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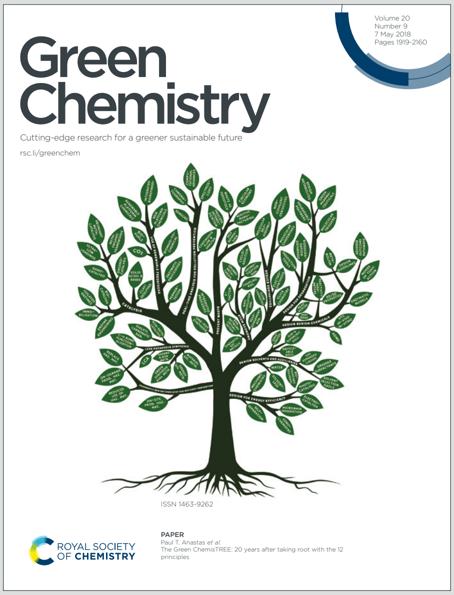

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Article: “Sustainability and Economic Boundaries of Micellar Catalysis in Fine Chemical Synthesis”

Authors: Mert Can Ince and Gianvito Vilé*

1. We present an integrated techno-economic and life-cycle assessment framework quantifying the sustainability and economic viability of micellar catalysis versus conventional solvent-based synthesis. Applied to six C–C coupling reactions, it links surfactant manufacturing and process performance, guiding greener industrial implementation within planetary boundaries.

2. We reveal that raw materials, utilities, and process energy dominate micellar catalysis impacts, contributing ~90% of operational costs and >80% of environmental burdens. Quantified differences in cost (55%), electricity (71%), and water use (41%) pinpoint priority areas for sustainable process optimization.

3. Our process can be further greened through: (i) sustainable surfactant synthesis using bio-based feedstocks, enzymatic or solvent-free routes, and simplified architectures to reduce raw-material intensity and enhance biodegradability; (ii) process intensification via continuous-flow micellar systems and energy-efficient heating; and (iii) closed-loop surfactant recovery and water reuse to minimize waste and resource demand.

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ARTICLE

Sustainability and Economic Boundaries of Micellar Catalysis in Fine Chemical Synthesis

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Aqueous surfactant-based systems have emerged as promising media for fine chemical synthesis, offering a sustainable alternative to traditional organic solvents. In these systems, water serves primarily as a dispersing phase, while chemical transformations take place within the hydrophobic cores of self-assembled micelles that concentrate reactants and catalysts in an organic-like microenvironment. Despite significant progress in this area, most existing studies have focused on the assessment of individual reactions or isolated case studies, often under laboratory conditions. As a result, a comprehensive quantitative evaluation of micellar catalysis across multiple industrially relevant processes has remained elusive. Yet, such a comparative approach is essential to capture the diversity of chemistries, reaction environments, and surfactant systems that define the true potential and limitations of micellar media. Here, we present the first integrated techno-economic and life-cycle assessment comparing six representative industrial processes performed under optimized micellar and conventional conditions. Eighteen environmental impact categories were quantified and interpreted within the planetary boundaries framework, together with key economic indicators such as capital, operational, and raw material costs. While certain organic solvent-based routes currently show lower environmental burdens in specific categories, the analysis identifies the main technological and material hotspots that limit micellar systems today and outlines clear pathways to enhance their sustainability and scalability. Overall, this work establishes a quantitative foundation for guiding the next generation of aqueous micellar processes toward truly sustainable chemical manufacturing.

Introduction

Organic solvents play a key role in fine chemical manufacturing, providing the medium in which chemical transformations take place. Despite their functional importance, they represent a prominent source of environmental concern,[1-3] accounting for approximately 90% of the total waste generated during the synthesis of a typical active pharmaceutical ingredient (API).[4,5] Moreover, a large fraction of solvents, including N,N-dimethylformamide (DMF), dichloromethane (DCM), and toluene, are classified in high-risk category groups for ecosystem and human health.[6] Therefore, the development of environmentally benign methods for API synthesis has become a central focus in the field. Guided by the 12 principles of green chemistry,[7] the use of water as a non-toxic, non-flammable, and cost-efficient solvent has received increasing attention in recent years.[8-11] Water possesses, in fact, excellent physicochemical properties, including a high heat capacity and enthalpy of vaporization that facilitate the regulation of exothermic reactions.[12] Despite these advantages, water remains one of the least utilized solvents in industrial organic chemistry, primarily because many organic molecules are poorly soluble in it. This limited solubility arises from high polarity of water and its extensive hydrogen-bonding network, which favour interactions with hydrophilic species while excluding nonpolar or moderately polar substrates.[13] To overcome the solubility limitations, the formation of micelles through the self-assembly of surfactants in water has emerged as a key strategy to broaden the applicability of aqueous media in organic transformations (**Figure 1a**). These nanostructures create hydrophobic cores capable of solubilizing otherwise water-insoluble substrates, forming microenvironments that mimic organic solvents.[14,15] In doing so, micelles enable a wide range of chemical transformations to proceed under homogeneous conditions. Nonetheless, although this methodology is often promoted as a greener alternative to toxic organic solvents, the environmental impacts associated with the synthesis of surfactant are frequently overlooked. In particular, the potential limited biodegradability of many surfactants, together with increased solvent demands during the work-up phase, raise important questions about the overall sustainability and economic feasibility of the approach.[16]. In this study, we report a first techno-economic analysis (TEA) and life cycle assessment (LCA) of micellar synthesis methods enabled by four commonly

