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Enzyme-Inspired Functional Surfactant for Aerobic Oxidation of Activated Alcohols to Aldehydes in Water

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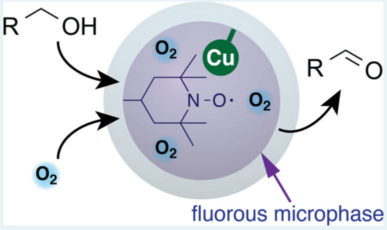
Supporting Information

ABSTRACT: We describe an enzyme-inspired catalytic system based on a rationally designed multifunctional amphiphile. The resulting micelles feature metal-binding sites and stable free radical moieties as well as fluorous pockets that attract and preconcentrate molecular oxygen. In the presence of copper ions, the micelles effect chemoselective aerobic alcohol oxidation under ambient conditions in water, a transformation that is challenging to achieve nonenzymatically.



KEYWORDS: *micellar catalysis, oxidation, copper, TEMPO, fluorous surfactant*

Nature's enzymes are extremely efficient catalysts. Their remarkable properties result from precise folding of constituent polypeptide chains; preorganization of the local environment and functional groups around the catalytic sites; and participation of metal ions, prosthetic groups, and cofactors.[1] The active sites and cofactor binding pockets are often isolated from the bulk solvent and buried in the hydrophobic interior of the enzyme.

Enzyme-inspired nanoscale catalysts,[2] including dendrimers,[3] functional polymers,[4] and supramolecular assemblies,[5] have been the subject of intensive investigation. Like enzymes, many of these chemist-designed catalysts feature spatially preorganized functional groups, hydrophobic interiors/hydrophilic exteriors, and catalytic sites isolated from the bulk solvent. Micelles, vesicles, and emulsion droplets are some of the simplest and most versatile systems of this kind.[6,7] They spontaneously self-assemble from amphiphilic small molecules, which can be tailored using the formidable arsenal of organic chemistry. Hydrophobic catalysts can be easily solubilized inside micelle interiors.[8] Alternatively, catalytic moieties, either metal-based[9] or organic,[10] can be incorporated into the amphiphile structures.[6] Here, we describe an enzyme-inspired catalytic system based on a rationally designed multifunctional amphiphile. The resulting micelles feature metal-binding sites and stable free radical moieties as well as fluorous pockets that attract and preconcentrate molecular oxygen. In the presence of Cu ions, the micelles effect chemoselective aerobic alcohol oxidation under ambient conditions in water, a transformation that is challenging to achieve nonenzymatically. A related catalytic system based on oxygen preconcentrating block copolymer micelles has been reported recently by us.[11]

The combination of Cu and TEMPO (2,2,6,6-tetramethyl-1-piperidine-*N*-oxyl) has emerged as one of the most attractive catalytic systems for selective aerobic oxidation of primary alcohols to aldehydes.[12,13] The established protocols for Cu/TEMPO-catalyzed alcohol oxidations rely on organic solvents, especially favoring acetonitrile.[13] The transfer of this catalytic system to water could be advantageous from a green chemistry standpoint (especially if the aqueous media could be reused).[14] The use of water for performing oxidations will also circumvent the usual safety concerns associated with combining oxygen or air with flammable organic solvents. Several groups have reported attempts to introduce Cu/TEMPO and related systems into water and water−organic mixtures. Typically, heating, elevated O_2 pressure, special strategies to increase dissolved O_2 concentration, and the presence of water-soluble ligands were required.[15,16] A recent report highlighted the use of a nonionic surfactant to perform the oxidations of activated alcohols under mild conditions.[17]

To improve upon the state of the art, we have aimed to design a functional surfactant architecture incorporating both TEMPO moieties and Cu-binding sites. We envisioned that a more efficient catalyst could result if a high local concentration of O_2 were to be created in the vicinity of the metal and free radical sites. Because perfluorocarbons and their aqueous dispersions are capable of dissolving significant amounts of molecular oxygen,[18] we chose a fluorous hydrophobic "tail" as another desirable structural feature. As an added benefit, an "everything-phobic" perfluorocarbon moiety is expected to prevent the accumulation of the starting materials/products within the micelles, thus improving the accessibility of the active sites and preventing undesirable overoxidation. Previously, the fluorous tagging strategy[19] has been used in Cu/TEMPO alcohol oxidations in organic solvents[20] as well as in biphasic ClO^-/TEMPO alcohol oxidations.[21] The structure of **1**, the surfactant we chose to explore, is shown in Figure 1. It was readily prepared in three

