

## An efficient renewable-derived surfactant for aqueous esterification reactions†

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An efficient and simple approach for the aqueous esterification of a range of carboxylic acids with alcohols has been developed using catalytic amounts of a glucose-derived *N*-alkanoyl-*N*-methyl-1-glycamine non-ionic biosurfactant (C12MG). Excellent yields to final products were obtained under mild conditions and the protocol was amenable to both aromatic and long alkyl chain acids (e.g. fatty acids).

### Introduction

Aqueous-based organic transformations have received significant attention in recent years from the Green Chemistry standpoint. Its wide availability, low toxicity and lack of flammability make water one of the most suitable green alternatives to organic solvents. However, the solubility of organic compounds in water, particularly for synthetic organic processes often limits the applicability of aqueous chemistries to biphasic reactions.<sup>1</sup> In this regard, the addition of surfactants in concentrations above critical micellar concentration (CMC) is often an interesting approach to facilitate the solubility of organic compounds as phase transfer catalysts.<sup>2</sup> Micellar aqueous media are of widespread importance in a variety of fields, with particularly promising applications in bionanotechnology, biomedicine, and catalysis.<sup>3–5</sup> For benign by design processes *in water* and *on water*, readers are kindly referred to the recent overview of Gawande *et al.*<sup>1</sup>

Particularly related to catalytic applications, micelles formed by self-assembly of surfactants have been used to catalyse important organic reactions including aldol,<sup>6</sup> Mannich-type,<sup>7</sup> and Michael reactions.<sup>8</sup>

Esterification of carboxylic acids and alcohols is a very important organic transformation both in academia and industry due to the usefulness of these products as important intermediates for drug formulations, fine chemicals, flavors, plasticizers, emulsifiers and biodiesel production.<sup>9–12</sup> Traditionally, the esterification of organic acids has been performed in organic solvents and using concentrated sulfuric acid media

equipped with azeotropic distillation system for continuous water removal to drive the equilibrium towards esters production. These reactions are in fact highly water-sensitive due to different equilibrium steps in which water is involved.<sup>11,13</sup>

Alternative heterogeneous catalytic systems to mineral acids have been reported in recent years. Some of them are included a range of solid acids, molecular sieves, and biocatalysts.<sup>14,15</sup> Nevertheless, while there are several reports of the partial or even complete replacement of organic solvents with water in selected catalytic processes, we firstly introduced the concept of heterogeneously catalyzed aqueous esterifications back in 2007 by using a water tolerant biomass-derived solid acid carbonaceous material.<sup>15,16</sup>

Commercial interest in polyol surfactants derived from glucose exist for several reasons which include the inexpensive nature of agriculture-based raw material as well as their green credentials. Moreover, short-chain polyol surfactants readily solubilize membrane polar lipids, and facilitate the isolation and study of membrane-bound proteins. A key member of the class, is *N*-dodecanoyl-*N*-methyl-1-glycamine (Scheme 1). The acronym “C12MG” will thereafter be used to refer to the above-mentioned compound.

In this work, we report a high efficient and green method for the aqueous esterification of a series of carboxylic acids by using a novel glucose-derived non-ionic biosurfactant (*N*-alkanoyl-*N*-methyl-1-glycamine polyol, C12MG) under mild reaction conditions.

### Experimental procedure

#### Biosurfactant preparation

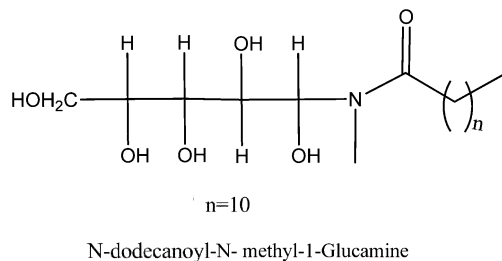
C12MG is in principle commercially available and for the particular case of these experiments a commercial C12MG was initially employed for the selected esterification reactions. However, the biosurfactant could be prepared according to the methodology illustrated in Scheme 2. A simple reductive amination of glucose followed by an amidation generates the final biosurfactant product in high yields (>90%) (Scheme 2).