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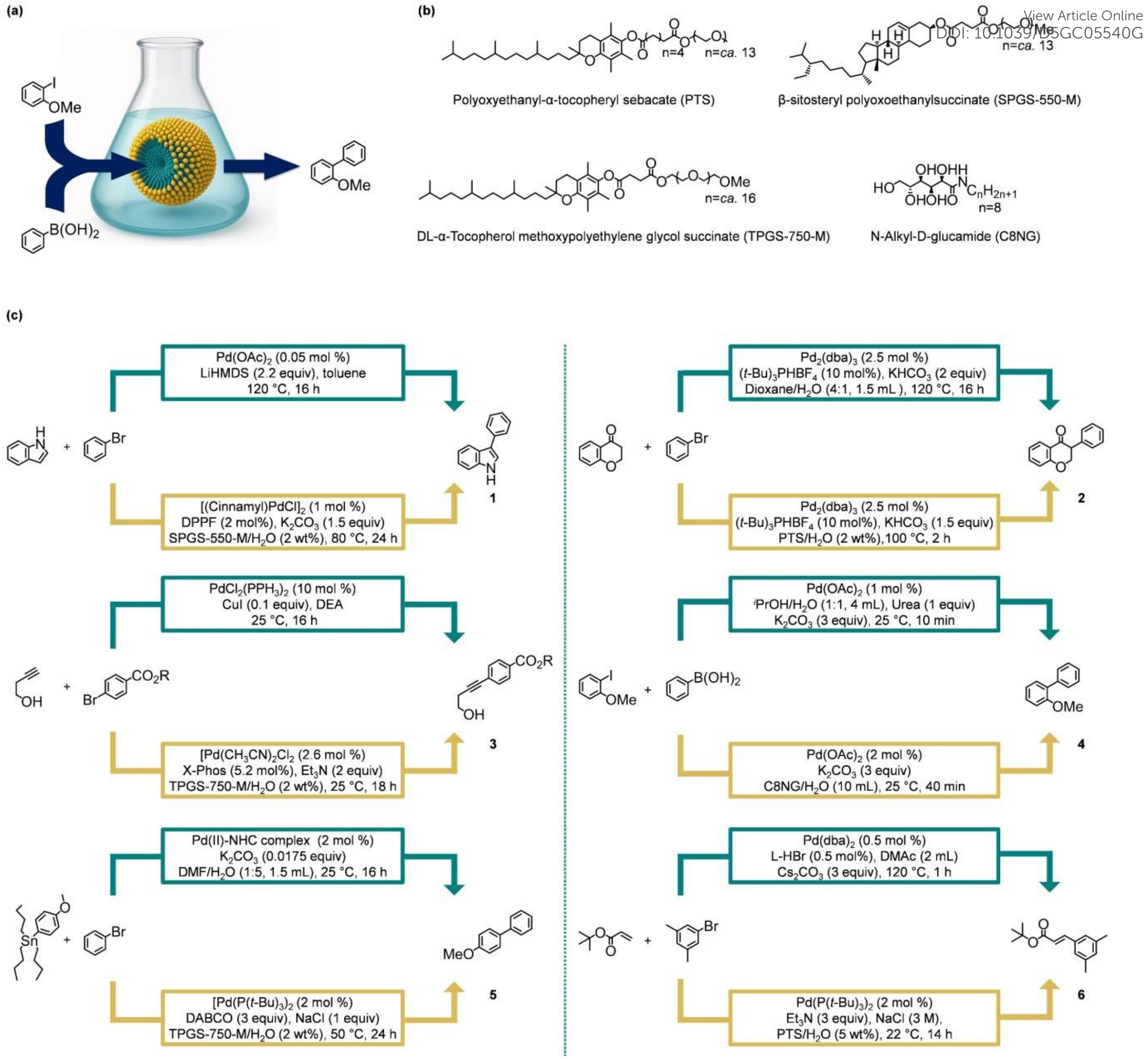

Figure 1. Schematic representation of reactions occurring within the hydrophobic core of surfactant assemblies in micellar catalysis (a). Chemical structures of PTS, SPGS-550-M, TPGS-750-M, and C8NG surfactants (b). Synthesis of 3-phenyl-1H-indole (**1**),[17,18] 3-phenylisocoumarin (**2**),[19,20] 4-(4-hydroxy-1-butynyl)benzoic acid ethyl ester (**3**),[21,22] 2-methoxybiphenyl (**4**),[23,24] 4-methoxybiphenyl (**5**),[25,26] and tert-butyl 3-(3,5-dimethylphenyl)acrylate (**6**),[27,28] performed under conventional organic-solvent conditions (dark green) and in aqueous micellar-based media (dark yellow) (c). Reaction conditions for (c) are reported in the corresponding literature references and in the Supplementary Information.

used surfactants: polyoxyethanyl-*α*-tocopheryl sebacate (PTS), *β*-sitosteryl polyoxoethanylsuccinate (SPGS-550-M), DL-*α*-tocopherol methoxypolyethylene glycol succinate (TPGS-750-M) and *N*-Alkyl-D-glucamide (C8NG) (**Figure 1b**). These surfactants were applied across a diverse array of reaction types, including C_3-arylation, Sonogashira, Suzuki-Miyaura, Stille, and Heck C–C couplings. The findings provide a broader and realistic perspective on the performance, sustainability, and scalability of micellar catalysis, establishing a foundation for targeted improvements toward its industrial implementation.

Results and Discussion

Assessment Framework and Reaction Selection

To enable a robust comparison between micellar and conventional organic solvent-based methods, an integrated TEA and LCA framework was applied to six representative reactions. These include the synthesis of 3-phenyl-1H-indole,[17,18] 3-phenylisocoumarin,[19,20] 4-(4-hydroxy-1-butynyl)benzoic acid ethyl ester,[21,22] 2-methoxybiphenyl,[23,24] 4-methoxybiphenyl,[25,26] and *tert*-butyl 3-(3,5-dimethylphenyl)acrylate.[27,28] For clarity, these compounds are denoted as **1**, **2**, **3**, **4**, **5**, and **6**, respectively (**Figure 1c**). Specifically, all six transformations were selected based on their demonstrated scalability and technological maturity, having reached technology readiness levels (TRL) 5-6 in industrial

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setting. During their industrial implementation, each reaction was independently optimized under both conventional and micellar conditions. We thus considered a single representative value for each process corresponding to its optimized conditions, to enable a fair and realistic comparison of their economic and environmental performance across the respective synthetic contexts. The protocols of the micellar and organic solvent-based reactions were obtained from patent and peer-reviewed literature. As the reader can appreciate, the selected reactions span a range of structurally distinct target molecules, ensuring broad representativeness in terms of reactivity and synthetic relevance. The complete retrosynthetic pathways of PTS,[29,30] TPGS-750-M,[31-33] SPGS-550-M,[34,35] and C8NG[23] were integrated into the study (**Figures 1b-c**, **Figures S1-9**, and **Tables S1-22**), to allow for a holistic evaluation that includes not only reaction performance, but also the upstream impacts of surfactant production.[23]

Economic Performance: CapEx and OpEx Analysis

The capital expenditures (CapEx) for both protocols were quantified across five standard categories comprising equipment, civil, instrumentation, electrical and piping costs, and the results together with key CapEx assumptions are presented in **Figure 2a** and **Table S23-24**. Comparable CapEx were observed for both micellar and organic methods. To explain this outcome, we performed a statistical analysis to investigate the cost distribution characteristics of both approaches, as presented in **Figure 2b**. The statistical analysis conducted in this study was based on comparisons of mean values and their associated standard deviations across the defined scenarios, reflecting the descriptive nature of the limited and heterogeneous data. Yet, variations in CapEx were found to be statistically insignificant. An investigation of the annual operating expenses (OpEx) per kilogram of target product was performed, encompassing cost components such as raw materials, utilities, maintenance, labor, operating charges, plant overhead, and general and administrative (G&A) expenditures (**Figures 2c**, **2d**, and **Table S25**). In this context, we aimed to provide essential insights into the industrial applicability of micellar protocols in comparison to conventional organic solvent-based methods, given that OpEx play a critical role in determining both the economic feasibility and long-term competitiveness of chemical processes at the industrial scale. It was observed that the use of micellar protocol results in annual OpEx between 9,000 € kg$_{\text{product}}^{-1}$ year^{-1} and 230,000 € kg$_{\text{product}}^{-1}$ year^{-1}, with an average OpEx of 65,300 € kg$_{\text{product}}^{-1}$ year^{-1}, whereas the organic solvent-based conditions demonstrated a substantially narrower cost range, from 5,000 € kg$_{\text{product}}^{-1}$ year^{-1} to 80,000 € kg$_{\text{product}}^{-1}$ year^{-1}, with an average of 29,300 € kg$_{\text{product}}^{-1}$ year^{-1}. The most significant reduction relative to the micellar protocol was noted in the organic solvent-based synthesis of **6** by 89% from 47,200 € kg$_{\text{product}}^{-1}$ year^{-1} to 4,900 € kg$_{\text{product}}^{-1}$ year^{-1}. The observed variability in OpEx was attributed to differences in raw material and utility costs, which collectively accounted for *ca.* 90% of total expenses. Building on this analysis, we conducted an evaluation of the contributions from the seven aforementioned OpEx categories to the total expenditures, with the aim of identifying cost-intensive hotspots within the processes, as illustrated in **Figure 2e** and **Tables S26-31**. Among the examined categories, raw material costs emerged as the dominant contributor, accounting for an average of 76% of total OpEx, followed by utility expenses of 14%. We then compared the micellar protocol vis-à-vis conventional organic solvent-based systems in terms of material cost distribution in **Figures 2f**, **2g**, and **Table S32**. Under micellar conditions, raw material costs varied from 7,000 € kg$_{\text{product}}^{-1}$ year^{-1} to 163,000 € kg$_{\text{product}}^{-1}$ year^{-1}, with an average of 47,900 € kg$_{\text{product}}^{-1}$ year^{-1}, while organic solvent-based method led to an average reduction of 52% in cost, with values spanning from 4,500 € kg$_{\text{product}}^{-1}$ year^{-1} to 65,500 € kg$_{\text{product}}^{-1}$ year^{-1} and an average of 22,800 € kg$_{\text{product}}^{-1}$ year^{-1}. The most pronounced reductions in raw material costs were observed for the syntheses of **4**, **5**, and **6** when organic solvents were used. From the economic standpoint, the broader distribution and higher average of raw material costs observed in this analysis highlight a key limitation with respect to the long-term industrial feasibility of micellar methods. Full details of the individual cost breakdowns and specific case comparisons are provided in **Figure 3** and **Tables S33-44**.

