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Transforming Anionic Reverse Micelles: The Potential of Hydrophobic Natural Deep Eutectic Solvents. How the Mixture Between Camphor and Menthol Can Be an Excellent Choice for Reverse Micelle Preparation †

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Abstract

Reverse micelles (RMs) are versatile nanostructures traditionally formed in low-polarity organic solvents, but the need for greener alternatives has limited their broader applicability. Here, we demonstrate for the first time that a hydrophobic Natural Deep Eutectic Solvent (NADES), prepared from a simple 1:1 mixture of camphor and menthol (CM), can act as the continuous external phase for RM formation. Remarkably, CM dissolves the benchmark surfactant sodium dioctyl sulfosuccinate (AOT) at concentrations up to 0.5 M without co-surfactants and supports water solubilization up to $W_0 = [H_2O]/[AOT] = 5$, yielding thermodynamically stable systems. 1H and DOSY NMR analyses reveal clear structural rearrangements of the micellar interface, confirm the encapsulation of water in the polar core, and provide quantitative evidence of size modulation as a function of W_0. The resulting CM/AOT/water assemblies represent the first example of NADES-based reverse micelles, offering an easily prepared, sustainable, and biocompatible platform. This breakthrough opens new perspectives for the development of green self-assembled systems with promising applications in areas such as food technology, pharmaceuticals, and nanomedicine.

Keywords: NADES; AOT; reverse micelles; NMR; DOSY; camphor; menthol

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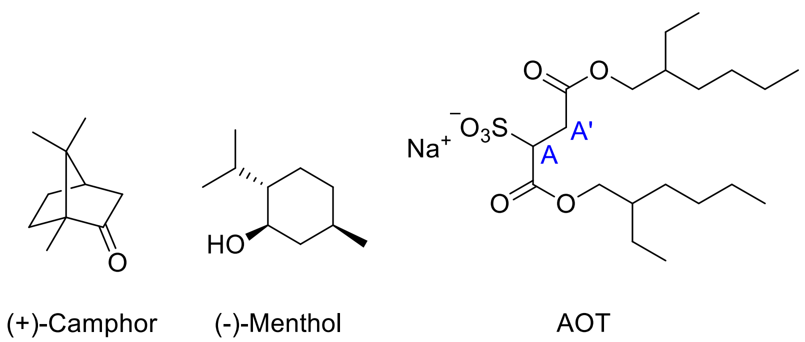
1. Introduction

Reverse micelles (RMs) are nanostructures formed by dissolving surfactants in low-polarity organic solvents. A widely used anionic surfactant is AOT (sodium dioctyl sulfosuccinate), which forms aggregates capable of encapsulating water in their core [1]. The amount of solubilized water is expressed as $W_0 = [H_2O]/[\text{Surfactant}]$. In the context of green chemistry, Natural Deep Eutectic Solvents (NADES), such as the 1:1 mixture of camphor and menthol (CM, Scheme 1), represent a sustainable alternative to conventional nonpolar solvents. Notably, CM exhibits a hydrophobic character, making it a promising candidate to serve as the continuous organic phase in reverse micelle systems.



Scheme 1. Molecular structures of the NADES components (camphor and menthol) and the AOT surfactant. The most relevant hydrogen atoms on AOT are labeled.

In this study, we evaluate the potential formation of RMs using AOT (Scheme 1) as the surfactant, water as the polar component, and CM as the hydrophobic external phase. NMR technique was employed to assess the structural and dynamic features of the resulting systems [2].

2. Experimental Section

2.1. Materials

Sodium 1,4-bis(2-ethylhexyl) sulfosuccinate (AOT) (Sigma, >99% purity) was used as received and kept under vacuum over P_2O_5 to minimize water absorption. Water from Sintorgan (HPLC quality) was used without further purification. The NADES CM was synthesized by weighing appropriate amounts of each component into a 50 mL Erlenmeyer flask. The amounts were adjusted to get the desired molar ratio of components (1:1). After weighing, the Erlenmeyer flask was capped, and the mixture was heated at 60 °C for approximately 30 min to assist the melting process. After melting, the mixture was vortexed for 10 s to ensure a homogeneous liquid.

2.2. Methods

Preparation of CM/AOT RMs Solutions: Stock solutions of AOT in CM were prepared by mass and volumetric dilution. Aliquots of these stock solutions were used to make individual reverse micelle solutions with different amounts of water, defined as W_0 = $[H_2O]/[AOT]$. The incorporation of water into each micellar solution was performed using calibrated microsyringes. To obtain optically clear solutions, they were shaken in a sonicating bath. The resulting solutions were clear with a single phase, and they were used in the NMR experiments. The W_0 was varied between 0–5 for CM/AOT RMs. Higher values of W_0 could not be obtained due to turbidity problems. The lowest value for W_0 (W_0 = 0) corresponds to a system without water addition. It is important to note that, at room temperature, the water solubility in CM is very low.