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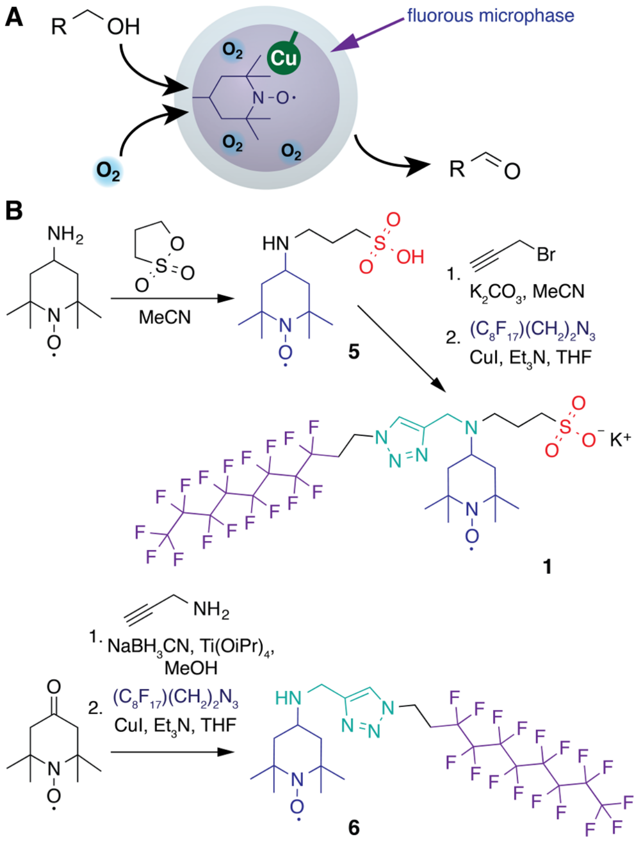


Figure 1. Design of a trifunctional surfactant for aerobic oxidation of alcohols in water. (A) The proposed design for self-assembled fluorous “nanoreactors”. (B) Synthesis of TEMPO derivatives **1**, **5**, and **6**.

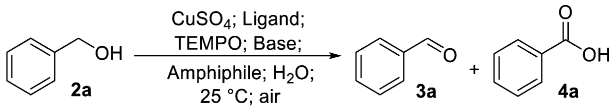
steps, starting with commercially available amino-TEMPO. We also synthesized compounds **5** and **6**, each featuring only two of **1**’s three functional groups.

To establish the baseline for Cu/TEMPO reactivity in aqueous and micellar media, we initiated our study by performing a range of model aerobic oxidation reactions in the presence of common surfactants. The conditions were selected to be similar to well-established organic solvent protocols.[13] Data for selected reactions is summarized in Table 1 (see the Supporting Information (SI), Sections 3−4 for the full set of experiments). The nature of the base and polydentate ligand added (if any) has a profound effect on the outcome of the reactions in organic solvents.[22,16,23] We found that the same holds true for water and micellar media. The nature and amount of surfactant present had an equally significant impact on reactivity. Generally, we found the catalytic system is less well-behaved in water than in organic solvents.

Although TEMPO is moderately soluble in water/benzyl alcohol mixtures, the aerobic oxidation of the alcohol is relatively slow in the absence of surfactants (Table 1, entry 1, and Figure S5, SI) and does not proceed to completion. In the presence of sodium dodecyl sulfate (SDS), the rate improves markedly at the cost of a significant amount of overoxidation (Table 1, entry 2). The overoxidation can be prevented by introducing 2,2′-bipyridine (bpy) (Table 1, entry 4; see Figure S4, SI, for additional ligands). However, this necessitates the addition of 50 mol % of DMAP base (Table 1, entries 3 and 4, and Figure S1, SI). DMAP was found to be an optimal base/cocatalyst, with other bases we tried, resulting in low conversion, poor selectivity, or both (Table 1, entries 8−12, and Figure S3, SI).

