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β-Amino acid derived gemini surfactants from diformylfuran (DFF) with particularly low critical micelle concentration (CMC)†

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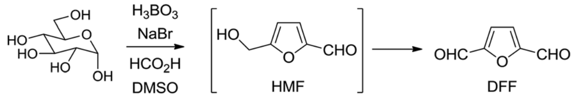
Starting from diformylfuran (DFF) obtained from biomass, a new family of gemini surfactants has been synthesized. The polar group is composed of two amphoteric amino acids attached to a tetrahydrofuran ring. During the preparation, the formation of metal salts is avoided in the final steps. At very low critical micelle concentrations (CMCs) of around 1.5 μmol L^{-1}, an efficient decrease of the surface tension of up to 30 mN m^{-1} is measured. Below the CMC, the surface excess Γ varies with the surfactant bulk concentration. In a concentration interval below the CMC, a linear relationship between Γ and the bulk concentration is observed. Wetting properties are reported and bactericidal activities have been detected. Efficient antifungal activity against *Fusarium graminearum* has been detected.

Introduction

The use of biomass as a renewable feedstock in the chemical industry has become a key strategy of green or sustainable chemistry.[1] In this context, the production of surfactants from biomass is of outmost importance.[2,3] New surfactants should possess a high efficiency in order to limit the impact of chemicals. Especially for zwitterionic or amphoteric surfactants, syntheses should be developed in which the concomitant formation of salts is avoided in order to simplify the purification.

Gemini surfactants are a compound family within the surfactants possessing particularly high surface activity.[4–6] Thus the critical micelle concentration (CMC) is often very low. Values between 4 and 55 000 μmol L^{-1} are reported. The CMC of sodium dodecylsulfate as an example of an efficient conventional surfactant is around 10 000 μmol L^{-1}. Generally, gemini surfactants are composed of two connected surfactant molecules each possessing a polar head moiety and a hydrophobic hydrocarbon tail group. Both, the hydrophobic hydrocarbon, often *n*-alkyl substituents, and the hydrophilic head group are obtained from the compounds of renewable biomass. For example, amino acids have been used in this context.[7,8] We became interested in using the compounds obtained from the oxidation of furans for the preparation of the hydrophilic surfactant moiety.[9–11] Some of them are biodegradable. In these particular cases, the hydrophobic moiety is easily released from the hydrophilic part. Both constituents are biodegraded.[12] Furans such as furfural or hydroxymethyl furfural (HMF) are available from pentoses and hexoses containing biomass respectively.[13–16] In contrast to furfural, the availability of HMF is more difficult and a lot of research work is currently carried out to facilitate its production from biomass. 2,5-Diformylfuran (DFF) is a less valorized furan derivative obtained from HMF and primary biomass.[17,18] Recently, we developed a convenient one pot method for the synthesis of DFF directly from carbohydrates (Scheme 1).[19,20] Similar processes have been published.[21,22] DFF is also an interesting platform chemical due to the fact that it is biodegradable (see the ESI†). The presence of two reactive aldehyde functions in positions 2 and 5 of this molecule makes it interesting as a precursor in the synthesis of many symmetric molecules among the gemini surfactants.



Scheme 1 One pot procedure for the transformation of carbohydrates into DFF.[19,20]

Synthesis of gemini surfactants

The synthesis started with a condensation of DFF with primary amines **1a–d** (Scheme 2). Reduction of the resulting imines to