Energy Demand and Environmental Impact Assessment

Annual electricity costs were examined for both the micellar and organic solvent-based techniques to highlight differences in energy consumption between the two methodologies (**Figure 4a** and **Table S45**). Throughout the analysis of electricity costs, it was identified that batch duration and the energy demand of the equipment were the principal influencing factors. Energy demand was particularly affected by the reactor volume (**Table S46**). Electricity costs under micellar conditions ranged from 900 € kg$_{\text{product}}^{-1}$ year^{-1} to 11,100 € kg$_{\text{product}}^{-1}$ year^{-1}, whereas the organic solvent-based systems exhibited substantially lower values, ranging from 80 € kg$_{\text{product}}^{-1}$ year^{-1} to 8,400 € kg$_{\text{product}}^{-1}$ year^{-1}, corresponding to an average reduction of 71%. The greatest reduction compared to the micellar protocol was observed in the synthesis of **6**, with electricity costs decreasing by *ca.* 93% as a result of a 14-fold shorter production duration with organic solvent-based conditions. Given the wide variation in electricity costs observed across both methods, a statistical analysis was conducted to assess the significance of these differences (**Figure 4b**), and the analysis supported the significance of the observed patterns. We extended the analysis to the equipment costs, but the variations between the two approaches were not found to be statistically significant, as illustrated in **Figures 4c-d** and **Table S47**. We then conducted an LCA to investigate the environmental impacts of the six reactions in both synthetic approaches, and identify key hotspots for future development. The environmental impact analysis began with the assessment of carbon emissions, in **Figures 4e**, **4f**, and **Table S48**. Given that carbon emissions serve as a one of the indicators of a process's environmental footprint, its quantification provides critical insights into the sustainability of both methodologies. However, no major variability in carbon emissions was observed across both

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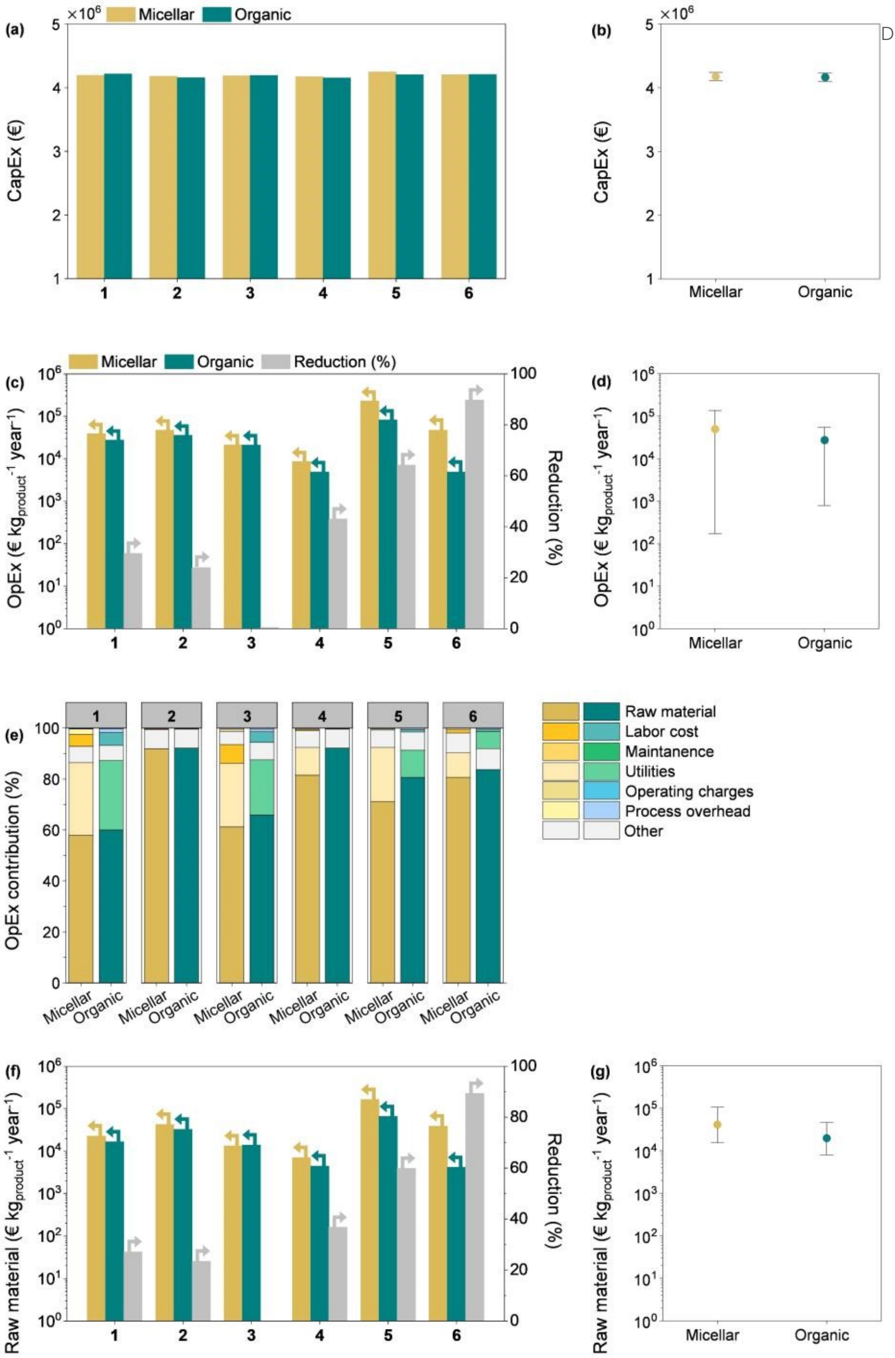