It is important to note that a high concentration of SDS (100 mM, 12 times higher than the critical micellization concentration, CMC) is necessary for the $CuSO_4$/TEMPO/bpy system to function effectively (Table 1, entries 4 and 5; Table S2, entries 19−22, SI; Figure S6, SI). Anionic SDS and the neutral Triton X-100 surfactants outperform the cationic cetyltrimethylammonium bromide (CTAB), even though the latter features a much lower CMC than SDS. This does suggest

Table 1. Aerobic Oxidations of Benzyl Alcohol Catalyzed by a Variety of Cu/TEMPO/Amphiphile Systems[a]



entry	surfactant (mM)	TEMPO derivative (mol %)	base (mol %)[d]	ligand[b,d]	$CuSO_4$ (mol %)	O_2 source	**3a** (%)[c]	**4a** (%)[c]
1		TEMPO/5%	DMAP/20%		2	O_2	48 ± 4	
2	SDS/100 mM	TEMPO/5%	DMAP/20%		2	O_2	83 ± 4	10 ± 3
3	SDS/100 mM	TEMPO/5%	DMAP/10%	bpy	5	air	3 ± 0.5	
4	SDS/100 mM	TEMPO/5%	DMAP/50%	bpy	5	air	100	
5	SDS/20 mM	TEMPO/5%	DMAP/50%	bpy	5	air	57 ± 1.5	
6	TX-100/100 mM	TEMPO/5%	DMAP/50%	bpy	5	air	92 ± 1	
7	CTAB/100 mM	TEMPO/5%	DMAP/50%	bpy	5	air	40 ± 1	
8	SDS/100 mM	TEMPO/5%	NMI/50%	bpy	5	air	5.5 ± 1	
9	SDS/100 mM	TEMPO/5%	DABCO/50%	bpy	5	air	5.5 ± 1	
10	SDS/100 mM	TEMPO/5%	KOH/50%	bpy	5	air	31 ± 7	12 ± 3
11	SDS/100 mM	TEMPO/5%	DIPEA/50%	bpy	5	air	35 ± 2	9 ± 1
12	SDS/100 mM	TEMPO/5%	DBU/50%	bpy	5	air	62 ± 4	19 ± 1
13		**5**·K/5%	DMAP/20%		2	O_2	26 ± 1	
14		**6**/5%	DMAP/20%		2	O_2	39 ± 4	
15	**1**/5 mM	**1**/5%	DMAP/20%		2	air	93	
16	**1**/5 mM	**1**/5%	DMAP/20%		2	O_2	98 ± 2	

[a] Reaction conditions: 0.5 mmol of BnOH in 5 mL of water, 25 °C, magnetic stirring, 1 h. [b] Ligand:Cu ratio has been set to 1 for all ligands. [c] Determined by ^1H NMR. Each result is an average from three independent experiments. [d] DMAP, 4-dimethylaminopyridine; NMI, *N*-methylimidazole; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DIPEA, *N*,*N*-diisopropylethylamine; bpy, 2,2′-bipyridine.

that surfactants may play a role in catalysis beyond simple solubilization of hydrophobic TEMPO or bpy/Cu.

Next, we examined the catalytic activity of compounds **5** and **6**. The hydrophobic, poorly soluble **6** was less active than parent TEMPO (Table 1, entry 14). The readily soluble potassium salt of **5** (**5**·K) was even less active: only 26% yield was realized after an hour, and the reaction did not proceed to completion. We attribute this loss of activity to the poor accessibility of the hydrophobic benzyl alcohol substrate by the highly hydrophilic catalyst. Although the reaction mixture appears homogeneous, its phase behavior is known to be complex, with up to three distinct phases coexisting.[24] With **5**·K and Cu^{2+} confined to different phases, we expect the reactivity will be impacted.

To our delight, we found that functional surfactant **1** was an efficient and selective catalyst for alcohol oxidations. The oxidation of benzyl alcohol proceeded to completion in the presence of 5 mol % of **1**, with significantly lower loadings of DMAP (20 mol %) and CuSO$_4$ (2 mol %) than were necessary for reactions in SDS micellar media (Table 1, entry 16). No additional ligand was necessary to avoid overoxidation. The oxidations proceeded well with both air and pure O$_2$ (Table 1, entries 15, 16). Even lower amounts of CuSO$_4$, down to 0.2 mol %, could be used to effect the oxidation reactions, at the cost of slower reaction rates (Table S3, SI). We found the parent TEMPO/CuSO$_4$ system in water loses its catalytic competency completely with low Cu loadings.