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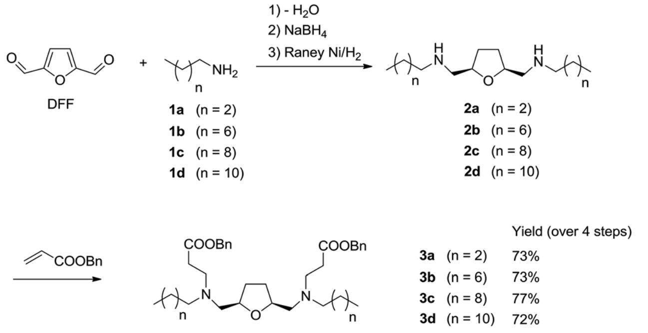
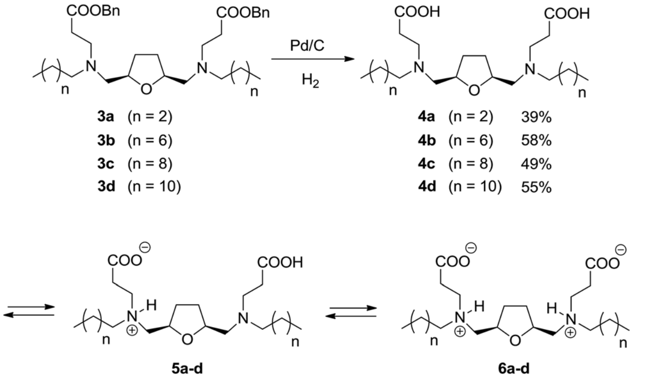


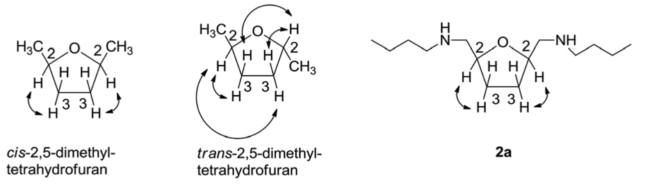
Scheme 2 Synthesis of tetrahydrofuran bis-aminoester derivatives **3a–d** as precursors for the preparation of surfactants.



Scheme 3 Final step of the synthesis of amphoteric surfactants **4a–d**.

secondary amines was performed with $NaBH_4$. Similar transformations have recently been carried out.[23,24] A more convenient method for reductive amination with hydrogen using Pd/C catalysis was not successful. Further reduction of the furan ring with RANEY® Ni yields the corresponding tetrahydrofuran derivatives **2a–d**. Similar reaction conditions have been previously reported, for example for the hydrogenation of 2,5-di(hydroxymethyl)furan.[25] Although reductive amination has also been carried out with RANEY® Ni, we have not yet found the reaction conditions or a method to efficiently perform both reductions at the same time. All compounds have been obtained in high yields so that purification was not necessary. Furthermore, it must be pointed out that compounds **2a–d** were selectively obtained as *cis* isomers (C_S symmetry, *meso* form). In heterogeneous metal catalyzed hydrogenations and due to the adsorption of the substrate at the surface, this stereochemistry is often favored.[26,27] Furthermore, decomposition of the furan ring is often observed as a competing reaction.[26,28] In our case, the reaction was highly selective and we performed additional NMR analyses to determine the *cis* selectivity of the reaction (see the ESI†). We recorded NOESY spectra of compound **2a** and of a mixture of *cis* and *trans* 2,5-dimethyltetrahydrofuran. The observed Nuclear Overhauser Effects (NOEs) are indicated in Fig. 1. In the spectrum of **2a**, a NOE for protons in 2 and 3′ or *vice versa* was not observed as it would be expected for a corresponding *trans* isomer.

Hydrogenolysis was chosen to generate the carboxylic acid function (Scheme 3). This method avoids the addition, for example of bases for saponification, and the formation of the corresponding salts which otherwise have to be eliminated during the workup of the reaction mixture. Under almost neutral conditions, the carboxylic acid compounds **4a–d** are obtained. These compounds are capable of forming zwitterionic species with betaine structures such as **5a–d** or **6a–d**. Such functional groups are highly polar. Incorporated into a gemini pattern, these compounds should possess high surfactant activities.



cis-2,5-dimethyl-tetrahydrofuran

trans-2,5-dimethyl-tetrahydrofuran

2a

Fig. 1 Structure assignment for compound **2a** by comparing significant NOE.