Figure 2. Capital expenditures (CapEx) for the six reactions conducted under micellar and organic-solvent conditions (a). Statistical analysis of the CapEx results (b). Operational expenditures (OpEx) for the six reactions under micellar and organic-solvent protocols (c). Statistical analysis of the OpEx results (d). Comparative illustration of OpEx contributions for micellar and organic solvent-based methods for the six reactions (e). Raw material costs for the six reactions in micellar and organic solvent-based protocols (f), and statistical analysis of the raw material costs results (g). The circle in the statistical analysis in (b), (d), and (g) denotes the mean value, and the whiskers represent ±1 standard deviation.

techniques. While micellar protocol exhibited emissions ranging from 400 kg CO_2 equiv $kg_{product}^{-1}$ to 1840 kg CO_2 equiv $kg_{product}^{-1}$, the organic solvent-based system demonstrated an even broader span, from 120 kg CO_2 equiv $kg_{product}^{-1}$ to 1990 kg CO_2 equiv $kg_{product}^{-1}$. Despite the variability in emissions across both methods, we observed that the use of organic solvent-based systems led to approximately 100 kg CO_2 equiv $kg_{product}^{-1}$ less CO_2 compared to micellar conditions. A component-wise analysis aimed at quantifying the relative environmental advantages and limitations inherent to each methodology is shown in **Figure 5** and **Tables S49-60** for the interested reader. The comparative assessment highlighted that, despite the innovative appeal of micellar media, organic solvent-based systems often yielded less carbon emissions. This finding emphasizes the necessity of holistic environmental evaluations that go beyond solvent identity, particularly for industrial scalability.

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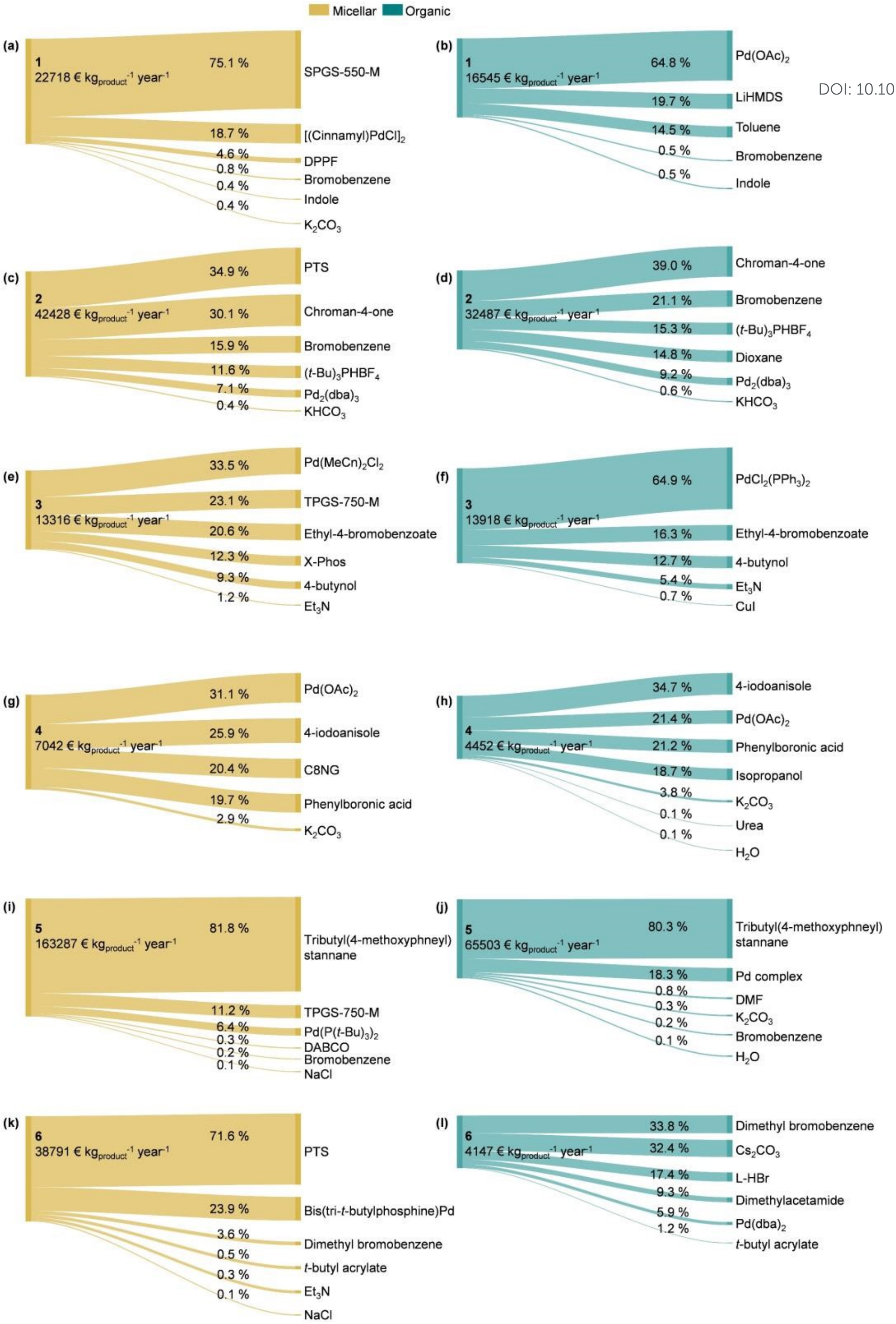

Figure 3. Component-wise raw-material cost analysis for the six reactions performed under micellar conditions (a, c, e, g, i, k) and under organic-solvent conditions (b, d, f, h, j, l). The colour scheme shown in the legend applies to all panels.

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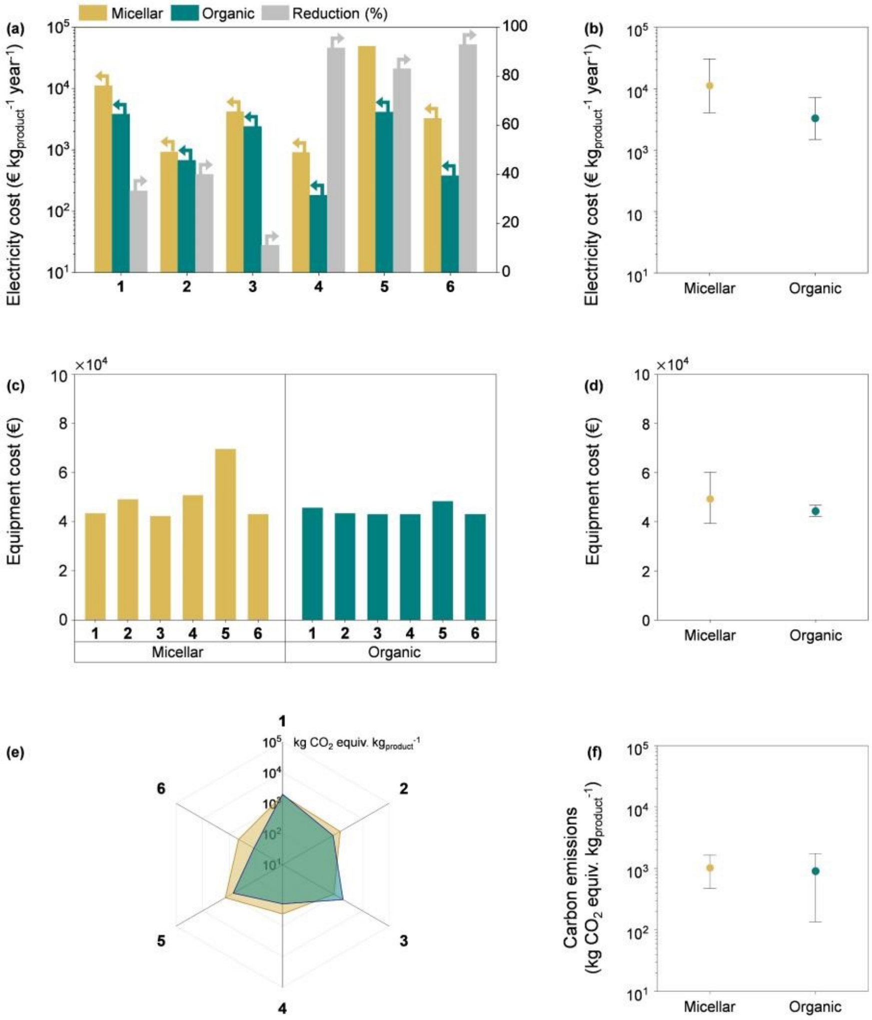

