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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

Aiman Sadaf[a], Seonghoon Kim[b], Hyoung Eun Bae[a], Haoqing Wang[c], Andreas Nygaard[d], Yuki Uegaki[e], Yang Du[c], Chastine F. Munk[d], Satoshi Katsube[e], Hyun Sung Lee[a], Jungnam Bae[h], Chul Won Choi[h], Hee-Jung Choi[h], Bernadette Byrne[g], Samuel H. Gellman[f], Lan Guan[e], Claus J. Loland[d], Brian K. Kobilka[c], Wonpil Im[i], Pil Seok Chae[a,*]

[a] Department of Bionano Engineering, Center for Bionano Intelligence Education and Research, Hanyang University, Ansan 155-88, South Korea
[b] School of Computational Sciences, Korea Institute for Advanced Study, Seoul 02455, South Korea
[c] Department of Molecular and Cellular Physiology, Stanford University, California 94305, USA
[d] Department of Neuroscience, University of Copenhagen, Copenhagen, DK-2200, Denmark
[e] Department of Cell Physiology and Molecular Biophysics, Center for Membrane Protein Research, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, 79430, USA
[f] Department of Chemistry, University of Wisconsin, Madison, Wisconsin, 53706, USA
[g] Department of Life Sciences, Imperial College London, London SW7 2AZ, UK
[h] Department of Biological Sciences, Seoul National University, Seoul 08826, South Korea
[i] Department of Biological Sciences, Chemistry, and Bioengineering, Lehigh University, Bethlehem, PA 18015, USA

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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 (methoxyethoxylmethyl 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 methoxyethoxylmethyl 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

* Corresponding author.
E-mail address: pchae@hanyang.ac.kr (P.S. Chae).

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