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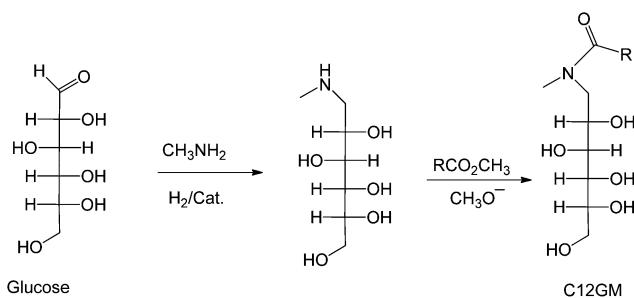
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Scheme 1 Structure of the catalytically active biosurfactant.



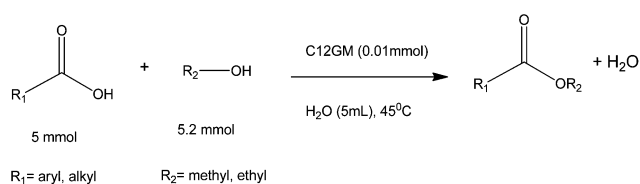
Scheme 2 Preparation of C12MG.

### Esterification reaction

The esterification reaction was conducted in a 50 mL round bottom flask, equipped with a magnetic stirrer and a condenser. In a typical reaction run, 5 mmol of carboxylic acid were introduced in the round bottom flask with 5.2 mmol of methanol or ethanol in water (5 mL). 0.002 mmol of C12MG were subsequently added as catalyst and the reaction mixture was stirred at 45 °C. Upon reaction completion, the final mixture was quenched with saturated aq. NaHCO<sub>3</sub>, diethylether was then added and the organic layer was consecutively washed with water and brine. Final products were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated, and purified by silica gel chromatography with hexane–EtOAc (5 : 1). <sup>1</sup>H and <sup>13</sup>C NMR characterization of most esters synthesized in this work has been included in the ESI.†

## Results and discussion

In order to optimize reaction conditions, we initially investigated the synthetic potential of the glucose-derived biosurfactant in the model reaction of benzoic acid (5 mmol) with methanol (5.2 mmol) in 5 mL water (Scheme 3). Systematic studies were conducted under a range of conditions using different amounts of C12MG as micellar catalyst.



Scheme 3 Esterification reaction of carboxylic acids and alcohols.

Table 1 Esterification reaction of benzoic acid and methanol at different conditions<sup>b</sup>

Entry	C12MG (mmol)	HCl (mL)	T (°C)	Time (h)	Yield <sup>a</sup> (%)
1	—	—	25	10	Trace
2	0.1	—	25	5	65
3	0.1	—	45	5	88
4	0.1	—	100	5	89
5	0.1	0.1	45	5	98
6	0.05	0.1	45	5	98
7	0.002	0.05	45	3	98
8	0.002	0.05	45	2	98
9	0.002	0.05	45	1.5	86
10	—	0.05	45	2	Trace

<sup>a</sup> Isolated yield. <sup>b</sup> Reaction conditions: benzoic acid (5 mmol), methanol (5.2 mmol), and water (5 mL).

Selected results are summarized in Table 1. Blank runs provided no conversion to ester products even after long times of reaction (Table 1, entry 1), similarly to results obtained using a homogeneous base-catalysed reaction. Room temperature reaction runs indicated that the aqueous esterification could be simply catalyzed by the proposed biosurfactant, providing moderate yields to methylbenzoate after only 5 hours of reaction (65% yield, Table 1, entry 2). Performing the reaction at higher temperatures (up to 45 °C) had a significant effect on reaction yields which reached values close to 90% (Table 1, entry 3). A further temperature increase to 100 °C did not seem to influence reaction rates as almost identical yields were obtained (Table 1, entry 4). As a comparison, a reaction run using concentrated hydrochloric acid as catalyst in the absence of the biosurfactant gave only traces of ester after a two hours of reaction (Table 1, entry 9). The use of sulfuric acid (0.01 mmol) provided similar yields to products in the model reaction. Interestingly, a quantitative yield to methylbenzoate was obtained when a single drop of concentrated HCl was added to the reaction mixture (Table 1, entry 4) which indicated a synergetic catalytic effect of traces of acid in the biosurfactant catalyzed esterification. Up to this point, a selected concentration of 0.1 mmol C12MG was utilized. In order to demonstrate the efficiency of the micellar media as catalyst, the effect of the amount of the surfactant C12MG was subsequently examined. Gratifyingly, the esterification reaction could still afford an excellent 98% isolated yield of methylbenzoate within 2 h under mild conditions when the amount of surfactant was decreased to 0.2 mol% (Table 1, entry 8).

