Current Opinion in Colloid & Interface Science 22 (2016) 80–87

Contents lists available at ScienceDirect

Current Opinion in Colloid & Interface Science

journal homepage: www.elsevier.com/locate/cocis

Macromolecular compaction by mixed solutions: Bridging versus depletion attraction

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ARTICLE INFO

Article history:
Received 13 February 2016
Received in revised form 26 February 2016
Accepted 27 February 2016
Available online 10 March 2016

Keywords:
Preferential inclusion
Preferential exclusion
Excluded volume
Soft interactions
Correlations
Adsorption
Cononsolvency

ABSTRACT

From colloidal dispersions to solvated polymers or proteins, solution composition is known to strongly influence the stable state of the bathing macromolecules. Mixed solvents containing species with different affinities to specific macromolecular states can shift equilibrium towards the thermodynamically preferred state with lower free energy, even when the molecular interactions with the solvent are weak. We review two known mechanisms, bridging and depletion attraction, and discuss how each can emerge, depending on the molecular size and interaction of the mixed solvent species. We show that simple theoretical considerations predict that the macromolecular state that is stabilized by each mechanism possesses unique structural properties, as well as distinct thermodynamic fingerprints. Furthermore, we demonstrate the mechanistic role of enthalpy and entropy, as seen in a simple mean field model of macromolecules in mixed solvents. These thermodynamic contributions determine the temperature dependence of cosolute induced effects. Finally, we review the possible role of fluctuations, and point to possible implications and open questions.

1. Introduction

Key in many colloidal and polymer applications is the ability to modulate and control the stable state of macromolecules in solution. Examples include tailored colloidal suspensions or stabilized polymeric dispersions, and the design of new materials that can respond to their environment [1,2]. To achieve this aim, varying solution conditions (by adjusting pH, salt, or other solute concentrations) is often the most simple and straightforward [3,4]. A pervasive example is the use of amphiphilic molecules that favor specific interfacial compositions to dissolve colloids. Interestingly, evolution has allowed nature similar yet highly refined control over biological macromolecular states, such as protein conformations, through finely tuned cellular compositions [5].

Here, we discuss the effect of solutes added to solution on the conformational stability of macromolecules or colloids. We focus on the regime of relatively weak interactions that act at short distances; the case of strong cosolute–macromolecule interactions, such as ions acting on macroions through electrostatic forces, has been previously extensively reviewed, see for example refs. [6••,7]. And yet, as we demonstrate, the two regimes share some mechanistic similarities, and informative links can be made between analogous phenomena.

There are two extreme ways by which added solutes can modify the thermodynamic stability of macromolecules in solution. Both mechanisms are directly related to the excess or deficit of added solute (often referred to "cosolvent" or "cosolute") at the macromolecular interfaces, as described by the Gibbs adsorption isotherm [8–10]. This interfacial adsorption refers to the result of the complex interactions between cosolute, solvent, and macromolecule, and is influenced by cosolute structure and excluded volume [11•–14].

The first of the two mechanisms acts when the cosolute shows a higher affinity towards one of the macromolecular states, and subsequently stabilizes that state. This constitutes adsorption-like behavior of the binders, with an expected free energy change that will be roughly linear in solute chemical potential [9••]. Many drugs act this way at their protein target, thus favoring specific conformational states that, according to their prescribed action, are more active or inactive. Analogously, polymer collapse [15–19•] or colloid assembly [20–22••] in mixed solvents can be driven by binding and, in some cases, by the cross-linking or "bridging" of distant parts of macromolecular interfaces by one of the solution components, Fig. 1A. A prominent example, which has recently attracted significant interest, is the collapse of polymers such as PNIPAm in mixed aqueous solvents such as water-alcohol or water-urea. Although both solvents act as good solvents to the polymer, with increasing cosolute concentration at a given temperature, the polymer chain first collapses and then reswells at higher cosolute concentrations, an effect termed "cononsolvency" [17••–19•,23–32]. Of note is some degree of confusion in the literature concerning related nomenclature; we shall use the term "bridging" solely to mean that the cosolute mediates an effective attraction between distant macromolecular parts by virtue of its presence in the intervening space.

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http://dx.doi.org/10.1016/j.cocis.2016.02.010
1359-0294/