Figure 4. Electricity costs for the six reactions in micellar and organic solvent-based protocols (a). Statistical analysis of the electricity costs results (b). Equipment costs for the six reactions in micellar and organic solvent-based protocols (c). Statistical analysis of the equipment costs (d). Carbon emissions for the six reactions in micellar and organic solvent-based protocols (e), and statistical analysis of the carbon emissions results (f). Colour codes in (a) apply to all. The circle in the statistical analysis in (b), (d), and (f) denotes the mean value, and the whiskers represent ±1 standard deviation.

Life Cycle and Planetary Boundary Assessment

Building on this analysis, we compared both methodologies in terms of water consumption, another key environmental metric that holds industrial relevance, as large-scale consumption can contribute to regional water scarcity, thereby imposing stress on local ecosystems, affecting biodiversity and limiting water availability (**Figures 6a**, **6b**, and **Table S61**). The micellar method resulted in a water consumption range from 20 $\mathrm{m^3\ kg_{product}^{-1}}$ to 190 $\mathrm{m^3\ kg_{product}^{-1}}$. In contrast, the use of more conventional organic solvents introduced a certain variability, with values spanning from 2 $\mathrm{m^3\ kg_{product}^{-1}}$ to 360 $\mathrm{m^3\ kg_{product}^{-1}}$. Throughout the analysis, we observed that, with the exception of the syntheses of **2** and **3**, all other reactions demonstrated a lower water consumption in the case of organic solvents. Finally, the E-Factor serves as a simple metric for approximating the greenness of synthetic systems, as it quantifies the total mass of waste generated per unit mass of the target product ($\mathrm{kg_{waste}\ kg_{product}^{-1}}$).[36] We identified two distinct E-Factor distribution patterns, as shown in **Figures 6c**, **6d**, and **Table S62**. The micellar systems exhibited a broader range, spanning from 5 $\mathrm{kg_{waste}\ kg_{product}^{-1}}$ to 105 $\mathrm{kg_{waste}\ kg_{product}^{-1}}$, while the organic solvent-based systems showed a more confined distribution between 10 $\mathrm{kg_{waste}\ kg_{product}^{-1}}$ and 40 $\mathrm{kg_{waste}\ kg_{product}^{-1}}$. It is critical to highlight that, in this study, the post reaction aqueous phase in micellar reactions was accounted as wastewater within the sustainability evaluation criteria. This decision was based on the consideration that, following the reaction, the aqueous phase typically contains organic residues such as including surfactants, unreacted reagents, and by-products, thus, making its treatment a compulsory process.[37] Finally, a boundaries analysis comprising ocean acidification, biosphere integrity (both functional and genetic), carbon emissions, radiative forcing, atmospheric aerosol loading, land-system change, biogeochemical flows (phosphorus and nitrogen cycles), and freshwater use (both blue and green water) was performed, as

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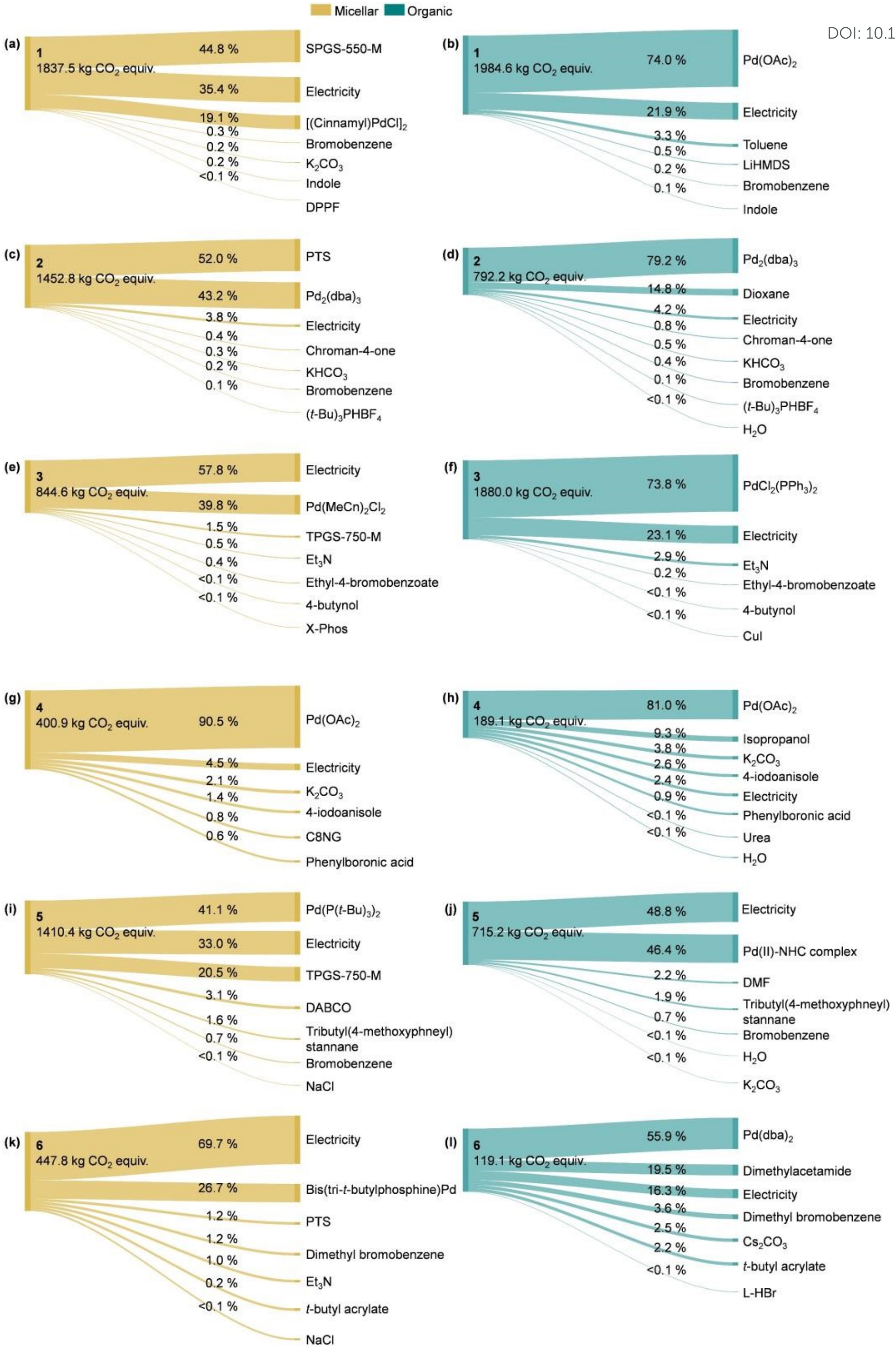

