

# Improved Green Synthesis and Crystal Structures of Symmetrical Cationic Gemini Surfactants

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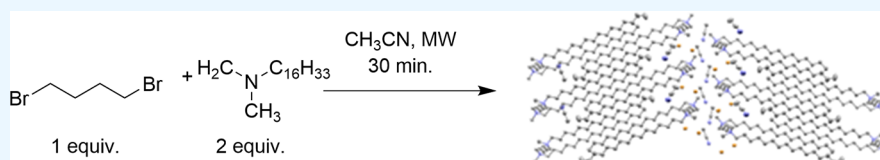
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**ABSTRACT:** Gemini surfactants are composed of two hydrocarbon tails with corresponding polar headgroups, linked via a covalent spacer. The synthesis of these surfactants is a very active area of research due to their application as catalysts and other applied areas of study. The modification of green microwave techniques developed in our research on ionic liquids has resulted in the significant improvement of the synthesis of *N,N'*-bis(dimethylalkyl)- $\alpha,\omega$ -alkanediammonium dibromide (*m-s-m* type) symmetrical gemini surfactants. This approach utilizes a remarkably more economical, green, and sustainable methodology for the production of symmetrical gemini surfactants that can be utilized in numerous commercial applications. The improved synthetic approach of these gemini surfactants has led to the characterization of their crystalline packing for the first time ever using X-ray crystallographic analysis.

## INTRODUCTION

Surfactants are molecules that contain one or more hydrophilic headgroups and one or more hydrophobic tails. Gemini (or dimeric) surfactants consist of two hydrophobic chains and two polar headgroups that are covalently linked by a spacer. Research on gemini or dimetric surfactants has steadily grown in recent years due to their various applications. Many studies have shown that gemini surfactants have superior wetting, lower critical micelle concentration values, and higher surface activities than monomeric surfactants seen more commonly. The superior properties that gemini surfactants present make their application in fields such as detergents, biocides, nanotechnology, and oil recovery all the more useful.<sup>1–12</sup> Prior methods for the synthesis of symmetric cationic surfactants of type *N,N*-bis(dimethylalkyl)- $\alpha,\omega$ -alkanediammonium dibromide (*m-s-m* type) have been demonstrated to be inefficient. Many previous methods conducted the reaction by refluxing in high-performance liquid chromatography-grade acetonitrile, which would take  $\geq 48$  h, an excessive amount of solvent, and repeated recrystallizations afterward.<sup>13–18</sup>

In studies of related compounds known as ionic liquids, microwave heating has proven to afford high yields in short reaction times, thus minimizing the need for solvent.<sup>19</sup> Microwave electromagnetic radiation is not powerful enough to break bonds by direct absorption (i.e., photochemistry) because the photon energy from a microwave source is not high enough.<sup>20–23</sup> This approach employs dielectric heating, as molecules absorb the energy and convert it to heat. In

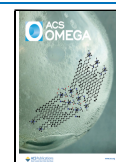
dielectric heating, the dipole moment of the molecules will tend to orient and reorient under the influence of the microwaves' electric field. The use of dielectric heating in the synthesis of gemini surfactants therefore increases the rate of nucleophilic substitution that occurs by targeting the high polarity of the headgroups, causing local heating. This method does not rely on the convection of a system as in conventional heating, which is energy inefficient because the temperature of the reaction vessel being higher than the reaction mixture and temperature gradients throughout the reaction vessel. This phenomenon allows an entire solution to be heated simultaneously and more efficiently. By utilizing microwave methodology, the synthesis of gemini surfactants can be conducted in an overall more efficient, effective, and sustainable manner.

The dramatically improved syntheses of a range of symmetrical gemini surfactants of the type *N,N*-bis(dimethylalkyl)- $\alpha,\omega$ -alkanediammonium dibromide (*m-s-m* type; 8-4-8, 10-4-10, 12-4-12, 14-4-14, and 16-4-16) are reported herein (Scheme 1). The use of dielectric heating has led to several advantages, making the synthesis of this class of