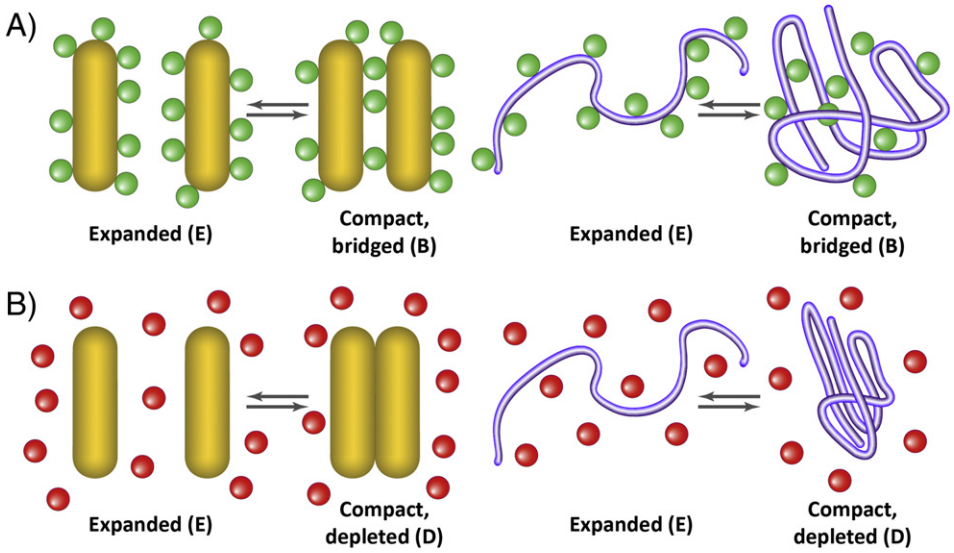

Fig. 1. Schematic of cosolute effects on macromolecular interactions for two types of systems: Rod-like colloid dimerization (left), and polymer collapse or protein folding equilibrium (right). (A) Preferentially excluded cosolutes (red spheres) stabilize the dimer or the compact, folded, state of the protein or polymer (D state) with respect to the expanded state (E state) through depletion attraction (B) Preferentially included cosolutes (green spheres) can stabilize either the two separate monomers (expanded state, E) or another compact state (the compact bridged state, B) mediated by bridging attraction.

The second mechanism constitutes an alternative strategy to preferential adsorption. If a cosolute is more strongly excluded from one macromolecular state, then that state will be destabilized, thereby effectively stabilizing other macromolecular states. It may be useful here to think about the solvent as the preferentially adsorbed species (e.g., preferential hydration in aqueous solutions), with the result that free energy changes are roughly linear in cosolute concentration [9••]. The mechanism by which excluded solutes lead to effective attraction between macromolecules is termed the depletion interaction, Fig. 1B [33]. Examples of depletion interactions range from protein stabilization by osmolytes under cell-like conditions to colloidal flocculation or precipitation in solutions that contain excluded cosolutes such as salt or other polymers [1,34]. Interestingly, the effect of salts on solvating ("salting in") or precipitating ("salting out") macromolecules has been known for over a century to depend sensitively on the ions' identity, as described by the Hofmeister series.[7,35] The Asakura-Oosawa theoretical model of depletion attraction suggests that reduced excluded volume in compacted macromolecular states results in added entropy to solute molecules, thereby stabilizing the compact state [36•,37]. To contrast, recent experiments as well as theoretical considerations indicate that the mechanism can often be driven by enthalpic terms that originate in the solute-interface interactions [34,38–43].

Stabilizing cosolutes typically act between these two extreme scenarios, bridging or depletion attraction, with resulting adsorption isotherms that do not completely conform to either. Variations in cosolute-macromolecular affinity accordingly alter the resulting effective macromolecular interaction, Fig. 1 [42–44•]. Strongly attractive cosolute-macromolecule interactions will lead to bridging between or within macromolecules. Less attractive cosolute–macromolecule interactions will stabilize the extended macromolecular state or denature proteins. Even more weakly attractive (or repulsive) cosolute–macromolecule interaction will induce effective attractive depletion forces between or within macromolecules.

Over the past couple of decades, significant advances have been made in describing the effect of mixed solutions on macromolecular or colloidal interactions, as long as the cosolute interactions with the macromolecular interfaces are not weak. For example, similarly electrostatically charged colloids or polyelectrolytes, can be bound by the bridging attraction exerted by small, oppositely charged polyvalent ions or by polyelectrolytes that span the intervening space [45–50]. This macromolecular compaction is often accounted for within electrostatic theory by the strong coupling regime, which describes the concerted action of bound ions that are strongly correlated at the two apposed macromolecular interfaces. Polyelectrolyte bridgers added to solutions of oppositely charged colloids can add a degree of complexity, since these polymers can in addition deform and reshape in order to optimize interfacial contacts [6••,51–53]. In simple terms, the thermodynamic advantage of bridging can be explained by the energetically favorable higher coordination of each ion to the two apposed surfaces, while still allowing some residual entropy of adsorbed species, too. The result is a compaction of the now crosslinked polymer, or precipitation of bridged colloids. This attraction between similarly charged macroions in the presence of oppositely charged ions has been described to result from correlated counterion environments on the two macroions, or a Wigner-Seitz crystal [54–57••].

In contrast to the depletion forces that favor states that minimize interfacial exposure, thereby tending to stabilize the most compact macromolecular states, bridging attraction favors the formation of locally bound sites between or within macromolecules. Importantly, bridging and depletion interactions not only stabilize specific macromolecular states, but in the process can also alter the structure of the equilibrium states themselves. Thus, depending on their particular interactions, cosolutes favor and select different macromolecular conformations [44•,58]. For example, the cosolute-decorated state of a polymer at high cosolute concentrations differs both structurally and thermodynamically from the bare polymer state in the pure solvent [44•]. With analogy, the equilibrium ensemble of folded or unfolded proteins in the presence of denaturants such as guanidinium could be different from their structure in pure water [59,60]. Thus, importantly, the compacted state stabilized by bridging need not be the same state as that stabilized by depletion interactions, as each is favored by different molecular interactions.

When an included cosolute ion concentration increases beyond some threshold, the free energy cost of removing cosolute from solution for subsequent binding drops, so that enough of the solute molecules are bound to each of the interfaces. Under these conditions the simultaneous binding of a single cosolute to more than one interface becomes rare. This results in a decoupling of bridged interfaces each laden with adsorbed species, and leads to a "reentrant" behavior, whereby the expanded state of the polymer or solvated state of the colloids becomes increasingly more favorable with increased cosolute concentration.