

Rational Design of Sugar-Based-Surfactant Combined Catalysts for Promoting Glycerol as a Solvent

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Since the last decade, catalysis in water has attracted a lot of attention.^[1] Indeed, it has been well established that the design of catalytic processes in water offers indisputably environmentally friendlier pathways. However, to get over the reactivity of water and the low solubility of most of organic substrates in water, researchers, especially Kobayashi's group, have developed a new concept based on the use of surfactant combined catalysts (SCCs).^[2] These SCCs are able to form stable emulsions in water, which results in a considerable increase in both the reaction selectivity and the reaction rate. However, even if spectacular results were reported under micellar catalysis, emulsification of the reaction mixture unfortunately makes extraction of the reaction products highly difficult. Indeed, in most cases assistance of an organic solvent is required, which considerably decreases the environmental benefit of using water as solvent.^[2,3] It has to be noted that cyclodextrins appear to be a good alternative to overcome this issue because these carbohydrates avoid emulsification of the reaction media while maintaining a good diffusion of the organic reactants in the aqueous phase.^[4] However, even if extraction of the reaction products was considerably facilitated, the use of highly hydrophobic substrates is still subject to strict limitations.

Seeking new improvements for catalysis in water, we found that using glycerol as a solvent offers as many advantages as water, and our aim herein is to convince the reader that glycerol could be familiarly considered as "organic water". Indeed, like water, glycerol is natural, highly hydrophilic, nontoxic (LD50 (oral rat) = 12 600 mg Kg⁻¹), abundant (1.5Mt year⁻¹ in 2008), biodegradable and very cheap ($\approx 1\text{€}/\text{kg}$).^[5] Moreover, compared with water, glycerol has a higher boiling point (290 °C) and a lower vapour pressure (< 1 mmHg at 50 °C), which makes the development of catalytic processes at temperatures around 100 °C technically easier. Surprisingly, despite having very similar solvent properties to those of water, only pioneer catalytic studies have been investigated in glycerol.^[6] This tendency might arise from 1) the very low solubility of organic substrates in glycerol and 2) the intrinsic reactivity of this natural polyol, which leads to the formation of side products.

Herein, we wish to show that the use of SCCs allow all drawbacks to the use of glycerol as a solvent to be overcome by favouring a better diffusion of organic substrates in the glycerol phase and creating some hydrophobic environments inside which it is possible to inhibit the reactivity of glycerol. Moreover, we found that micellar catalysis in glycerol offers a remarkable advantage compared with water because the emulsions formed in glycerol were found to be unstable. Consequently, two phases rapidly formed at the end of the reaction, which allowed an easy extraction of the reaction products without the assistance of any organic solvents, as is generally the case in water.

In the first set of experiments, we investigated the base-catalyzed ring opening of 1,2-epoxydodecane with dodecanoic acid as a model reaction. For the reasons mentioned above, when this reaction was performed at 110 °C in glycerol by using conventional basic catalysts, such as chitosan, silica-supported methylamine, ZnO or K₂CO₃, the reaction rate was low and total conversion only occurred after 18 h (Table 1, entries 2–5). Similarly, the selectivity of the reaction was poor because glycerol ethers that resulted from the

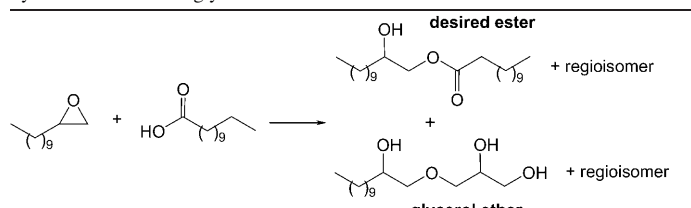
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Table 1. Ring opening of 1,2-epoxydodecane with dodecanoic acid, catalyzed by different bases in glycerol.^[a]