Having explored the potential of C12MG as micellar catalyst in the proposed model esterification, the scope of the reaction was subsequently attempted for a variety of carboxylic acids with two short chain alcohols, namely methanol and ethanol.

Table 2 summarises the main findings of the different investigated reactions. To our delight, the reaction was found to be amenable to a wide range of substrates including aromatic

and aliphatic carboxylic acids, tolerating at the same time a variety of functional groups including methyl, methoxy, nitro, fluoro, bromo, iodo groups (Table 2). In all cases, good to excellent yields to products were obtained. These included the esterification of important platform chemicals (*e.g.* succinic acid, Table 2, entry 10) for which a complete selectivity to diethylsuccinate (87% yield) was obtained after only 6 hours of reaction. The process was not selective to the production of monoethylsuccinate. Methyl levulinate could also be obtained in similar yields to those of succinic acid (Table 2, entry 13).

Of particular interest were chemistries related to the esterification of long alkyl chain carboxylic acids (*e.g.* fatty acids) for which very good yields to products were obtained under mild reaction conditions and reasonable times of reaction (typically 8 h). These esterifications in fact lead to fatty acid methyl esters (biodiesel type compounds) which have a significant potential to be employed in biofuel blends. Both the esterification of stearic acid and palmitic acids with methanol gave the desired yield to biodiesel-like products (Table 2, entries 11, 12).



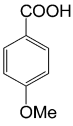
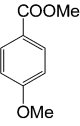
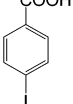
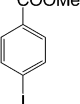
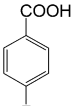
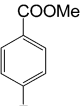
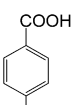
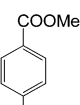
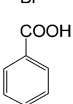
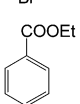
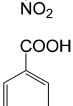
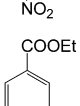
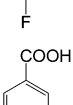
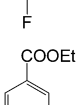
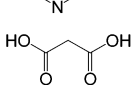
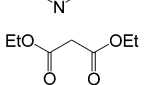
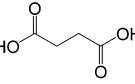
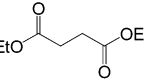




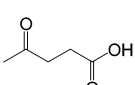
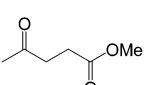
To ascertain the possibility to recycle the C12MG catalyst from the reaction mixture, the aqueous mixture was evaporated upon reaction completion, followed by acetone reconstitution to recover C12MG. Once C12MG was recovered, the acetone phase was removed under vacuum and fresh substrates were subsequently added to the reaction vessel for further reactions. Excellent yields of methylbenzoate were obtained after various uses (up to three uses) which demonstrate the usefulness of the protocol in terms of recyclability and catalyst activity. The efficiency of the proposed catalytic micellar system is believed to be related to a synergistic dual activation through hydrogen bond mediated formation of supramolecular assemblies involving water and the reactants, acting in a similar way to that of a phase transfer catalyst.

In conclusion, the aqueous esterification of carboxylic acids with short chain alcohols (typically methanol or ethanol) has been proved to be efficiently performed in the presence of catalytic amounts of a novel non-ionic renewable-derived surfactant such as *N*-alkanoyl-*N*-methyl-1-glycamine polyol. This catalyst promoted an efficient aqueous esterification of various aliphatic and aromatic carboxylic acids under reaction mild conditions. The use of novel and renewable nonionic surfactant, simple work-up of the reaction and recyclability of the catalyst in the proposed methodology make this protocol a practical and economically attractive approach for further developments.

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Table 2 Esterification of various carboxylic acids in micellar C12MG solution<sup>a</sup>

Entry	Substrate	Product	Time (h)	Yield <sup>b</sup> (%)
1			2	98
2			2	94
3			3	92
4			3.5	95
5			3	93
6			4	90
7			4	93
8			5	90
9			6	85
10			6	87
11			8	82
12			8	84
13			6	88

<sup>a</sup> Reaction conditions: carboxylic acid (5 mmol), alcohol (5.2 mmol), C12MG (0.002 mmol), water (5 mL) at 45 °C. <sup>b</sup> Isolated yield.

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