Figure 5. Component-wise carbon emissions analysis for the six reactions performed under micellar conditions (a, c, e, g, i, and k) and under organic solvent conditions (b, d, f, h, j, and l). The colour scheme shown in the legend applies to all panels. The unit kg CO_2 equiv. represents kg CO_2 equiv. $kg_{product}^{-1}$.

illustrated in **Figure 7** and detailed in **Tables S63-74**. This framework has also been utilized in our earlier contributions for the evaluation of synthetic methodologies with respect to global environmental thresholds.[38,39] The most pronounced average reduction among the assessed planetary boundaries were observed in the biogeochemical flows, considering nitrogen (N) and phosphorus (P) cycles, with decreases of 75% and 55%, respectively. This outcome was attributed to the

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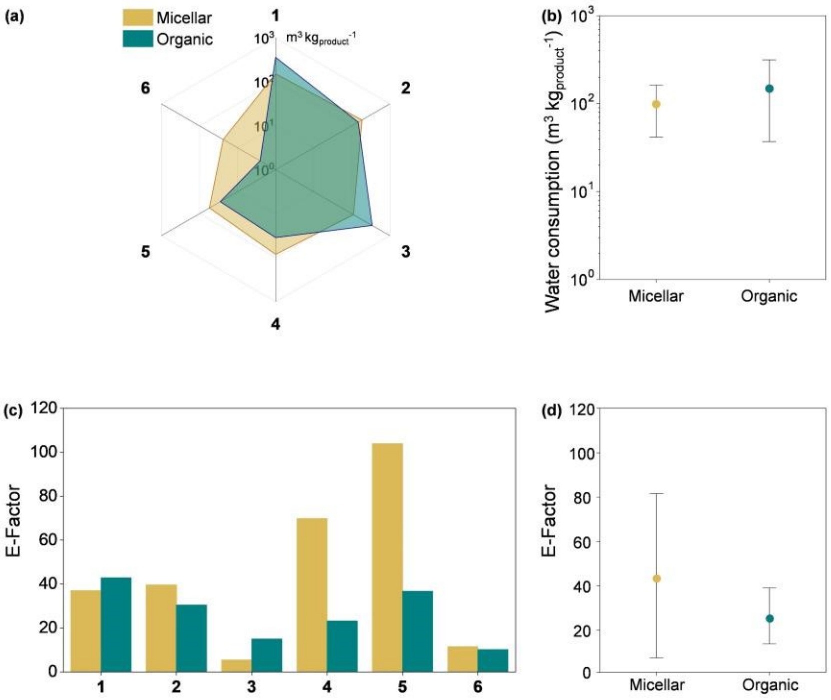

Figure 6. Water consumption for the six reactions in micellar and organic solvent-based conditions (a). Statistical analysis of the water consumption results (b). E-Factor results for the six reactions in micellar and organic solvent-based conditions (c). Statistical analysis of the E-Factor results (d). Colour codes in (a) apply to all. The circle in the statistical analysis in (b) and (d) denotes the mean value, and the whiskers represent ±1 standard deviation.

dominant contribution of the SPGS-550-M surfactant used in the **1** synthesis, accounting for over 90% of the total impact in both the P and N cycles categories. Moreover, the application of the organic solvent-based technique resulted in a notable average reduction of 62% in radiative forcing relative to the micellar approach. The synthesis of **2** exhibited the greatest reduction in radiative forcing *via* utilization of organic solvent protocol, with an average 76% decrease compared to micellar conditions, primarily driven by the replacement of the PTS surfactant with dioxane, which alone accounted for 92% of the total impact in this category. In contrast, we observed a comparatively modest average reduction (*ca.* 20%) in ocean acidification following the utilization of organic solvent-based conditions compared to micellar method. However, a notable case was identified in the synthesis of **4**, where ocean acidification impacts were mitigated by 56%. This significant decrease was largely linked to the higher palladium catalyst loading under micellar conditions. Specifically, $Pd(OAc)_2$ catalyst accounted for 97% of the total impact within this category, corresponding to 4.91 mol H^+ equiv $kg_{product}^{-1}$, whereas the use of organic solvents showed lower acidification potential, ca. 2.07 mol H^+ equiv $kg_{product}^{-1}$ in average. The use of conventional organic solvents during synthesis resulted in average lower genetic and functional biosphere integrity values, respectively. In addition, freshwater change was evaluated to reflect the pressures exerted by chemical manufacturing on global water availability and ecosystem resilience. We proceeded with a comparative analysis across the six synthetic routes, aiming to elucidate how micellar and organic solvent-based systems influence both blue and green water usage. The analysis revealed that the organic solvent-based system resulted in 41% and 37% lower freshwater use impacts than those observed under the micellar method, respectively. Although this difference is reflected in the freshwater indicators, its applicability remains closely linked to water quality. Most micellar catalysis protocols employ purified or deionized water to ensure consistent micelle formation and prevent interference from inorganic salts or organic contaminants. In regions where water availability is limited, water quality can also vary significantly, and this may influence the practical implementation of micellar catalytic systems. Regarding environmental factors such as water hardness, it is known that high concentrations of divalent cations (e.g., Ca^{2+}, Mg^{2+}) can affect the critical micelle concentration and, in some cases, the stability of specific surfactants.[40] However, studies on micellar catalysis have shown that many commonly used designer surfactants (e.g., TPGS-750-M and related amphiphiles) are highly robust and generally tolerate moderate variations in ionic strength without compromising catalytic efficiency.[41] While a systematic investigation of water purity and hardness across different geographical contexts is beyond the scope of the present work, and it is an important aspect for the future implementation of micellar catalysis under resource-limited conditions. Beyond water demand and quality considerations, metal leaching is another critical concern, particularly in the context of industrial-scale fine chemical and pharmaceutical manufacturing, where stringent regulations limit the amount of residual metal allowed in the final product.[42] It is important to acknowledge that micellar systems are not exempt from this challenge: previous studies on related micellar media have reported low (but not entirely negligible) amounts of residual metal both in the isolated products and in the aqueous phase.[43]