Entry	Catalyst	Time [h]	Conv. ^[b] [%]	Ester ^[c] [%]	Ether ^[c] [%]
1	–	18	30	20	5
2	chitosan	18	98	54	15
3	SiO ₂ -NHMe	18	98	80	15
4	ZnO ^[d]	18	80	70	10
5	K ₂ CO ₃	18	70	60	10
6	HN(CH ₂ CH ₂ OH) ₂	6	98	70	10
7	AP-1a	3	98	95	trace
8	AP-2	5	90	85	5
9	AP-3	6	95	85	5
10	AP-1b	4	98	95	trace
11	AP-1a ^[e]	6	98	95	trace

[a] Epoxide (1 mmol) and carboxylic acid (1 mmol) were stirred in glycerol (4 mL) at 110 °C in the presence of catalyst (20 mol %). [b] Conversion of 1,2-epoxydodecane. [c] Determined by gas chromatography (GC) with dodecane as internal standard. GC response factors are given in the SIES. [d] 5 wt %. [e] Reaction performed at 90 °C.

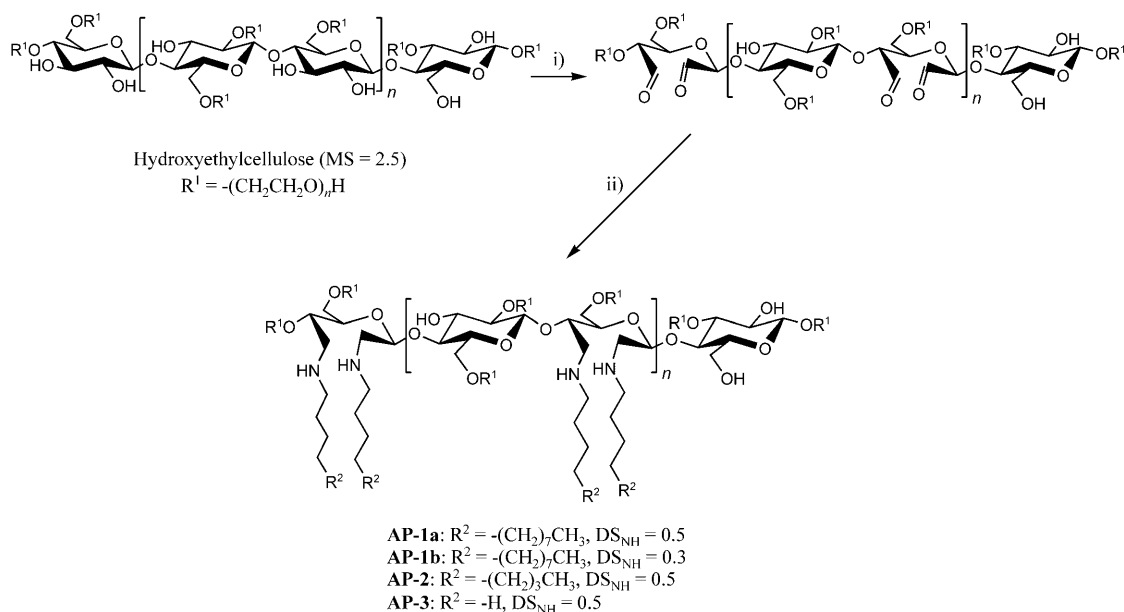
addition of glycerol to 1,2-epoxydodecane were produced as secondary products in 10–15% yield.

Interestingly, compared with other tested catalysts, use of diethanolamine led to a decrease in reaction time from 18 to 6 h (Table 1, entry 6). In this case, we assumed that diethanolamine rapidly reacted with dodecanoic acid at the interface to form an amphiphilic ammonium carboxylate. This

amphiphilic intermediate may act as a phase-transfer agent that favours better diffusion of organic substrates in the glycerol phase. However, despite this clear rate acceleration, glycerol ethers were unfortunately still produced as a side product in more than 10% yield, which confirmed the harmful reactivity of glycerol towards 1,2-epoxydodecane.

