Statistical thermodynamics unveils the dissolution mechanism of cellobiose

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**Abstract**

In the study of the cellulose dissolution mechanism opinion is still divided. Here, the solution interaction components of the most prominent hypotheses for the driving force of cellulose dissolution were evaluated quantitatively. Combining a rigorous statistical thermodynamic theory and cellobiose solubility data in the presence of chloride salts, whose cations progress in the Hofmeister series (KCl, NaCl, LiCl and ZnCl2), we have shown that cellobiose solubilization is driven by the preferential accumulation of salts around the solutes which is stronger than cellobiose hydration. Yet contrary to the classical chaotropy hypothesis, increasing salt concentration leads to cellobiose dehydration in the presence of the strongest solubilizer ZnCl2. However, thanks to cellobiose dehydration, cellobiose-salt interaction still remains preferential despite weakening salt accumulation. Based on such insights, the previous hypotheses based on hydrophobicity and polymer charging have also been evaluated quantitatively. Thus, our present study successfully paved a way towards identifying the basic driving forces for cellulose solubilization in a quantitative manner for the first time. When combined with unit additivity methods this quantitative information can lead to a full understanding of cellulose solubility.

1. **Introduction**

The most abundant biomass on Earth, cellulose, is not soluble in conventional mono-component solvent such as water, alcohol and hydrocarbons. The dissolution of cellulose requires additional components, namely co-solvents, as well as specific thermal conditions: Aqueous 2M alkali solution below 5°C,1,2 aqueous 7M lithium bromide solution above 120°C, 3 and 8% lithium chloride in dimethylacetamide solution below 4°C are the typical examples.4 The origin of such a wide variety of optimal conditions, "heat or cold" and compositions "aqueous or non-aqueous", has been an unanswered question, hindered by a lack of explicit explanation on how cellulose molecule dissolves into solvents on a molecular scale.

The dissolution mechanism of cellulose has been studied by the cutting-edge approach in each *époque*. From early bulk solution studies, based on viscosity and osmotic pressure,5,6 through to direct interaction characterizations with the development of the nuclear magnetic resonance (NMR) technique, where dissolution mechanism was proposed by determining the locations where (co)solvent species interact with cellulose.7–12

**Co-solvent binding.** Through these studies, it has since been assumed that in most cellulose solvents, co-solvents play a dominant role in dissolution by interacting with hydroxyl (OH) groups of cellulose leading to the currently-prevailing view that co-solvent disruption of hydrogen bonding present in the cellulose crystal is crucial for dissolution of cellulose.11–14

On top of this, further developments lead to two hypotheses which provide alternative, though related, candidates for the driving force of solubilization:

**Cellulose Charging Up.** The OH group-cosolvent interactions are re-highlighted in recent studies as the "cellulose charging up” hypothesis. They claimed that cellulose-ion interaction can make cellulose into a “polyelectrolyte” which drives its dissolution.15,16 The cellulose polyelectrolytes are in solution together with a number of small ions whose increase of the entropy of mixing is claimed to be the driving force of their cellulose solubility enhancement.17

**Amphiphillicity – “Like dissolves like”**. The limitation of previous co-solvent binding hypotheses is that they do not explain the insolubility of cellulose as demonstrated in the following example: Polyvinyl alcohol (PVA), a highly water-soluble polymer, contains 3 OH groups per 6 carbons, an identical number to cellulose. To rationalize this inconsistency, the hypothesis that insolubility is attributed to the structure of cellulose, particularly its amphiphilic nature, was proposed.18–22 Consequently, the “like dissolves like” principle has inspired the view that the solvent would need to be amphiphilic like cellulose. However, the discussion on such amphiphilic nature remains qualitative, because hydrophobic interaction cannot be quantified or detected experimentally, and thus the main methods are based on modeling23.

We have thus seen the co-existence of different hypotheses on cellulose dissolution mechanisms, none of which can put numbers to each of the driving forces. Especially, to focus solely on cellulose-cosolvent interaction cannot give an accurate explanation of cellulose dissolution because it neglects another essential contributory factor, namely the cellulose-solvent interactions. It is not even clear which of the proposed driving forces are dominant or minor, or whether some of the proposed driving forces are interrelated or equivalent to one another. The major hindrance towards elucidating the mechanism of cellulose dissolution is the lack of a link between the proposed mechanisms and solubility on a quantitative basis.

Such a hindrance towards elucidating cellulose dissolution can be overcome by employing a statistical thermodynamic theory that can explain solubility on a quantitative basis from the interactions between individual species. Indeed the rigorous theory of solvation based on Kirkwood Buff (KB) theory has recently been applied to biomolecular, pharmaceutical and food systems successfully to bring clarity on their long-disputed mechanisms directly from first principles.24–26 Based on such a track record, here we clarify the mechanism of cellulose dissolution by putting numbers to each of the key interactions taking place in solution.