For the ^{1}H NMR experiments, a Bruker Avance III 400 NMR spectrometer was used. The spectra were recorded at a digital resolution of 0.06 Hz/data point. The temperature of the spectrometer probe was stabilized at 25 °C, as evidenced by consistent measurements of the sample's chemical shift. After allowing 10 min for thermal equilibration, the observed shifts remained within the digital resolution limit. For the study of RMs, a capillary tube containing D_2O was introduced in the NMR tube and was used as a frequency "lock." Chemical shifts were measured relative to the external D_2O, and the values were reproducible within 0.01 ppm.

2D DOSY experiments were carried out on freshly prepared solutions of CM/AOT at different water contents. To ensure locking of the systems, a coaxial tube containing D_2O was employed. For each sample, before running the 2D DOSY experiment, simple 1D

DOSY spectra were recorded in order to optimize the magnetic field pulse gradients (δ) and diffusion time (Δ) values to ensure proper signal abatement during the 2D experiment. All NMR data were processed using MestReNova software.

3. Results and Discussion

To assess the suitability of the new non-polar solvent as the continuous phase for reverse micelle formation, the solubility of the well-known surfactant AOT in CM was examined. The NADES was able to dissolve AOT up to 0.5 M without requiring the addition of a co-surfactant. Moreover, the system proved capable of solubilizing water, reaching a maximum W_0 of 5, and yielding thermodynamically stable solutions.

From the 1H NMR spectra shown in Figure 1, a decreasing trend in the chemical shifts of protons A and A′ of AOT (see Scheme 1) is observed as the water content of the system increases. For instance, proton A resonates at 4.35 ppm at $W_0 = 0$, shifting to 4.26 ppm at $W_0 = 5$. This upfield shift indicates that the environment of the sulfonate group becomes more polar upon water incorporation, likely due to group hydration and a rearrangement of micellar interfacial interactions. These findings highlight how the addition of water modulates different regions of the surfactant and provide further evidence for the formation of a micellar system [3].

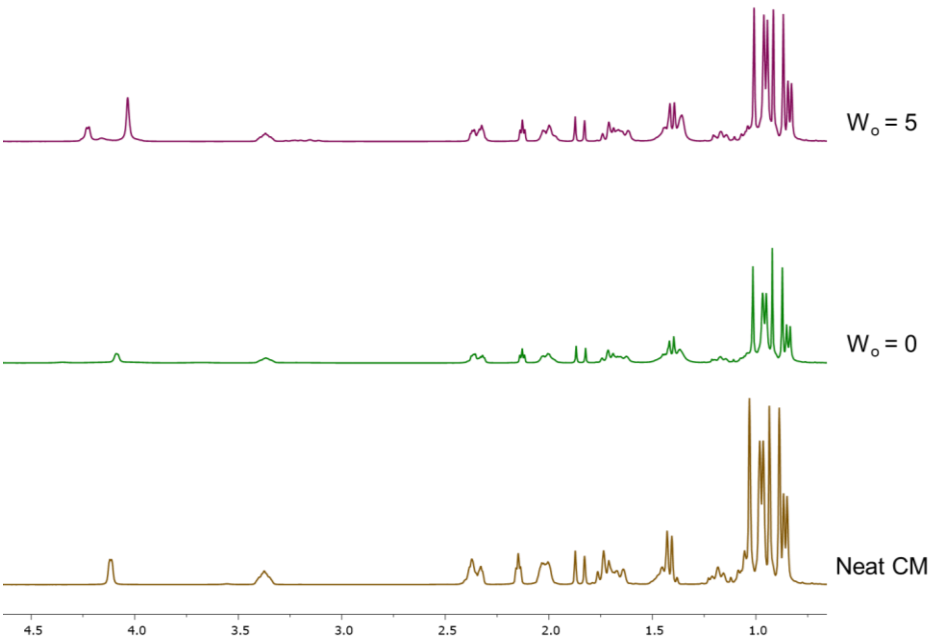


Figure 1. 1H NMR spectra for neat CM and CM/AOT solutions at different W_0. [AOT] = 0.5 M. T = 25 °C.