To overcome this problem, we synthesised a new family of SCCs. As observed in water, the SCCs were expected to form some hydrophobic environments in glycerol. Thanks to hydrophobic–hydrophilic interactions, diffusion of glycerol inside these hydrophobic pockets should be difficult, which thus makes the development of selective catalytic processes possible. The success of this approach closely depends on the localization of the catalytic sites, which have to be as close as possible to this hydrophobic environment. To reach our goal, we prepared different aminopolysaccharides (APs). These APs were synthesised by oxidation of hydroxyethylcellulose with sodium periodate^[7] followed by a catalytic reductive amination^[8] over Pd/C starting from dodecylamine, octylamine and butylamine to afford the basic catalysts **AP-1a,b**, **-2** and **-3**, respectively (Scheme 1). Physico-chemical data concerning these APs are provided in the Supporting Information Experimental Section (SIES). The structures of these APs are highly interesting owing firstly to their amphiphilic properties and secondly because the hydrophobic core is surrounded by some amino moieties that can act as basic catalysts.

As expected, when a solution of **AP-1a** (25 g L⁻¹, which corresponds to catalytic conditions) in glycerol was vigorously stirred with 2 mL of a solution of 1,2-epoxydodecane (0.1 M) in ethyl acetate, a white turbid mixture, corresponding to the diffusion of the 1,2-epoxydodecane solution in glycerol, formed rapidly (see Figure 1, left).



Scheme 1. Synthesis of amphiphilic AP catalysts. DS = degree of substitution, MS = molecular weight and is commonly used to describe hydroxyethylcellulose. Conditions: i) NaIO₄, H₂O, 24 h, ii) MeOH/H₂O (80:20), fatty amine, Pd/C, H₂ (10 bar), 30 °C, 15 h.

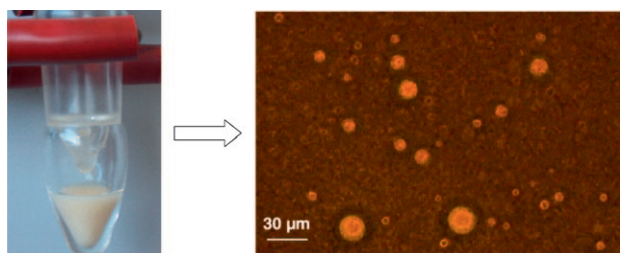


Figure 1. Micelles in a mixture of **AP-1a** and a solution of 1,2-epoxydodecane in glycerol, as detected by phase contrast microscopy.

The average size of spherical colloidal particles formed in glycerol from **AP-1a** and 1,2-epoxydodecane was determined by phase-contrast microscopy. This analysis showed a large distribution of particle sizes (from 5 to 30 μm; Figure 1, right), which is in perfect agreement with the structure of **AP-1a**. As mentioned in the SIES, an important fragmentation of the polysaccharide structure occurs during the synthesis of APs, and **AP-1a** is actually a mixture of different oligomers with a large distribution of molecular weights, which might explain the large distribution of particle sizes observed by phase-contrast microscopy.

Taking into account the unique ability of **AP-1a** to form emulsions in glycerol in the presence of an organic substrate, we investigated its catalytic performances, activity and selectivity in the ring opening of 1,2-epoxydodecane with dodecanoic acid. As shown herein, if amphiphilic **AP-1a** was used as the catalyst, the reaction rate was considerably increased and total conversion was achieved within 3 h (Table 1, entry 7). Decreasing the hydrocarbon chain length of APs from dodecyl to octyl and butyl resulted in a decrease in the reaction rate, which further indicates the key role played by the amphiphilic nature of APs in conducting organic transformations in glycerol (Table 1, entries 7–9).