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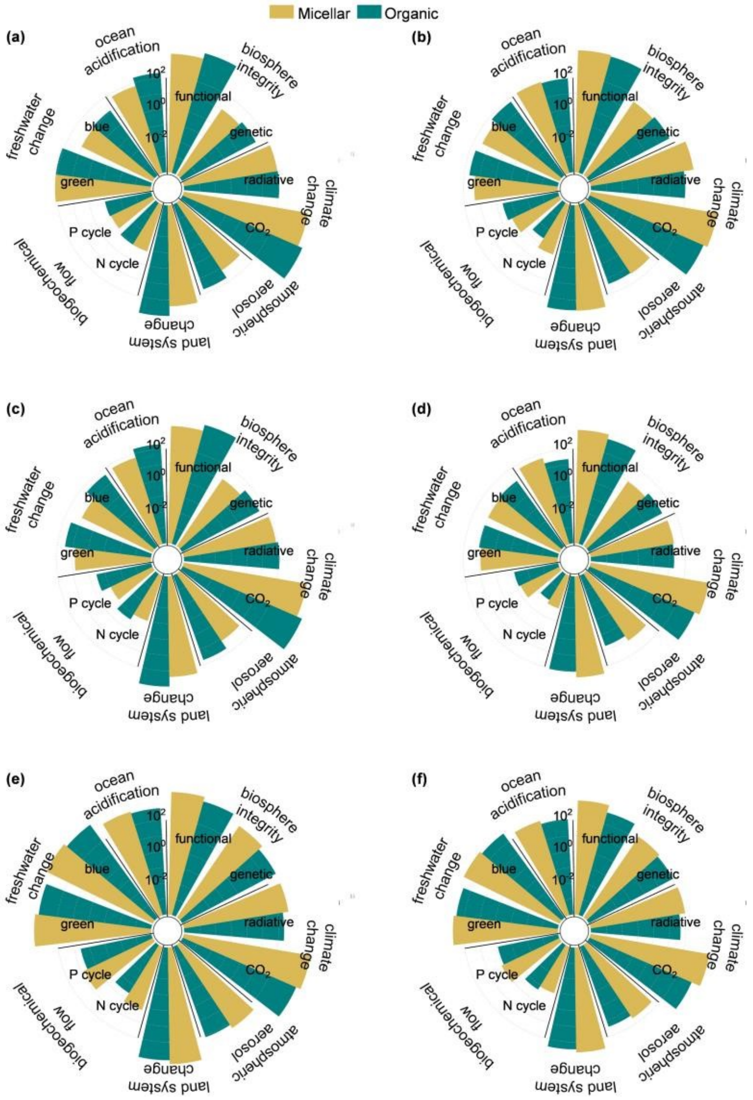

Figure 7. Integrated planetary analysis for the six reactions in micellar and organic solvent-based conditions. The reactions analysed are the ones to obtain **1** (a), **2** (b), **3** (c), **4** (d), **5** (e), and **6** (f).

This confirms that metal leaching does occur, in line with the broader literature. However, a comprehensive investigation of how the leached metal partitions between the organic and aqueous phases, and how this might influence sustainability factors such as catalyst recovery or wastewater treatment, falls outside the scope of the present study. Regarding air quality outcomes, fine particulate matter formation was largely determined by the specific Pd catalysts employed across the six evaluated reactions. Specifically, the major contributors were identified as $[(Cinnamyl)PdCl]_2$in the synthesis of **1** (48%), $Pd_2(dba)_3$ in the route to obtain **2** (80%), $Pd(MeCn)_2Cl_2$ in the **3** synthesis (85%), $Pd(OAc)_2$ for **4** (96%), $Pd(P(t\text{-}Bu)_3)_2$ to make **5** (97%), and Bis(tri-*t*-butylphosphine)Pd to prepare **6** (96%). These findings emphasize the severe environmental impact of platinum-based metal catalysts. In general, we conducted a detailed midpoint-level LCA across aforementioned 18 environmental categories to compare micellar and organic solvent-based systems for the six representative reactions. To further elaborate on these findings and provide a complementary perspective, both micellar and organic solvent methodologies were evaluated across the six processes using an Endpoint-level assessment (**Figure S9** and **Tables S75-86**). Our findings confirmed that, at their current stage, there is further potential in process optimization when exploiting micellar protocols.

To contextualize micellar catalysis within the broader solvent-reduction paradigm, we extended our analysis to mechanochemistry, a complementary strategy that eliminates solvents altogether while pursuing similar sustainability objectives. Both methodologies (micellar catalysis and mechanochemistry) share a common principle: concentrating reactants within confined domains, micelles in aqueous media or molecular contact zones in solid-state mixtures, to achieve enhanced reaction efficiency with minimal solvent waste. Specifically, the synthesis of **4** was comparatively assessed (**Figure S10** and **Table S87**). Despite the elevated energy demand, primarily due to current limitations in scale-up efficiency for kilogram-scale production, mechanochemistry demonstrated a potential for environmental impact mitigation, with reductions observed in carbon emissions (33%), land

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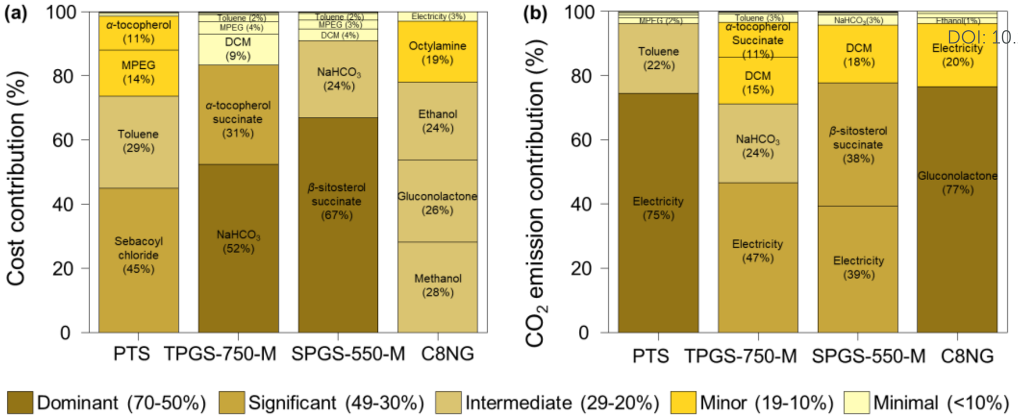

Figure 8. Environmental hotspots in the synthesis of six surfactants used in micellar catalysis. Electricity demand and selected raw materials dominate total impacts, defining the main levers for enhancing the sustainability of aqueous micellar systems.

system change (30%), and carcinogenic toxicity (25%) compared to organic solvent-based system. These findings suggest that micellar catalysis holds strong potential to emulate the sustainability principles of mechanochemistry, inspiring the design of aqueous systems that replicate its solvent-free efficiency through highly concentrated, low-waste reaction environments.

Pathways Towards Sustainable Micellar Chemistry

Although the comparative TEA-LCA framework demonstrated that micellar protocols presently underperform conventional organic solvent-based systems in both economic and environmental dimensions, these outcomes largely reflect the current state of manufacturing technology rather than intrinsic limitations of the chemistry itself. As our analysis showed, manufacturing-related contributions, comprising raw materials, utilities, and process energy, accounted for approximately 90% of total OpEx and more than 80% of the overall environmental burden, underscoring that sustainability gains must be achieved primarily through improvements in how micellar reactions are engineered and manufactured rather than how they are conceptually designed. As illustrated in the previous paragraphs, the pronounced dominance of raw material costs (76% of OpEx) and utility expenditures (14%) highlights the importance of optimizing surfactant production, recovery, and recycling. For instance, SPGS-550-M and PTS alone contributed over 90% of the impacts in the nitrogen and phosphorus cycles and more than 60% of the radiative forcing in certain cases. Moreover, as illustrated in **Figure 8**, electricity demand and selected raw materials dominate total impacts, defining the main levers for enhancing the sustainability of aqueous micellar systems, indicating that greener surfactant synthesis routes, bio-based feedstocks, or simplified molecular architectures could drastically lower both cost and footprint.