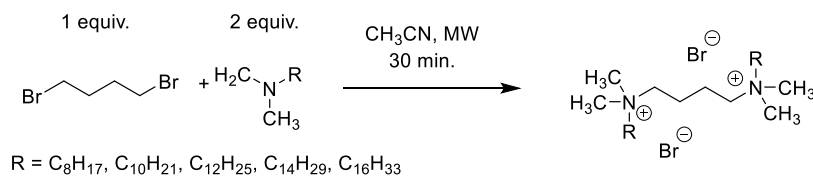
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### Scheme 1. Synthesis of Cationic Symmetric Surfactant *N,N*-Bis(dimethylalkyl)- $\alpha,\omega$ -Alkanediammonium Dibromide (*m-s-m* Type) Using Microwave Irradiation



compounds more sustainable and amenable for scale-up. Advantages of using the methodology reported herein include higher isolated yields, shorter reaction times, lower energy consumption, minimal solvent requirement, higher purity, and less waste/by-product formation. Furthermore, the high purity of the compounds obtained using this new methodology has led to the isolation of single crystals of three of these compounds, despite containing long, conformationally mobile alkyl chains, thus allowing for their characterization using X-ray crystallographic analysis. The results reported herein are comparatively much improved relative to those reported previously for the same compounds or analogues thereof.<sup>24–27</sup> Previous reports obtained isolated yields of only ca. 80%, which were diminished after repeated recrystallizations, whereas the method reported here consistently obtained yields greater than 92% in high purity without requirement for further recrystallizations.

## MATERIALS AND METHODS

**Materials.** *N,N*-Dimethyloctylamine, *N,N*-dimethyldodecylamine, *N,N*-dimethyldodecylamine, *N,N*-dimethyltetradecylamine, *N,N*-dimethylhexadecylamine, and 1,4-dibromobutane were obtained from Sigma-Aldrich with purity ranging from 95 to 99% and used without further purification. Solvent grade acetonitrile and ethyl acetate were used throughout.

Syntheses of surfactants were performed in a CEM Discover microwave reactor using 35 mL microwave reaction tubes with Teflon lids. Scaled-up reactions were conducted in a CEM MARS 6 microwave reactor equipped with a carousel for multiple reaction vessels. All glassware was cleaned in a highly concentrated isopropanol and potassium hydroxide bath and then rinsed with tap water and left to air dry.

Electrospray ionization (ESI) mass spectrometry was performed on a Bruker Compact QTOF Mass Spectrometer. The ionization method used for analysis was positive (or negative) ESI. The sample was introduced by a syringe pump at a flow rate of 3  $\mu$ L/min. The spray voltage applied to the ESI needle was 3.5 kV. The dry gas flow rate was 3 L/min. The nebulizer gas was 0.5 bar, and the source temperature was 180 °C. Nuclear magnetic resonance spectroscopy was performed on a Bruker 300 MHz ultrashield spectrometer and processed using Bruker TopSpin 4.0.6 software.

## METHODS

**Synthesis and Purification of Symmetrical Gemini Amphiphiles.** The detailed procedure for the preparation of 14-4-14 is given below; the other symmetric amphiphiles (8-4-8, 10-4-10, 12-4-12, and 16-4-16) were prepared in a similar manner. *N1,N1,N4,N4*-tetramethyl-*N1,N4*-ditetradecylbutane-1,4-diaminium bromide (14-4-14) was prepared by dissolving 1 equiv 1,4-dibromobutane (1.079 g, 5 mmol) and 2.1 equiv *N,N*-dimethyltetradecylamine (2.535 g, 10.5 mmol) in 10.0 mL of acetonitrile in a 35 mL microwave reaction vessel. The

reaction vessel was then placed in a CEM Discover microwave reactor set at 80 °C, with a pressure tolerance of 15 psi and max power of 30 W and stirred for 30 min following a 15 min ramp time. After microwave irradiation, the reaction vessel was set in a freezer overnight. The resulting precipitate was vacuum-filtered and rinsed with a minimum of cold ethyl acetate. The hygroscopic product was then placed into a vacuum desiccator for 24 h to afford 3.21 g (92.0% yield) of white solid. This yield could be reproduced after repetitive runs of the experiment to within 5% each time (typically >92%). Spectroscopic data for the symmetric amphiphiles are given in the [Supporting Information](#). Recrystallization was performed by dissolving the product in a minimum amount of boiling acetonitrile followed by slow cooling to room temperature and placing it in a refrigerator for 2 days.

**Reaction Procedure for Scaled-Up Synthesis of Symmetric Molecules.** The detailed procedure for the preparation of 14-4-14 at an increased scale is given below; the other symmetric amphiphiles (8-4-8, 10-4-10, 12-4-12, and 16-4-16) can be prepared in a similar manner. *N1,N1,N4,N4*-tetramethyl-*N1,N4*-ditetradecylbutane-1,4-diaminium bromide (14-4-14) was prepared by dissolving 1 equiv 1,4-dibromobutane (1.079 g, 5 mmol) and 2.1 equiv *N,N*-dimethyltetradecylamine (2.535 g, 10.5 mmol) in 15.0 mL of acetonitrile in a 75 mL microwave reaction vessel. This process was repeated for seven additional reaction vessels. The reaction vessels were then placed in a CEM-Mars 6 microwave reactor turntable set at 60 °C, with a pressure tolerance of 15 psi and max power of 15 W and stirred for 30 min following a 15 min ramp time. After microwave irradiation, the reaction vessels were emptied into a 500 mL beaker and set in a freezer overnight. The resulting precipitate was vacuum-filtered and rinsed with cold ethyl acetate. The hygroscopic product was then placed into a vacuum desiccator for 24 h to afford 25.68 g (92.0% yield) of white solid.