To our great delight, as described above, the hydrophobic environment created by APs in glycerol decreased the side-formation of glycerol ethers. Indeed, use of **AP-2** and **-3** as the catalyst led to a drop in the yields of glycerol ether from 10–15% in the case of conventional basic catalysts to only 5% yield (Table 1, entries 8, 9). Further increasing the fatty chain length from butyl/octyl to dodecylamine afforded an even more selective catalyst. Indeed, with **AP-1a** catalyst, glycerol ethers were only detected as trace and the desired ester was produced in 95% yield (Table 1, entry 7). A decrease in the number of fatty chains grafted on APs from a DS_{NH} of 0.5 to 0.3 (**AP-1b**) led to only a slight decrease in reaction rate but no change in selectivity was observed (Table 1, entries 7, 10). Interestingly, the catalytic reaction can be also successfully carried out at 90°C without any change in selectivity, whereas the other tested catalysts were found to be poorly active at such temperatures (Table 1, entry 11).

These experiments clearly demonstrate that 1) the amphiphilic properties of APs are responsible for the increase in the reaction rate of the ring opening of 1,2-epoxydodecane

with dodecanoic acid in glycerol and 2) the hydrophobic environments created by APs are crucial for performing highly selective organic reactions in glycerol.

The scope of this method was then studied by conducting the reaction with different carboxylic acids and epoxides. Reactions were performed at 90°C in the presence of **AP-1a** (20 mol% of basic sites; Table 2). Interestingly, in all cases **AP-1a** was found to be highly selective and the desired esters were always produced as the exclusive product. Indeed, this catalytic process was highly tolerant of the presence of functional carboxylic acids or epoxides, and their corresponding esters were obtained in yields of 80–95% (Table 2, entries 1–8). Lower yields were obtained when

Table 2. Selective ring opening of epoxides with carboxylic acids, catalyzed by **AP-1a** (20 mol% of basic sites) in glycerol.^[a]

Entry	Acid	Epoxide	Products		
			Conv. ^[b] [%]	Ester ^[c] [%]	Ether ^[d] [%]
1			95	80	trace
2			95	90	trace
3			90	80	trace
4			90	80	trace
5			98	95	<2
6			97	85	trace
7			98	90	<2
8			98	80	trace
9			85	60	<2
10			95	65	trace

[a] Epoxide (1 mmol) and carboxylic acid (1 mmol) were stirred overnight at 90°C in glycerol (4 mL). [b] Conversion of epoxide. [c] Isolated yield. [d] Determined by GC at the end of the reaction, trace means below the detection limit of the GC.

starting from 2-(3,4-dimethoxyphenyl)acetic acid and cyclohexanecarboxylic acid (60–65%; Table 2, entries 9, 10). In these cases the epoxides were partially degraded, which explains the observed drop in yield. However, in both cases, only trace amounts of glycerol ethers were detected, which confirms the great efficiency of APs.

Following these results, we then studied the extraction of the reaction products with the aim of recycling the homogeneous amphiphilic AP catalysts and showing all the possibilities offered by glycerol as a solvent. To our great delight, we found that the emulsion formed by APs in glycerol was much less stable than in water (Figure 2). Consequently,

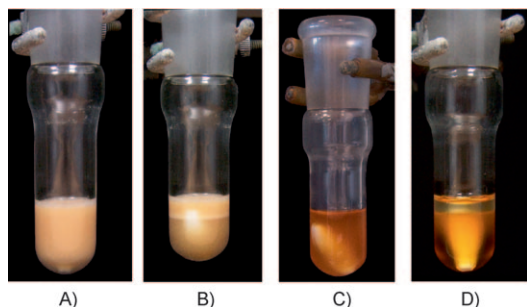


Figure 2. Emulsion behaviour of APs in A) water during the reaction (70% yield after 8 h at 90 °C), B) in water after centrifugation at the end of the reaction, C) in glycerol during the reaction and D) in glycerol after centrifugation at the end of the reaction.

after centrifugation at the end of the reaction, the reaction media rapidly became biphasic, which allowed direct extraction of the reaction products without the assistance of any organic solvents as is generally required in water.