From a process standpoint, the data on electricity usage, ranging from 900 to 11,100 € $kg_{product}^{-1}$ $year^{-1}$ under micellar conditions, demonstrates that batch duration and reactor volume drive much of the energy demand. Transitioning to continuous-flow micellar reactors, characterized by enhanced heat and mass transfer and shorter residence times, could reduce energy intensity by an order of magnitude, in line with the 14-fold shorter cycle time already observed under optimized organic solvent-based conditions for synthesizing **6**.[38] Moreover, process intensification through inline emulsification,[44-46] static mixing,[47] and microstructured[48] reactors can minimize solvent and surfactant inventories, while closed-loop aqueous phase recovery systems would drastically reduce wastewater volumes currently counted in the E-Factor.

Collectively, these insights suggest that micellar chemistry is critical towards sustainable and competitive manufacturing platform. However, through redesign of surfactant life cycles, process electrification, and adoption of continuous, digitally optimized, and circular production models, the economic and environmental gaps observed in this study could be narrowed, transforming micellar catalysis from a potential innovation into an industrially viable, scalable, and low-impact technology for next-generation sustainable manufacturing.

Conclusion

We have assessed a diverse set of reactions, comparing micellar and organic solvent-based methodologies in terms of economic and environmental impacts. Micellar processes displayed average operating expenditures (OpEx) of 65,300 € $kg_{product}^{-1}$ $year^{-1}$, compared with 29,300 € $kg_{product}^{-1}$ $year^{-1}$ for optimized organic solvent systems. The difference was primarily driven by raw material costs (76±8 % of OpEx), and largely attributable to surfactant synthesis. Nevertheless, the comparable capital costs (CapEx) and robust reaction performance at TRL 5-6 highlight that micellar systems are already technically mature and scalable. Importantly, micellar media demonstrated competitive performance in several categories, achieving up to 41% lower water consumption and 20% smaller ocean acidification footprints in selected cases.

Across all reactions, life-cycle greenhouse gas emissions averaged 100 kg CO_2 equiv $kg_{product}^{-1}$ higher under current micellar conditions, but sensitivity analysis indicated that a 60% reduction in surfactant footprint or a tenfold productivity increase would reverse this balance. Transitioning to

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continuous-flow micellar reactors, capable of reducing residence times by an order of magnitude, combined with 80% recovery and reuse of the aqueous phase could lower total OpEx below 30,000 € $kg_{product}^{-1}$ $year^{-1}$ and cut life-cycle emissions to < 500 kg CO_2 equiv $kg_{product}^{-1}$.

These quantitative insights demonstrate that the sustainability gap between micellar and conventional routes is not intrinsic but technological. By redesigning surfactant synthesis from renewable feedstocks, electrifying and digitizing production, and adopting circular water and material management, micellar catalysis can evolve from an emerging green concept into a fully deployable, low-impact manufacturing strategy. The framework presented here provides both the data foundation and the strategic direction to accelerate this transition toward truly sustainable aqueous-phase synthesis at industrial scale.

Methods

Techno-Economic Analysis

To evaluate the financial viability of the investigated synthetic routes, a techno-economic framework was developed using Aspen Plus® V11 software.[49] Each process simulation was designed to operate under steady-state conditions, enabling consistent comparison across different operations. A stoichiometric reactor model was employed, integrated with fractional conversion approach to reproduce the performance derived from experimental data. Physical and thermodynamic properties of all reactants and products were sourced from built-in Aspen databases (APV110, APESV110, and NISTV110)[50] to ensure accurate phase and energy behaviour modelling. Process energy demand was quantified by incorporating electricity consumption as a defined utility input. Unit electricity prices used for the economic analysis were obtained from the European Commission's 2025 report on energy prices and costs in Europe, specifically referring to rates for industrial consumption.[51] Economic outputs such as CapEx and operating expenditure (OpEx) were computed *via* the Aspen Process Economic Analyzer (APEA) module, enabling standardized economic comparison across all processes.[52] To determine material expenses, raw material unit prices were referenced from the Merck commercial database, reflecting current market values.[53] Sensitivity and uncertainty analyses of the TEA and LCA simulations are presented in **Figure S11**.

Life-Cycle Assessment

The life-cycle analysis was performed using SimaPro® V10.1.0.4 software, adopting a cradle-to-gate system boundary and a cut-off approach.[54-56] The LCA simulations were conducted employing a functional unit of 1 kg product manufacturing scale. Material flows for each component were normalized to 1 kg of product, consistent with the process operating parameters, to ensure comparability across techniques (**Tables S88-99**). The system boundary was defined from the extraction of raw materials to the production of the target compound, excluding disposal and recycling stages. To evaluate the micellar and organic solvent-based processes from a comprehensive perspective, both midpoint- and endpoint-level characterization methods were carried out. The environmental impact assessment simulations were performed employing ReCiPe 2016 Midpoint (H),[57] ReCiPe 2016 Endpoint (H), [57] and Environmental Footprint 3.1 methodologies.[58] These methods enabled us to investigate the processes from 18 midpoint and 3 endpoint categories. Consequently, selected midpoint categories were mapped onto the nine Planetary Boundaries (9PB) framework,[59] covering as ocean acidification, biosphere integrity (genetic and functional), climate and radiative forcing, atmospheric aerosol loading, land-system change, biogeochemical flows (phosphorus and nitrogen cycles), and freshwater use (green and blue water). More precisely, subcategories of ReCiPe 2016 Midpoint (H)[57] method were utilized to construct the following boundaries, climate change (*via* global warming potential and ionizing radiation), atmospheric aerosol loading (*via* fine particulate matter formation), land-system change (*via* land use), biogeochemical flows (*via* freshwater and marine eutrophication), freshwater change (*via* freshwater and marine ecotoxicity), and biosphere integrity (*via* carcinogenic toxicity, mineral and fossil resource depletion, terrestrial acidification, and ozone formation). Additionally, Environmental Footprint 3.1 method was used to determine the ocean acidification boundary. Lastly, the ReCiPe 2016 Endpoint (H) methodology was employed to quantify environmental damage across human health, ecosystems, and resources. Life cycle inventory (LCI) data for all relevant material and energy flows were sourced from the Ecoinvent v3.1 database[60]. For material selection, The modelling was performed within a European geographic context. Accordingly, European {RER} providers were used if available; if not, the corresponding global {GLO} datasets were applied. All process-specific energy demands were obtained directly from Aspen Plus® V11 simulations to ensure consistency between process modelling outputs and environmental impact quantification.[49] Electricity was modelled as medium-voltage {EU+EFTA+UK} supply.

Author contributions

GV conceived and designed the study. MCI performed the techno-economic analysis, life-cycle assessment, and the integrated planetary analysis. MCI and GV wrote the manuscript. All authors gave approval to the final version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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Data Availability Statement

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The data supporting this article have been included as part of the Supplementary Information.