The aim of this paper is to rationalize the dissolution mechanism of cellulose by the combination of a rigorous statistical thermodynamic theory and a model compound for the cellulose monomeric unit as a starting point. Statistical thermodynamics can link the solubility data to the interactions between cellulose and solvents and between the solvent species in a quantitative manner.24,27,28 A quantitative evaluation will then be possible for the first time on the predominant hypotheses of cellulose dissolution mechanisms, summarized above.

**2. Theory and Methods**

**2.1. Model system and target for quantification**

In our theoretical approach, the principal data necessary for quantitative characterization is the change of cellulose solubility against co-solvent concentration. However, cellulose solubility is poorly reproducible, due to the intricate intermediate steps such as swelling29,30 and complexation.31 The energetic barrier of these intermediate steps can be moderated by the pre-treatment such as steam-explosion32 and crystal transition.33 Therefore, cellulose dissolution can exhibit strong dependency on the severity of the pre-treatment.32,34,35 Consequently, literature data of cellulose solubility inherently contains errors brought about by kinetic traps, which complicates the thermodynamic measurements.36

To circumvent such difficulties, we must employ a model compound which consists of cellulose constituent units. For this purpose, we have chosen cellobiose, the repeating unit of cellulose, which is composed of two β-1,4 linked D-glucose units. Cellobiose retains "cellulosic" characteristics: aqueous solubility of cellobiose is much lower (12%) than its isomeric disaccharide maltose (α-1,4 linked two D-glucose units, 48%37), and dissolution of cellobiose in dimethylacetamide necessitates the addition of lithium chloride as cellulose does.38 It should be noted, however, that cellobiose can take a cis conformation,39 whereas cellulose takes a trans conformation.40 Also, when considering the reducing end of these polysaccharides, which can exist in both α and β anomers and open chain form40, cellobiose, being a dimer, demonstrates a non-negligible contribution from these possible arrangements in contrast to cellulose.

Nevertheless, thanks to the smaller molecular size compared with cellulose, the above-mentioned intermediate steps are rendered negligible, and thus the use of cellobiose assures the reproducibility of solubility measurement.20,41 This is a necessity for the quantification of the interactions that the constituent disaccharide unit of cellulose has respectively with solvent and cosolvent molecules, neither of which have been quantified previously. From the understanding of constituent unit solvation contributions, we can build up to the understanding of cellulose solvation as a whole.

To this end, we employ recently published data on cellobiose dissolution.42 The enhancement of cellobiose solubility in the presence of Hofmeister cations with chloride has been reported as the function of salt concentration. The solubility data (Figure 1) has been complemented by the cellobiose partial molar volumes in the presence of the same salts, as well as the activity coefficients of water and salts. As will be discussed in Section 2.2, the combination of solubility, volumetric and activity data are sufficient to draw a complete picture of interactions in cellobiose-water-salt solutions in a quantitative way.

**Figure 1:** Solubility enhancement of cellobiose by chloride salts. Experimental data have been obtained from Fig. 1 of Liu et al.42 (see Supporting Information (SI:D) for further information).

**2.2. Quantifying interactions in solutions**

Our goal is to quantify how each of the interactions (cellobiose-salt, cellobiose-water, salt-salt, salt-water and water-water) contribute to the dissolution of cellobiose, thereby shedding light onto the mechanism of cellulose dissolution in a quantitative manner and, enabling the evaluation of different proposed scenarios towards cellulose dissolution. The interactions between a pair of species (say, between the species and ) can be quantified in terms of the KB integral (KBI) defined as

(1)

where is the radial distribution function between the species and . *Gij* is the average affinity between the species *i* and *j*.27 These pair affinities can be calculated from experimental data (Section 2.1), through this, the theory we apply in this paper will quantify the dominant role in cellobiose solubility.

Throughout this paper, the following convention has been used: : cellobiose, : water and : salt ions. The theory used here is exact and without model assumptions. One limitation of the theory, however, is that it is not possible to study the independent effects of each ion, due to the fact that the number of cations or anions, formed by the dissociation of salts, cannot be altered independently, as a consequence of this it is a standard practice to use the concentration of “indistinguishable ions” as opposed to salt concentration.43,44 Therefore, *c*s refers to the concentration of the salt’s ions. We emphasize that this inability of changing anion and cation concentrations separately in solution poses difficulty from the experimental determination of contain separate KBIs for cations and anions, despite the seminal extension of the KB theory by Patey and coworkers.45,46

Indeed, experimental evidence suggests that anions and cations both contribute to cellulose dissolution and dissecting dissolution capability into individual ion contributions may be extremely challenging. Due to the rarity of systematic cellobiose solubility data, here we summarize the dissolution of cellulose itself:

1. LiCl/water does not dissolve cellulose polymers47 but LiBr/water mixture dissolves cellulose.3
2. To solubilize cellulose with LiCl, a complete removal of the solvent water is indispensable, i.e., the complete replacement of water by ethanol, acetone, or dimethylacetamide.38,48

Such a strong anion dependence suggests that both anions and cations are engaged in the interaction with cellulose molecules in a hard-to-separate manner.