## RESULTS AND DISCUSSION

The synthesis of symmetrical gemini surfactants (*m-s-m* type) using microwave heating afforded excellent yields for the series 8-4-8, 10-4-10, 12-4-12, 14-4-14, and 16-4-16 ([Table 1](#)). Given the dipolar character of both reactants and products in these reactions, the use of microwave/dielectric heating was readily facilitated, requiring the use of lower volumes of acetonitrile solvent.<sup>22,23</sup> The resulting isolated yields are far superior (i.e.,  $\geq 85\%$  vs ca. 30%) than those reported earlier in which reactions were refluxed for up to 3 days under conventional conditions.<sup>27</sup> Reactions required far shorter reaction times than earlier reported methods and were completed within 30 min. Products could be easily isolated using suction filtration to afford white solids. The isolated yields of highly pure products were observed to be somewhat dependent on what solvent was used to wash the solids in the suction filter. Whereas some *m-s-m* gemini surfactants could

**Table 1. Synthesis of *N,N'*-Bis(dimethylalkyl)- $\alpha,\omega$ -alkanediammonium Dibromide (m-s-m Type) Symmetric Surfactants**

entry	surfactant (m-s-m)	method	yield (%)
1	8-4-8	RT EtOAc	87
2	10-4-10	cold EtOAc	98
3	12-4-12	RT acetone	92
4	14-4-14	cold EtOAc	92
5	16-4-16	cold EtOAc	83
6	8-6-8	RT EtOAc	88
7	10-6-10	cold EtOAc	98
8	12-6-12	cold EtOAc	92
9	14-6-14	RT EtOAc	96
10	16-6-16	cold EtOAc	96
11	8-8-8	RT EtOAc	89
12	10-8-10	cold EtOAc	89

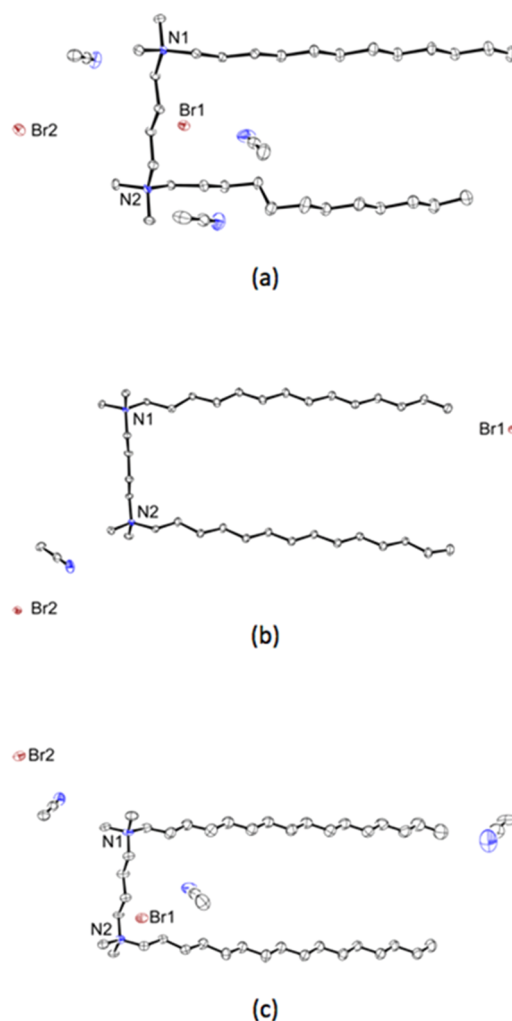
be best washed with cold ethylacetate (Table 1, Entries 2,4, and 5), higher purity of isolated products was obtained when others were washed with room temperature ethylacetate or cold acetone (Table 1, Entries 1 and 3). This can be attributed to the differential solubility of trace unreacted starting materials and by-products under the specified conditions (Table 1).

The microwave methodology described herein was easily extended to the preparation of other m-s-m type gemini surfactants (Table 1, Entries 6–12). In all cases, products were isolated in very good to excellent yields with high purity directly from reactions without further purification. These reactions also required less solvent than previously reported, with far shorter reaction times.

