

Hofmeister Series of Ions: A Simple Theory of a Not So Simple Reality

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Editorial

In their Perspective¹ based on recent work of the group,² Xie and Gao outline a simple theory for rationalizing the specific effects of ions on proteins, i.e., the Hofmeister series.³ Their approach is thermodynamic, based on activity coefficients, surface tension and solubility data. It is also systematic, detailing individual contributions to the overall protein salting-out/salting-in and stabilizing/destabilizing action of salts and osmolytes. In particular, the authors choose to focus on the effects of interactions of ions with the protein backbone and on ion pairing in the solution.

Traditionally, the Hofmeister series, the original version of which is depicted in Figure 1, has been rationalized in terms of the ability of certain ions (kosmotropes) to organize water molecules and the lack thereof for other ions (chaotropes).⁴ Such a long-range water ordering contradicts, however, observations on salt solutions from modern spectroscopic measurements and molecular dynamics simulations, which point to a local influence of ions on water.^{5,6} Moreover, the traditional approach leaves a key player – the protein itself, completely out of the picture. As a result, it does not allow for explanation why salting out of some proteins (most notably lysozyme at low to normal pHs and up to moderate salt concentration) follows a reversed rather than normal Hofmeister ordering.⁷

Within the approach of Gao et al. the protein is explicitly brought into play in terms of its surface functional groups interacting with salt ions from the solution. This is consistent with modern

thermodynamic approaches to modelling of the Hofmeister phenomena.⁸ The most significant advance made by Gao et al. is the explicit inclusion of ion pairing into the thermodynamic model. This allows including counter-ion effects, typically neglected when the Hofmeister effects of salts are separated into independent cationic and anionic contributions. As a result, Gao et al. are able to account at least qualitatively for many of the experimental and computational observations on the Hofmeister effects, namely, how salts (and osmolytes) affect solubilities of various solutes.

In order to keep their model easily tractable, Gao et al. deliberately opt for several simplifications. First, for the protein they include only the backbone, neglecting the effects of the side chains. This may be in line with earlier models,⁹ nevertheless, recent studies point to the fact that the protein backbone and the side chains play comparable roles in the Hofmeister phenomena.^{10, 11} Second, the authors invoke a rather cartoonish models of hydrogen bonding (Figure 3 in their Perspective¹) and ion pairing (the so called “law of matching water affinities”¹²) which, e.g., leads them to a somewhat oversimplified conclusion that only the C=O groups are important for interactions of ions with the protein backbone while the effects of the N-H groups could almost be neglected.¹³ The good news is that the resulting model is simple and straightforward. The not so good news is that by leaving out important parts of the puzzle, the model is necessarily only of a limited predictive power. But this is the price for a simple theory of a not so simple Hofmeister reality.



Figure 1: The original anionic series, as depicted on a commemorative plaque on the building of the Medical faculty of the Charles University in Prague, where Hofmeister conducted his pioneering experiments on salting out egg-white proteins in the 1880s.

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