Surfactant properties

Surfactant properties such as surface tension reduction or the CMC have been determined as the most significant parameters of detergency activity. The surface tension at the interface of the water phase and air decreases progressively when the surfactant concentration is increased according to the Gibbs equation for ionic surfactants (eqn (1)). γ is the surface tension, C is the concentration of the surfactant, R is the gas constant and T is the temperature. Γ is the surface excess or the concentration of the surfactant at the interphase. When the concentration at the surface reaches a particular value, aggregates of the surfactant such as micelles are formed in the aqueous phase. Using the Wilhelmy plate method,[29] the CMC was determined for compounds **4b–d** (Fig. 2, Table 1). Compound **4a** does not possess a surfactant activity.

$$\Gamma = -\frac{1}{2RT}\left(\frac{\mathrm{d}\gamma}{\mathrm{d}\ln C}\right)_T \qquad (1)$$

In the case of **4b**, two moderate breaks in the curve are observed. According to the interpretation of the CMC with the help of the Gibbs equation, two values for this parameter are obtained. In the case of **4c**, a clearer intersection of strayed lines is detected indicating a very low CMC of 1.9 μmol L^{-1}. Obviously, the formation of aggregates (micelles) is very favorable. A similar CMC is measured for compound **4d**. In this case however, the surface excess Γ is not a constant when the concentration is increased towards the CMC (for further discussion see below). The C_{20} value indicates the concentration of the surfactant at which the surface tension is reduced by 20 mN m^{-1}. The values for compounds **4c** and **4d** are also very low and characterize them as efficient surfactants. A correlation[6] of the corresponding pC_{20} values with the number of

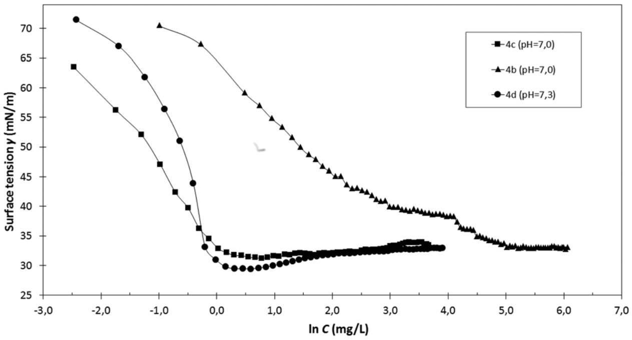


Fig. 2 Surface tension γ depending on the bulk concentration of the surfactants **4b–d** measured using the Wilhelmy plate method.

Table 1 Surfactant properties of compounds **4b–d** (Fig. 2)

Compound	pH	CMC [μmol L^{-1}]	C_{20} [μmol L^{-1}]	γ_{CMC} [mN m^{-1}]
		2460		40
4b	7.0		7.0	
		26		33
4c	7.0	1.9	0.5	31
4d	7.3	1.5	0.8	30

Table 2 Surfactant properties of compound **4d** at different pH values (Fig. 3)

Entry	Compound	pH	CMC [μmol L^{-1}]	C_{20} [μmol L^{-1}]	γ_{CMC} [mN m^{-1}]
1	**4d**	9.0	1.3	0.8	35
2	**4d**	7.3	1.9	0.5	31
			0.2		49
3	**4d**	4.0		0.2	
			2.1		30

CH_2 groups in the hydrophobic chains of these two gemini surfactants is not observed. The surface tension values at the CMC concentrations γ_{CMC} are around 30 mN m^{-1} which are typical values of effective surfactants.

The present compounds possess betain functionality (Scheme 3). As amphoteric compounds, their surfactant properties are pH-responsive. The effect of the pH on surfactant parameters, in particular the CMC, was determined for compound **4d** (Fig. 3, Table 2). At pH = 9, a bent curve rather than a straight line is detected when the concentration is increased towards the CMC. At very low concentrations, no significant decrease of the surface tension is observed. At a concentration higher than 0.3 mg L^{-1} (0.5 μmol L^{-1}) a sudden decrease of surface tension to the value of γ_{CMC} = 35 mN m^{-1} is detected. This effect is less pronounced at pH 7. At pH 4 two intersections have been found. The first one at a very low concentration of 0.2 μmol L^{-1} of **4d** may be caused by the formation of particular aggregates which are different from those formed at the higher surfactant concentration of 2.1 μmol L^{-1}. Similar observations have previously been reported for amphoteric surfactants at low pH[9,10] and for anionic polymer water solutions containing cationic surfactants.[30–32] In the present case, the surfactant concentration at the first intersection diminishes the surface tension to the value of 49 mN m^{-1}, while at the second break, the habitual value of 30 mN m^{-1} is reached. At pH 7.3 or 9.0, an anionic species acts as a polar group of the surfactant while at pH 4 a neutral zwitterionic or a cationic species is present.[9,10]

