Biophysical Chemistry 163–164 (2012) 35–43

Contents lists available at SciVerse ScienceDirect

Biophysical Chemistry

journal homepage: http://www.elsevier.com/locate/biophyschem

The effect of lithium ions on the hydrophobic effect: does lithium affect hydrophobicity differently than other ions?☆

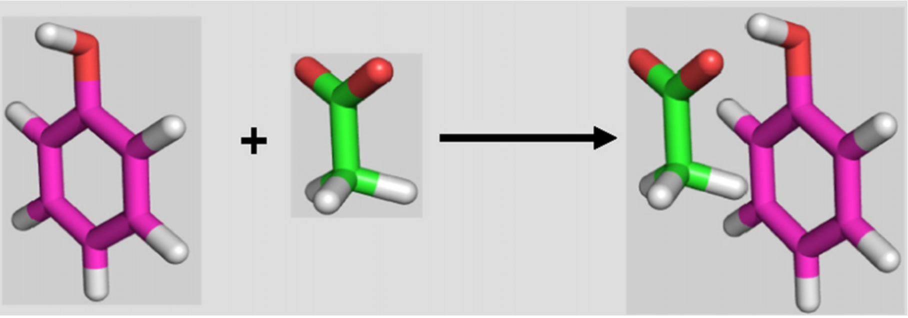
David L. Beauchamp, Mazdak Khajehpour *

Department of Chemistry, University of Manitoba, Winnipeg, Canada MB R3T 2N2

HIGHLIGHTS

- ► We determine how cations influence the hydrophobic effect.
- ► Cations with high charge density are shown to enhance the hydrophobic effect.
- ► Cations with low charge density are shown to diminish the hydrophobic effect.
- ► Lithium cations influence the hydrophobic effect as expected from their ionic size.
- ► No lithium anomaly is observed in the methyl-phenyl ring model system.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 28 January 2012
Received in revised form 6 February 2012
Accepted 6 February 2012
Available online 14 February 2012

Keywords:
Hydrophobic effect
Fluorescence quenching
Salt effects
Continuum model
Ion stickiness

ABSTRACT

Ionic species have been shown to significantly perturb the interactions between non-polar solutes in aqueous solution. These perturbations are often analyzed in terms of the interactions existing between hydrophobic surfaces and ions. It has been known for some time, that ions with a high charge density are repelled from hydrophobic surfaces while ions with a low charge density tend to stick to these surfaces. Therefore, from a continuum model standpoint, small monovalent ions promote hydrophobicity by minimizing the exposed hydrophobic surface area, while "sticky" large monovalent ions interact with the hydrophobic surfaces and discourage aggregation. However, the charge-dense lithium ion often exhibits anomalous behaviour different from these predicted trends: instead of enhancing, the addition of lithium ions often seems to weaken the hydrophobic effect and on the contrary help dissolve hydrophobic molecules. This weakening of apparent hydrophobicity is considered to be one of the reasons for the protein denaturing properties of lithium salts. Recent theoretical and experimental results however have shown that lithium cations can interact with a variety of molecular functional groups. This suggests that this apparent lithium-induced lowering of hydrophobicity, that is often reported in the literature may be a result of specific interactions between these molecular functional groups and lithium, rather than weakening the interaction between hydrophobic surfaces. This work examines these possibilities by studying the effect of various cations on the simple hydrophobic interaction existing between methyl and phenyl contact-pairs and demonstrates that the effect of lithium cations on the hydrophobic effect follows the trend predicted by continuum models. In other words, the influence of an ion on the hydrophobic interaction between two non-polar surfaces is a function of the interaction of that ion and each non-polar surface.

1. Introduction

The hydrophobic effect is perhaps one of the most biologically important solvent-induced interactions between non-polar aqueous

---

☆ This work was supported in part by the University of Manitoba UMRG.

* Corresponding author. Tel.: +1 204 272 1546.
E-mail address: khajehpo@cc.umanitoba.ca (M. Khajehpour).

0301-4622/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.bpc.2012.02.003

solutes [1]. The magnitude of this interaction has been shown to be significantly influenced by the presence of electrolyte co-solutes. This influence is not merely a function of ionic strength, but is also highly dependent on the nature of the ionic species as well. For example, the solubility of proteins (the Hofmeister Effect) [2], the critical micelle concentration of surfactants [3], catalytic activity of enzymes [4], salt-induced stability of proteins [5,6], the modulation of protein–ligand interactions [7] and the salting-out of non-polar molecules [8] from aqueous solution are all dependent on the nature of the salt co-solute.

These salt specific influences on hydrophobicity have originally been interpreted from a continuum electrostatic model standpoint [9]. In this case, the aqueous solvent is represented by a high dielectric continuum, the salt ions are represented by spherical charges and the hydrophobic surface is a region with a low dielectric constant. Based on this model, the interaction between the salt ion and the hydrophobic moiety is a sum of two opposing forces: first, the repulsive “image force” that exists between an ion in a region of high dielectric constant and a nearby region of lower dielectric constant which results from the preference of the electric field of the ion to remain in a region of high dielectric constant [6,10–12]; second, the cohesive force of water which results from the strong interaction between water molecules and tends to minimize the water-exposed surface area of dissolved solutes [11,13]. From these considerations it can be inferred that small monovalent ions are repelled from the vicinity of hydrophobic moieties, while large monovalent ions should preferentially accumulate in the hydrophobic neighbourhood.

