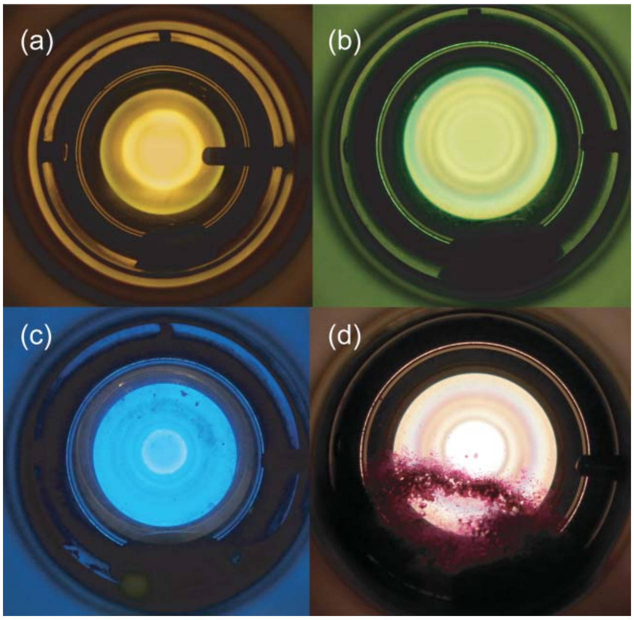


Fig. 5 Photographs of different photosensitisers in a variable volume view cell.[36] (a) TPFPP (2.7 μmol with no surfactant) showing full solubility, (b) TPP (1.8 μmol) showing full solubility (345 mg Krytox), (c) methylene blue (8.4 μmol) showing high solubility (216 mg Krytox), (d) rose bengal (7.3 μmol) showing negligible solubility (190 mg Krytox). All photographs taken with 200 bar $scCO_2$ at 40 °C and 0.5 g of α-terpinene.

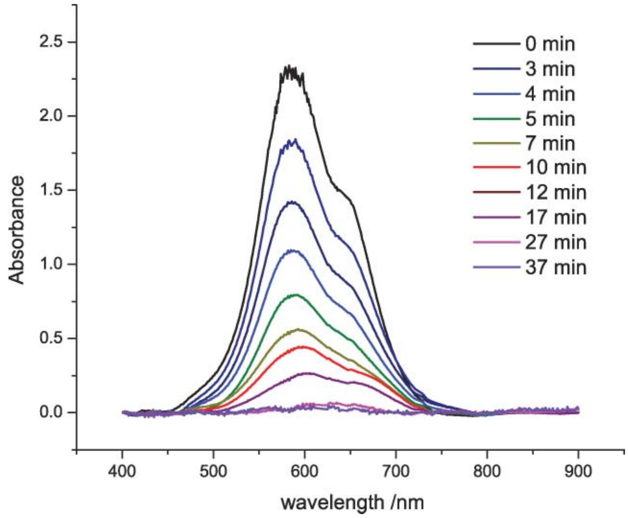


Fig. 6 UV/visible spectra of methylene blue in $scCO_2$ with Krytox system showing steady photo-bleaching during the photo-oxidation of α-terpinene over a period of 37 min.

kinetics and a high TOF of 11 s^{-1}. As with the α-terpinene system, a slight drop in the TOF, from 14 s^{-1} to 11 s^{-1} was observed when the TPP–surfactant rather than TPFPP was used for the oxidation of 2,3-dimethyl-2-butene, see Table 1, entries 9 and 10. However this reaction also clearly demonstrates the potential applicability of the significantly less expensive TPP plus surfactant. In addition, the photo-oxidation of MCH was also performed using the TPP and Krytox surfactant system; however the TPP in this reaction system exhibited a significantly lower TOF of 3 s^{-1} compared to 9 s^{-1} with TPFPP, Table 1, entries 11 and 12.

Conclusions

In summary, the $scCO_2$-soluble photosensitiser TPFPP has been used to perform $^1O_2$ reactions of α-terpinene, 2,3-dimethyl-2-butene and 1-methyl-cyclohexene in $scCO_2$. These three reactions were all monitored using FTIR, showing zero-order kinetics and quantitative conversions with reasonable TOFs. The insoluble photosensitisers, TPP, methylene blue and rose bengal, were also evaluated with two highly fluorinated surfactants, Krytox or Fluorolink, to generate $^1O_2$ for reaction. TPP and methylene blue display considerably enhanced solubility in $scCO_2$ in the presence of these surfactants. However, methylene blue undergoes photo-bleaching during irradiation; hence the reactions do not reach full conversion. TPP plus a fluorinated surfactant showed very similar results to those achieved with TPFPP albeit with slightly lower TOFs. The solubility of rose bengal in $scCO_2$ is still very low even with the addition of surfactants. Finally photo-oxidation of a non-soluble substrate, 1-naphthol, was also tested using dimethyl carbonate as co-solvent to liquefy and solubilise the substrate into $scCO_2$. Quantitative conversion was achieved, but with a lower TOF. It is clear that the applicability of $^1O_2$ reactions in $scCO_2$ has been significantly enhanced by the use of these surfactants and co-solvents.

Experimental

Safety warning: *these reactions involve high pressures and should only be carried out in an apparatus with the appropriate pressure rating and with due regard to the potentially explosive reaction between O_2 and organic compounds.*

All reactions were performed using a multi-purpose photochemical and spectroscopic cell,[37] with CaF_2 windows and a path length of *ca.* 2 mm unless otherwise noted. The cell was heated to 40 °C in all experiments using aluminium heating blocks. For a schematic of the reactor please see our previous publication.[20]

Acknowledgements

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