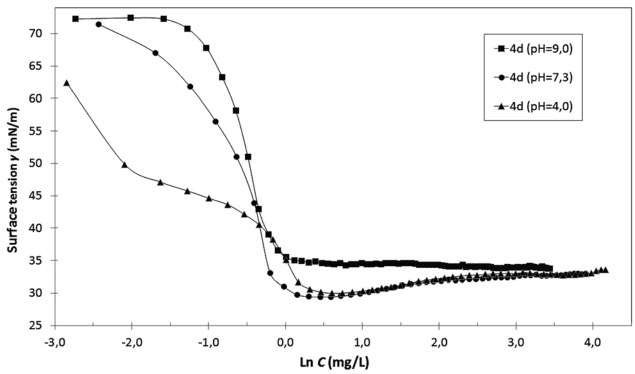


Fig. 3 Surface tension γ depending on the bulk concentration of the surfactants **4d** at different pH values measured using the Wilhelmy plate method.

Nonlinear relationships between the surface tension γ and $\ln C$ at concentrations < CMC have previously been reported and the validity of the Gibbs equation (eqn (1)) for the detection of the surface excess or surface saturation with a surfactant was critically questioned.[33–38] It is often assumed that the surface excess Γ is constant and in a large interval for surfactant concentrations < CMC.[39] In this discussion, Γ is considered as the maximum of concentration of the surfactant at the interface. This concentration does not necessarily correspond to a saturation of the surface with the surfactant.[34] The maximum is already reached after the addition of small quantities of the surfactant. In our studies on gemini surfactants with very small CMC, we observed such a case for **4c** at pH 7 with Γ = 23 μmol m^{-2}. Especially in cases where no linear relationship between the surface tension γ and $\ln C$ was detected such as for **4d** at pH 9.0 (Fig. 3 and Table 2, entry 1) or at pH 7.3 (entry 2), it was also assumed that the interface is not saturated and the surface excess Γ depends on the "bulk" concentration.[40–42] Such observations have also been discussed in connection with cooperating adsorption.[40] A maximum of surface coverage is observed at the CMC or close to it. Especially in the case of compound **4d** at pH 9.0 and for concentrations below the CMC, a linear relationship between the surface excess Γ and the bulk concentration of this surfactant is detected (Fig. 4). This observation is in line with the Nernst's partition law; a linear relationship exists between the concentrations of a solute in two non-miscible solvents. Similar relationships have been found in studies with a gemini surfactant in water–alcohol mixtures.[43] Further examples of the relationship between bulk surfactant concentrations and surface excess have been reported.[44]

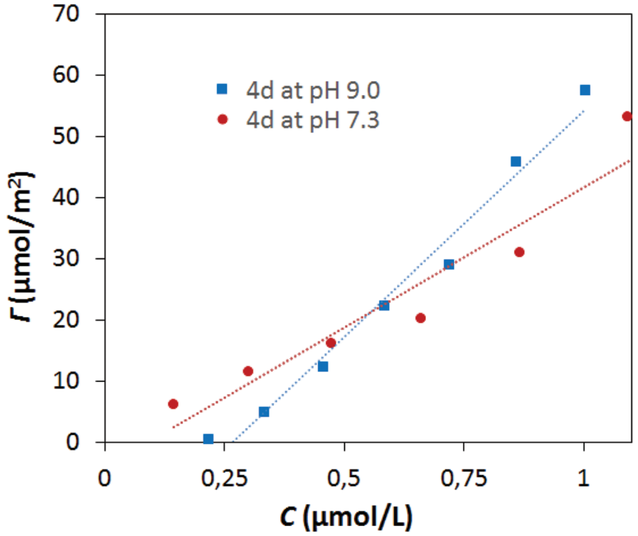


Fig. 4 Linear relationships between the bulk concentration C of surfactant **4d** and the surface excess Γ (compare Fig. 3).

