Effects of TMAO on the conformation of poly-peptides and its implication for protein folding

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Trimethylamine N-oxide(TMAO) is a small molecule that accumulates in cells in response to osmotic stresses accounting for an increase in the stability of native protein conformations. Deciphering how TMAO affects protein conformation at the molecular level may lead to new strategies to design drugs that can avoid protein misfolding related to degenerative diseases. This remains a question of debate. Here, we provide a systematic investigation of the effects of TMAO on deca-homopeptides made of glycine, alanine, valine and leucine. These peptides exhibit different levels of hydrophobicity. Consistent with the observed weakening of hydrophobic interactions by TMAO *[Rani, Anjeeta, et al.Scientific reports 6 (2016)],* we find that TMAO induces swelling of the most hydrophobic peptides made of valine and leucine. We also study effects of TMAO on model non-polar peptides for which terminal residues are charged: $A\beta_{16\text{-}22}$, Lys-Leu_5-Glu and Lys-Val_5-Glu. These peptides become more compact in the presence of TMAO compared to pure water. These simulations lead to the hypothesis that effects of TMAO on protein stability emerge to the competition of weakened hydrophobic interaction and strengthened charged residue interaction. To test this hypothesis, we performed replica exchange molecular dynamics simulations of the Trp-cage miniprotein in pure water and aqueous TMAO solutions. Consistent with our hypothesis, we observe that the addition of TMAO molecules accounts for an increase in the radius of gyration of hydrophobic core of Trp-cage while the distance between charged residues decreases.

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