Based on this remarkable advantage of glycerol compared with water, we chose to examine the possibility of catalyst recycling. After extraction of the reaction products by simple decantation, 1,2-epoxydodecane and dodecanoic acid were reloaded for another catalytic run. With **AP-1a**, a decrease in the catalytic activity was observed cycle after cycle, mainly because of its partial solubilization in the product phase (see the SIES). However, **AP-1b**, which has a lower fatty chain content, was found to be totally insoluble in the reaction product phase. Consequently, by using **AP-1b** as the homogeneous catalyst, up to ten consecutive catalytic runs were successfully performed without any change in activity or selectivity, which shows the great advantage of using glycerol as a solvent (Figure 3).

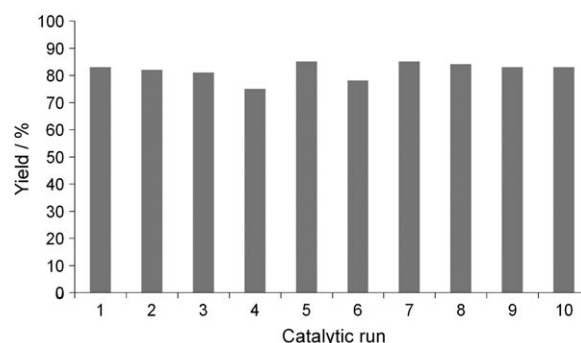


Figure 3. Recycling experiments in the presence of 20 mol% of **AP-1b** (conditions: dodecanoic acid (1 mmol), 1,2-epoxydodecane (1 mmol), glycerol (2 mL), 110 °C, 3 h).

To show the versatility of our procedure, we then moved on to other base-catalyzed reactions and in particular screened some Knoevenagel-type reactions between malononitrile and benzaldehyde derivatives and the Henry reaction and Michael addition of nitroethane to 2-cyclohexen-1-one (Table 3).

Remarkably, whereas in most cases diethanolamine catalyzed these reactions with a lot of difficulty, mainly because of the poor solubility of the reactants in glycerol (except for the Michael addition), **AP-1b** afforded all the desired products in yields ranging from 85 to 96%. Moreover, as observed above for the ring opening of epoxides, **AP-1b** was easily recycled by simple decantation/extraction of the reaction products. In this way, it was possible to successfully perform three successive catalytic runs for the Michael addition, which shows the versatility of our methodology.

In conclusion, we showed herein that glycerol could be a very convenient solvent for conducting environmentally friendly organic reactions. Like water, glycerol is safe and

Table 3. Versatility of **AP-1a** for conducting base-catalyzed reactions in glycerol.^[a]

Electrophile	Nucleophile	Catalyst	Product	Yield ^[b] [%]
		HN(C ₂ H ₄ OH) ₂ AP-1b		< 5 95
		HN(C ₂ H ₄ OH) ₂ AP-1b		25 85
		HN(C ₂ H ₄ OH) ₂ AP-1b		35 96
		HN(C ₂ H ₄ OH) ₂ ^[c] AP-1b ^[c]		15 86
		HN(C ₂ H ₄ OH) ₂ ^[c] AP-1b ^[c]		85 88 85 87

[a] Electrophile (1 mmol) and nucleophile acid (1 mmol) were stirred overnight in the presence of **AP-1b** (20 mol% of basic sites) at 70 °C in glycerol (4 mL). [b] Isolated yield. [c] 2 mmol of nitroethane was used.

very cheap, but its use as solvent requires the development of surfactant combined catalysts to favour better diffusion of organic substrates in glycerol and to limit the intrinsic reactivity of glycerol. However, if we showed here that glycerol behaves similarly to water as a solvent, note that glycerol also offers a unique advantage compared with water. Emulsions formed in glycerol were found to unstable, which thus allows easy extraction of the reaction products without the assistance of any organic solvents. This particular property of glycerol allowed the homogeneous **AP-1b** catalyst to be recycled up to ten times without any change in selectivity or reaction rate. Moreover, note that many renewable resources were used in this study, which further increases the environmental friendliness of this approach. We strongly believe that the use of glycerol as a solvent will provide improved results compared with those observed in water, and further investigations are currently underway in our group on this topic.

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Keywords: aminopolysaccharides • glycerol • green chemistry • homogeneous catalysis • solvent effects • surfactant combined catalysts

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