This interpretation has been extended to the molecular level by Collins [11], in which he provides a microscopic ruler for the interaction between ions and hydrophobic surfaces: monovalent anions having a radius smaller than 1.78 Å and monovalent cations having a radius smaller than 1.06 Å are repelled by hydrophobic surfaces, while larger monovalent ions are sticky and adsorb to the hydrophobic surface. For the specific case of alkali ions, this translates into lithium ions being strongly and sodium ions being weakly repelled from hydrophobic surfaces; while the capacity of potassium, rubidium and cesium ions to absorb on hydrophobic surfaces increases with the ion radius. The influence of ionic species on the hydrophobic effect is therefore a function of the interaction between ions and hydrophobic surfaces. Solutions that contain a large number of small monovalent ions are more stable if image “repulsion” forces are reduced by hydrophobic surface minimization (i.e. the hydrophobic effect is enhanced). Conversely, the adsorption of large monovalent ions on hydrophobic surfaces discourages the aggregation of hydrophobes. More recent molecular level calculations also follow the trend predicted by continuum models [14–19]. These calculations also indicate that large monovalent ions are attracted to non-polar moieties in aqueous solutions and that the presence of ions with high charge density in solution enhances hydrophobicity, while the presence of ions with low charge density disrupts hydrophobic aggregation.

The work cited above demonstrates that theory quite clearly predicts how various monobasic salts should affect hydrophobicity. However, experimental studies of the effects of cationic species on hydrophobicity often yield results that are in apparent contradiction with theoretical predictions. In particular lithium salts, which theoretically ought to enhance hydrophobic aggregation, often seem to weaken interactions that are usually thought to be the result of the hydrophobic effect. This is seen most notably in experimental studies of salt effects on the aqueous solubility of aliphatic and aromatic compounds [20–23]. For these compounds, the salting out capability of chlorides decrease from NaCl to CsCl, in other words, the strength of the hydrophobic effect is reduced as the size of the cation co-solute is increased, [20,21,23] this is consistent with theory. However, for the same aliphatic and aromatic compounds listed above, LiCl does not behave like a strong salting-out agent at all but exhibits behaviour similar to that of KCl or RbCl. [20,21,23] In other words, although the lithium cation has a large charge density, it behaves like a much larger ion and enhances hydrophobicity to a much more modest degree than that predicted by theory. Examples of this lithium anomaly can be seen in other biophysical phenomena. Studies of salt effects on micelle formation indicate that the addition of salt species promote the formation of micelles, however, although the efficiency of micelle promotion increases from CsCl to NaCl, it abruptly drops with LiCl [24–29]. Salt studies of cyclodextrin inclusion complexes indicate that LiCl salts promote the incorporation of hydrophobic hosts to a much smaller degree than NaCl and KCl [30]. Protein folding studies have also shown that in contrast to sodium chlorides that stabilize the protein folded state, lithium chloride stabilizes protein structure to a much more modest degree [5,6,31,32]. This anomalous behaviour of lithium cation has been explained by invoking the small radius and the lower water coordination number of the lithium cation [33,34]. However, other studies indicate that this anomalous behaviour of lithium is not universal and in certain cases LiCl has been shown to actually enhance hydrophobic interactions between non-polar moieties to a greater degree than other chloride salts [35–39]; thereby, ruling out the hydration properties of lithium cation as the only reason for its “anomalous” behaviour.

A closer examination of the experimental data cited above indicates that many of the model systems studied above are too complex and the interactions between lithium ion and these molecules can not be simply represented as that of a spherical charge and a hydrophobic surface. Lithium ions can interact with amide moiety of the polypeptide chain [40–43], therefore it is possible that any stabilizing effect that the cation has on protein hydrophobicity may be neutralized by interactions with the polypeptide backbone. The polar head groups of non-ionic surfactants [44–50] as well as cyclodextrin [51] have also been shown to interact with lithium cations, preventing a simple interpretation of the critical micelle concentration (or cyclodextrin incorporation) results in terms of the ion-hydrophobic surface interaction. Lithium ions have also been shown to interact with aromatic groups [52–55] and perhaps even with methyl moieties [56]. These interactions will contribute favourably to the solvation of these groups in water, complicating the interpretation of the solubility data. These results point to a previously unnoticed flaw in the model systems used to quantify the effects of ions on hydrophobicity: namely, that most of these model systems contain moieties that can potentially interact with lithium. Therefore, the observed discrepancy observed between theoretical predictions and experimental data may indeed be the result of the interaction of lithium ions with specific segments of hydrophobic molecules. On the other hand, in the instances cited above where the influence of lithium cation on hydrophobicity is in agreement with the predictions of continuum models, the hydrophobic molecules are simple and are less likely to interact with the lithium cation.

This work studies the effects of ionic co-solutes on the hydrophobic aggregation of methyl and phenyl moieties, a hydrophobic interaction that is often observed in the interior of proteins [57,58]. The model system chosen is the contact pair that forms between the phenol molecule and the acetate ion [59,60]. This system is simple enough to allow the complete isolation of the contribution of hydrophobicity to contact pair formation. The phenol molecule shows appreciable fluorescence in the excited state [61], allowing for low concentrations of phenol to be used and therefore the study of contact pair formation is not complicated by the formation of larger phenyl aggregates. The formation of contact pairs between phenol and acetate can be adequately probed via fluorescence because acetate quenches excited phenol via a reaction controlled mechanism [59,60]. In other words, the quenching of phenol by acetate initially involves the formation of an encounter complex, followed by rearrangement of the encounter complex to facilitate quenching via a proton transfer mechanism [62]. The formation of the encounter complex between phenol and acetate ion is dependent on a variety of