As alluded to in the introduction, gemini surfactants possess several superior properties relative to more typical surfactants with a single hydrophobic tail and a single polar head group. As such, they have attracted much interest for their potential commercial applications as detergents, wetting agents, dispersants, and in nanotechnology. Given the wide range of potential applications, the ability to scale-up the preparation of these m-s-m surfactants is imperative. Hence, a CEM-Mars 6 microwave reactor with capacity for numerous reaction vessels to be accommodated simultaneously was employed to accomplish such a scale-up. Quantities >25 g of the 14-4-14 gemini surfactant were easily prepared using this reactor in a single experimental run. This reactor has the capacity to accommodate additional reaction vessels, allowing for further scale-up where required.

All symmetrical gemini surfactants prepared using this vastly improved microwave methodology were afforded in high purity, as evidenced by their  $^1\text{H}$  NMR spectra and other characterization data obtained for the isolated products without further purification (see Supporting Information). However, crystallographic quality crystals were obtained after recrystallization from dry acetonitrile. Despite having rather long, conformationally mobile alkyl chains, the 12-4-12, 14-4-14, and 16-4-16 gemini surfactants afforded large, clear, and transparent single crystals suitable for X-ray crystallographic analyses.

The X-ray crystal structure for the 12-4-12 gemini surfactant displays one of its C-12 alkyl chains extended as expected, with staggered conformation along its entire length. However, the second C-12 alkyl chain displays a “kink” in the chain between C4 and C5 (Figure 1). The compound crystallizes with

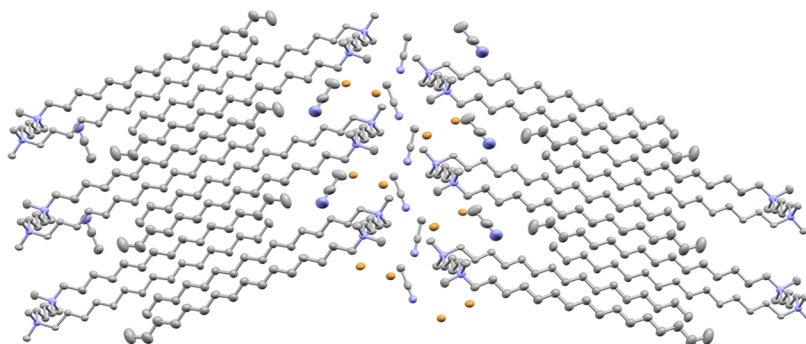


**Figure 1.** Anisotropic displacement ellipsoid drawings of acetonitrile solvates of (a) 12-4-12 ( $R = 5.89\%$ ), (b) 14-4-14 ( $R = 3.04\%$ ), and (c) 16-4-16 ( $R = 9.71\%$ ) at the 50% probability level.

acetonitrile solvent molecules in the lattice structure separating polar head groups between parallel arrays of interdigitated surfactant molecules. This is clearly shown in the lattice structure for the 16-4-16 gemini surfactant (Figure 2). The lattice structure shows the interdigitation of the two C16 chains, while the bromide counter ions align in proximity to the ammonium nitrogen atoms in the polar head groups. The lattice structures demonstrate bilayer-like structures with interlocking hydrophobic alkyl tails and polar head groups on adjacent bilayer motifs directed toward each other.<sup>28</sup> The organization of these alternating bilayer appears to be held in position through interactions with bromide counterions and co-crystallized acetonitrile solvent molecules. The 12-4-12, 14-4-14, and 16-4-16 gemini surfactants all display very similar lattice structures, except both the C14 and C16 alkyl chains in these compounds appear in staggered conformations without any kinking.

## CONCLUSIONS

The synthesis of symmetrical m-s-m type gemini surfactants has been accomplished using less energetically demanding microwave heating (relative to conventional, convective heating) to afford products in significantly reduced reaction times in very high isolated yields. This approach requires much



**Figure 2.** Anisotropic displacement ellipsoid drawing of the lattice structure of surfactant 16-4-16 at the 50% probability level.

less solvent to be used and permits facile isolation of products of high purity straight from crude reaction mixtures after adequate washing with an appropriate solvent. Scale-up of this reaction was facilitated using this approach with a bulk microwave synthesizer. Simple recrystallization from dry acetonitrile has afforded single crystals suitable for crystallographic analyses of compounds previously considered resistant to this type of analysis.

Future studies adapting this methodological approach are underway. This procedure eliminates the need to produce a monosubstituted intermediate and the long purification process of the amphiphiles described in earlier reports.<sup>27</sup> Hence, we feel that this methodology will radically improve the preparation of dissymmetric gemini cationic surfactants and other related amphiphiles of industrial and commercial interest. Extension of this methodology to the synthesis of gemini surfactants with varying spacer lengths is also feasible.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.2c05073>.

Experimental procedures, spectral and crystallographic data (PDF)

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## Notes

The authors declare no competing financial interest.

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