**To quantify the relative contribution of KBIs in solubilization,** let us employ how cellobiose solubility, , when dependent on the ion concentration, , can be expressed in terms of KBIs as

(2)

where the preferential affinity between cellobiose molecules and ions over cellobiose and water molecules, drives up the solubility, while the preferential self-association of ions, driven by ion-ion affinity () over affinity between ions and water or ion hydration () reduces the solubilization.49 and respectively denote the gas constant and the temperature. Eq. (2) thus quantifies the driving forces for cellobiose dissolution.

**The calculation of s** and the above expressions from experimental data requires not only the dependence of cellulose solubility on salt ion concentration (Eq. (2)) but also the partial molar volume of cellobiose in aqueous salt solutions, density and activities of aqueous salt solutions, all of which can be expressed in terms of KBIs. This procedure is well-established with a track record of successes in many applications,25,26,50–54 and will be detailed in the Supporting Information.

**3. Results and Discussion**

All of the proposed classical hypotheses for the mechanism of cellulose dissolution remain (for the most part) qualitative. To overcome such a limitation, we demonstrate in the following section that each of the driving forces for solubilization can be quantified, through statistical thermodynamics, using the experimental data identified previously. We then compare the findings of our new approach with those of the classical hypotheses to evaluate their veracity.

**3.1. Driving forces of solubilization: Preferential cellobiose-salt interaction versus preferential self-aggregation of salts**

**Figure 2:** Preferential cellobiose-ion interactions characterized quantitatively via the Kirkwood-Buff integrals () for NaCl, KCl, LiCl and ZnCl2 calculated from the solubility data.42 See Supporting Information for calculation procedure (SI:B).

**Figure 3.** Solubilization inefficiency due to the preferential self-aggregation of salt ions in bulk aqueous solution, which has been quantified by the KBIs via, plotted for KCl, NaCl, LiCl and ZnCl2. (Calculated via osmotic coefficient data – see SI:C)55

Statistical thermodynamics reveals the following two major driving forces for the increase of cellobiose solubility in the presence of salts:

1. The preferential cellobiose-ion affinity over affinity between cellobiose and water molecules, this being the dominant driving force (Figure 2);
2. Preferential self-association of salts in aqueous solution, which is the minor contribution, reduces per-ion solubilization efficiency (Figure 3).

This picture of cellobiose solubilization is general and universal, common to wide-ranging solvation phenomena including protein denaturation and stabilization, hydrotropic solubilization and food gel stabilization.24,25,56–59 In the following, we shall examine the individual contributions to 1 and 2 in more detail to link the novel quantitative insights from the KB theory to the classical hypotheses.

**3.2. Salt accumulation as the dominant contribution**

The salts that enhance cellobiose aqueous solubility (NaCl, LiCl and ZnCl2) have an energetic benefit to accumulation around cellobiose as indicated by the positive preferential affinity/ interaction exhibited in their solvent systems. It may be noted, however, that the corresponding KBIs () are negative. This counterintuitive value arises due to the excluded volume of cellobiose contributing in a dominant manner to make net negative.60 Increase of cellobiose solubility is seen when the affinity of salts with cellobiose exceed that of water. Salt accumulation around cellobiose should thus be considered the dominant contribution to cellobiose solubilization.