To further assess the ability of CM to promote AOT reverse micelle formation, DOSY-NMR experiments were performed [4]. Table 1 presents the diffusion coefficients obtained for proton A′ of the AOT surfactant, together with the micellar diameters calculated from these values using the Stokes–Einstein Equation (1). The measurements were carried out at 25 °C, with the viscosity of the CM medium determined to be 20.7 cP.

$$d_{app} = kT/3\pi\eta D \quad (1)$$

where k is the Boltzmann constant, T is the absolute temperature, and η is the solvent viscosity.

Table 1. Diffusion coefficients (D) and micellar diameters (dapp) calculated by DOSY for the CM/AOT/water system.

W_0	D (m^2/s)	dapp (nm)
0	1.80×10^{-11}	1.17
1	1.02×10^{-11}	2.06
2	7.41×10^{-12}	2.84
3	7.01×10^{-12}	3.00
4	6.77×10^{-12}	3.11
5	6.17×10^{-12}	3.41

The micellar diameter ranges from 1.17 nm in the absence of water to 3.41 nm at higher water contents, confirming the formation of larger aggregates. This increase in aggregate size is characteristic of reverse micellar systems, where the polar core expands as more water is incorporated. These results provide quantitative evidence of the self-assembly process in NADES-based RMs and demonstrate that micellar size can be tuned by adjusting W_0.

As part of the characterization, we monitored the water protons entrapped in CM/AOT RMs as a function of W_0. In neat CM, a low-intensity signal appears at 3.55 ppm, corresponding to residual water. Although this NADES is generally considered hydrophobic, this signal reveals that its precursors are capable of weakly interacting with water molecules through the hydroxyl group of menthol and the carbonyl group of camphor, thereby allowing trace amounts of water to be dispersed.

Upon addition of AOT without introducing extra water into the system ($W_0 = 0$), the water signal shifts to 3.67 ppm, indicating a more polar or less shielded environment, likely due to structural rearrangements induced by the surfactant. As the water content increases ($W_0 = 1$–5), the chemical shift of the water protons progressively shifts from 3.79 ppm to 4.03 ppm, suggesting strong interactions with the surfactant at the micellar interface (Figure 2).

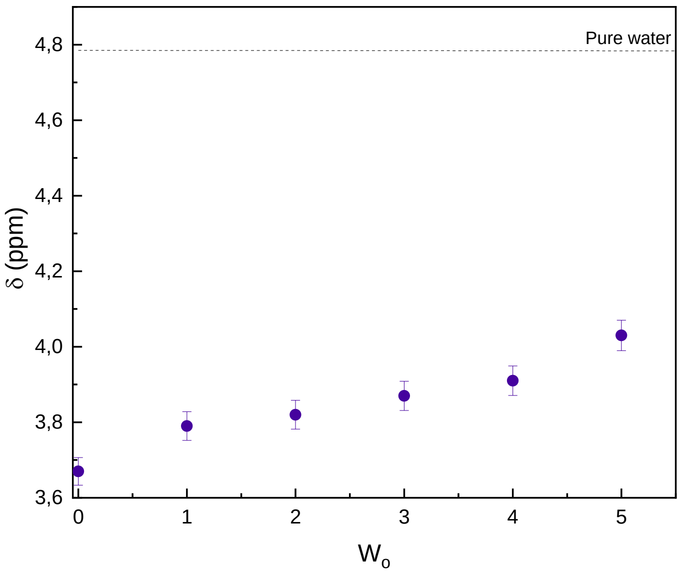


Figure 2. [1]H chemical shift values of entrapped water in CM/AOT RMs as a function of water content. [AOT] = 0.5 M. For comparison, the value of neat water (- - -) is also plotted.

Despite the presence of the hydroxyl group in menthol, no significant interaction with water was observed upon its addition. Both signals remain distinguishable (Figure 1), indicating that water is preferentially located in the polar core of the micelle, more distant from the NADES components, and therefore less available to interact with the hydroxyl group.

The results obtained from 1H and DOSY NMR allowed for a detailed characterization of the CM/AOT/water system. The chemical shifts of water protons, the hydroxyl group of menthol, and the surfactant protons provide clear evidence of structural and environmental changes associated with aggregate growth upon water incorporation. Moreover, the diffusion coefficients and micellar diameters confirm the formation of tunable RMs. The system's ability to encapsulate water, alter its chemical environment, and adjust micellar size through W_0 makes NADES-based RMs versatile platforms with potential applications in diverse fields.

4. Conclusions

This study demonstrates the formation of RMs and provides insights into the interface formed by CM/AOT at varying water contents. We show that RMs can be generated using a hydrophobic NADES, readily prepared, as the nonpolar continuous phase. This finding opens new avenues for the design of biocompatible organized systems, with promising perspectives for future applications in the food industry and medicine.

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Conflicts of Interest: The authors declare no conflict of interest.

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