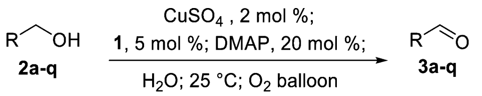
Under the optimized conditions, **1** effectively catalyzes oxidations of a wide range of primary alcohols to their corresponding aldehydes (Table 2). The aldehyde products could be readily isolated in all cases by extracting the aqueous mixture with ethyl ether, followed by a filtration through a pad of silica gel. Although the oxidations proceed nearly as well with air, we performed the experiments using pure O$_2$ because of the easier handling/better reproducibility achievable with our experimental setup.

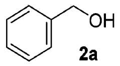
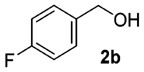
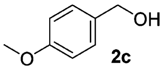
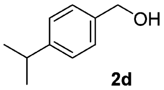
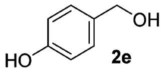
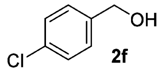
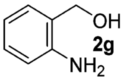
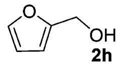
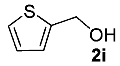
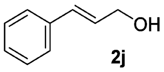
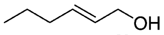
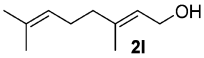
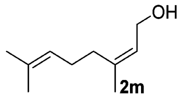
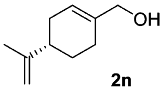
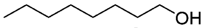
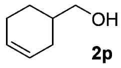
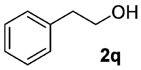
Benzylic and heteroaromatic alcohols were somewhat more reactive (Table 2, entries 1−9) than allylic substrates (Table 2, entries 11−14). Most benzylic alcohols could be completely oxidized within 1−3 h, whereas 20−24 h was required for allylic substrates. The transformations of **2e**, **2g**, and **2h** were more sluggish, possibly because of the competing coordination of the phenol, amine, and furyl groups with copper (Table 2, entries 5, 7, and 8). Consequently, only middling conversions were achieved in 24 h. It is worth mentioning that the sulfur-containing **2i** could be readily oxidized (Table 2, entry 9). Cinnamyl alcohol was found to be extraordinarily reactive, with the reaction complete in less than an hour. For geraniol and nerol, *Z* → *E* isomerization was observed (Table 2, entries 12 and 13). While this type of isomerization is facile for geranial and neral, it has also been observed for *Z*-enals in Cu/TEMPO-catalyzed oxidations in the presence of DMAP.[25]

Substrates lacking unsaturation a bond away from the OH group could not be oxidized (Table 2, entries 15−17). Although benzylic and allylic alcohols are known to be the more active substrates in the established organic solvent protocols, they can be oxidized in acetonitrile. We attribute the difference in reactivity to a change in Cu speciation between acetonitrile and water/micellar media.

To test our oxygen preconcentration hypothesis, we examined the solubility of oxygen in the aqueous solutions of **1** and SDS as well as the kinetics of O$_2$ release from oxygen-oversaturated solutions. Deionized water, as well as solutions of SDS and **1**, were stirred vigorously in vials filled with pure O$_2$. The vials were opened to air, and the evolution of dissolved oxygen (DO) concentration was followed using an Inlab

Table 2. Scope of Alcohol Oxidations Catalyzed by 1 in Water[a]



Entry	*Substrate*	*Time, [h]*	*Yield, [%]*[b]
1	 **2a**	1	94
2	 **2b**	1	98
3	 **2c**	1.5	99
4	 **2d**	2	99
5	 **2e**	24	51[c]
6	 **2f**	1	96
7	 **2g**	24	40[c]
8	 **2h**	24	78[c]
9	 **2i**	3	98
10	 **2j**	1	98
11	 **2k**	24	80[c]
12	 **2l**	20	92 (*E* : *Z* = 3 : 2)
13	 **2m**	10	94 (*E* : *Z* = 10 : 9)[c]
14	 **2n**	24	89
15	 **2o**	24	2[c]
16	 **2p**	24	0[c]
17	 **2q**	24	0[c]

[a]Reaction conditions: 0.5 mmol of alcohol, 5 mol % **1**, 2 mol % CuSO$_4$, 20 mol % DMAP, 5 mL of H$_2$O, 25 °C, 1 atm O$_2$. [b]Isolated yield. [c]Determined by ^{1}H NMR.

