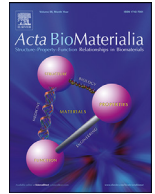




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Conformationally flexible core-bearing detergents with a hydrophobic or hydrophilic pendant: Effect of pendant polarity on detergent conformation and membrane protein stability

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ABSTRACT

Membrane protein structures provide atomic level insight into essential biochemical processes and facilitate protein structure-based drug design. However, the inherent instability of these bio-macromolecules outside lipid bilayers hampers their structural and functional study. Detergent micelles can be used to solubilize and stabilize these membrane-inserted proteins in aqueous solution, thereby enabling their downstream characterizations. Membrane proteins encapsulated in detergent micelles tend to denature and aggregate over time, highlighting the need for development of new amphiphiles effective for protein solubility and stability. In this work, we present newly-designed maltoside detergents containing a pendant chain attached to a glycerol-decorated tris(hydroxymethyl)methane (THM) core, designated GTMs. One set of the GTMs has a hydrophobic pendant (ethyl chain; E-GTMs), and the other set has a hydrophilic pendant (methoxyethoxymethyl chain; M-GTMs) placed in the hydrophobic-hydrophilic interfaces. The two sets of GTMs displayed profoundly different behaviors in terms of detergent self-assembly and protein stabilization efficacy. These behaviors mainly arise from the polarity difference between two pendants (ethyl and methoxyethoxymethyl chains) that results in a large variation in detergent conformation between these sets of GTMs in aqueous media. The resulting high hydrophobic density in the detergent micelle interior is likely responsible for enhanced efficacy of the M-GTMs for protein stabilization compared to the E-GTMs and a gold standard detergent DDM. A representative GTM, M-GTM-O12, was more effective for protein stability than some recently developed detergents including LMNG. This is the first case study investigating the effect of pendant polarity on detergent geometry correlated with detergent efficacy for protein stabilization.

Statement of significance

This study introduces new amphiphiles for use as biochemical tools in membrane protein studies. We identified a few hydrophilic pendant-bearing amphiphiles such as M-GTM-O11 and M-GTM-O12 that

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