Wetting properties of compounds **4b–c** have been determined using the Drave test (Table 3).[6,45] In the case of compound **4b**, a relatively long wetting time is measured. When the hydrophobic groups are increased the time is significantly reduced. Compounds **4c** and **4d** show almost the same values for this parameter, as it was also observed for the CMC and C_{20} values of these compounds (compare Table 1).

Gemini surfactants possessing amino functions can possess anti-microbial activities.[46–48] Applying test conditions of OCDE 301F for biodegradation,[49] we detected bactericidal activities for compounds **4b–d**.

Particularly, antifungal activities of gemini surfactants have been studied in detail.[47,48,50,51] We decided to test our gemini surfactants with respect to this activity. The filamentous ascomycete *Fusarium graminearum* is a ubiquitous plant pathogen commonly found on cereal grains. Usual fungicides from petrochemical resources are somewhat efficient for fighting this pathogen but resistance has been observed along years and new chemicals with better environmental profiles are required in this domain. This disease reduces the yield and may also contaminate the grain with fungal toxins (mycotoxins). These toxic metabolites have been found to be toxigenic for both humans and animals. Surveillance studies confirmed that mycotoxin contamination is a world-wide problem since it causes economic losses and is a potential threat to animal and human health. Therefore we decided to investigate antifungal properties of our gemini surfactants against *Fusarium graminearum* (Table 4).

Table 3 Wetting time determined using the Drave test[45]

Compound	Wetting time [s]
4b	546.7 ± 113.7
4c	64.7 ± 5.0
4d	67.0 ± 6.6

Table 4 Antifungal activity (growth inhibition of *Fusarium graminearum*)

Compound	Concentration [mmol L^{-1}]	Growth inhibition [%]
4b	1.00	0.00
	2.00	1.29
	6.01	23.92
	10.02	32.80
	20.05	29.38
4c	0.90	28.46
	1.80	40.10
	5.41	89.16
	9.01	91.28
	18.02	98.59
4d	0.82	43.65
	1.64	72.04
	4.91	87.57
	8.18	81.42
	16.37	82.56

Antifungal activity was dependent on the structure of cationic gemini surfactants and can be correlated to CMC. Among the tested compounds, the most active against *Fusarium graminearum* was the gemini surfactant **4c** at a concentration above 1.8 mmol L^{-1} (0.1 wt% solution). These results are in good agreement with the existing results in the literature as inhibition can be observed at a concentration higher than CMC (10–100 times higher) as the compound solubility is reduced.[52] Antifungal activity was also observed for compound **4d** and started at a lower concentration than compound **4c**. 40% of the inhibition growth is observed at concentrations of 1.8 mmol L^{-1} and 0.8 mmol L^{-1} for compounds **4b** and **4c** respectively. However for surfactant **4c**, above the concentration (0.1 wt% solution) efficiency was unchanged. Antifungal activities are in good agreement with the corresponding physicochemical properties for gemini surfactants **4b–d** (CMC's and wetting times). It is known that homologous series of surfactants showed a linear relationship with the antimicrobial activity only at the lower chain lengths. For example, MICs of betaine surfactants exhibited a plateauing effect with increasing alkyl chain lengths.[52] This has been an associated cutoff with a limit in solubility.[53,54]

Conclusion

Starting from DFF, a new family of gemini surfactants has been synthesized. These compounds possess a tetrahydrofuran moiety and two amphoteric groups (carboxylic acid and tertiary amine). The synthesis was optimized in such a way that the formation of metal salts in the last steps is avoided. Further optimization of the synthesis can be envisaged. For example, conditions with the same reduction system as that of the reductive amination and the hydrogenation of the furan moiety should be found.

The final compounds possess a very low CMC. As amphoteric compounds, the surfactant properties also depend on the pH. In the case of **4d** and in a neutral or basic medium, the surface tension and the surface excess depend in a specific way on the bulk concentration of the surfactant which resembles Nernst's partition law. Their biodegradation behavior pushed us to study their antifungal activity against *Fusarium graminearum* and revealed efficient activity and possible use of this type of gemini type surfactant as fungicides in crop protection applications.

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