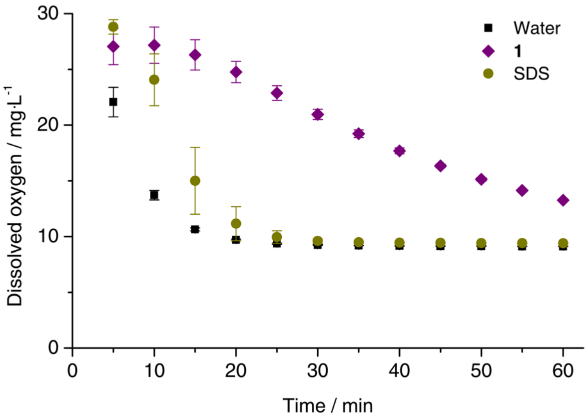


Figure 2. Kinetics of O_2 release from O_2-oversaturated solutions. Deionized water, black markers; 14 mM SDS, green markers; 5 mM **1**, purple markers.

605 immersion probe (Mettler Toledo) (Figure 2). We found that O_2-oversaturated solutions of SDS and **1** retain similar amounts of O_2 (~28 $mg{\cdot}L^{-1}$), measurably more than pure water. However, for both pure water and SDS solution, the DO concentration dropped to its air-saturated value of ~9 $mg{\cdot}L^{-1}$ within 20 min. As SDS solutions foam, the slightly slower O_2 release (and larger error of DO determination) can be attributed to gas retention within foam bubbles. In contrast, DO concentration in a dilute 5 mM solution of **1** is ~25 $mg{\cdot}L^{-1}$ 20 min after venting the headspace oxygen. That oxygen must reside in the aggregates of **1** in the vicinity of TEMPO and Cu catalytic sites.

We gained further insight into the structure of our catalytic system using cryogenic transmission electron microscopy (cryo-TEM) images of the aggregates of **1** (Figure 3). In 5 mM aqueous solutions of **1** (spiked with KCN to scavenge any residual Cu ions), vesicular structures with an average diameter of 42.4 ± 9.1 nm were observed. After the addition of 20 mM DMAP and 2 mM $CuSO_4$, the vesicles changed to more complex, electron-dense aggregates (d = 118.8 ± 33.2 nm). Interestingly, the reaction mixture with BnOH (100 mM) exhibited a completely different morphology: high-aspect-ratio cylindrical micelles (d = 8.2 ± 0.5 nm) were observed. In addition to the impact of BnOH and the aldehyde product, this structural rearrangement might be ascribed to the change in the coordination preference of Cu, which is expected to exist mostly in its reduced Cu^I state upon addition of the alcohol. Furthermore, the reduced TEMPO-H form of **1** could be detected in the reactions by LC/MS. This compound is more polar than **1** and likely has different self-assembly priorities.

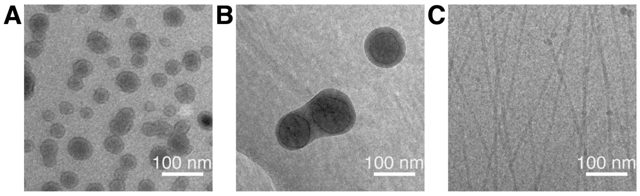


Figure 3. Cryo-TEM images of the aqueous solutions of **1**: (A) **1** spiked with KCN; (B) **1** with added DMAP and $CuSO_4$; (C) **1** with added DMAP, $CuSO_4$, and benzyl alcohol.

In conclusion, we explored the reactivity of the Cu/TEMPO catalytic system for oxidation of alcohols to aldehydes in aqueous micellar media. Although this chemistry could be coerced into water with the help of SDS, the optimal reaction conditions were found to be impractical. To address this problem, we synthesized an enzyme-inspired, trifunctional surfactant **1** that is catalytically competent at practical, millimolar concentrations. Unlike the TEMPO/SDS combination, **1** does not require additional Cu ligands or a high loading of base. There is evidence for O_2 preconcentration within the fluorous cores of the micelles formed by **1**. Investigations of functional soft materials capable of sequestering O_2 and other gases for reactions in liquid phase are under way in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs5020018

> Experimental details for organic synthesis, characterization (^1H, ^{13}C, and ^{19}F NMR) and catalytic studies (PDF)

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Notes

The authors declare no competing financial interest.

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