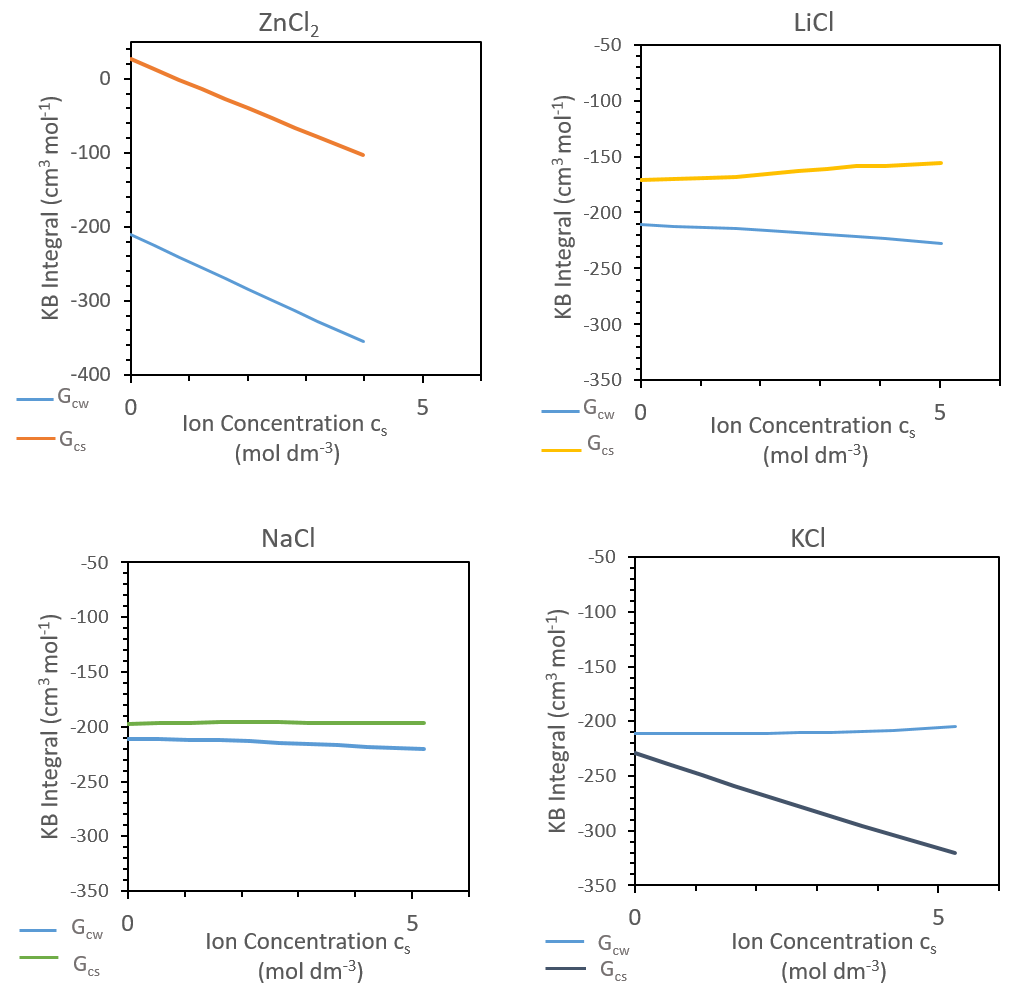
Salt accumulation as a driving force provides support for the cellulose charging up hypothesis in which ion binding is an important factor. Unlike this hypothesis, however, our theory does not involve any need for invoking the entropy of mixing, which, despite its historical importance, is problematic as a thermodynamic concept,61 because (1) it is not a reversible and hence a thermodynamic process, and (2) solubility (governed by the free energy) is the result of compensating, large entropic and enthalpic contributions of different signs. Our theory, instead, is based on a direct relationship between salt accumulation and solvation free energy – provided by the KB theory.

**3.3. Cellobiose dehydration – water structure hypothesis**

The solution phase interaction component of the amphiphilicity hypothesis presupposes the enhanced water structure around the hydrophobic group as a basis for insolubility.62 Insolubility of cellulose has also been attributed specifically to the hydrophobic section of cellulose.18,23,63 Within this framework, the effect of cosolvents on solubility, and especially Hofmeister ions, have been explained via water structure. Despite the lack of a sound theoretical and quantitative basis for this argument, solubilization according to the classical hydrophobic clathrate view in solubility theory,64,65 which corresponds to the solution phase interaction portion of the aforementioned hypothesis, can be summarized as:

1. The hydrophobic effect is due to the enhancement of the water structure around the solute (“clathrate” structure) which cannot hydrogen bond with water, which leads to entropic penalty;
2. Species called "chaotropes" break the “water structure”, or the hydrogen bond network of water molecules;
3. Chaotropes weaken the clathrate structure of water, thereby weakening the hydrophobic effect

This classical hypothesis has been the source of controversy over decades.62,66,67 Indeed, the presumed hydrogen bond enhancement by ions has been challenged spectroscopically,68 and the dynamic nature of the “clathrate” or “iceberg” has emerged since then.69 The consequence of this hypothesis is that, since the clathrate structure involves more hydrogen bonds, the water molecules are kept further apart on average and consequently the density is lower. Hence “water structure breaking” increases hydration, i.e., increase of the density of water in the hydration shell.



**Figure 4**. Individual Kirkwood-Buff integrals that lead to preferential association for ZnCl­2, LiCl, NaCl and KCl.

In stark contrast to this classical hypothesis, Fig 4 shows that decreases as the concentration of salts that enhance cellobiose solubilization (NaCl, ZnCl2 and LiCl) increase, which means that the chaotropic salts dehydrate cellobiose instead of enhancing its hydration, which is in contradiction to the water structure hypothesis. Thus, our analysis suggests strongly that the water structure hypothesis cannot explain cellulose solubilization. Figure 4 also shows us that the relationship between the KBIs should not be neglected. As the salt ion concentration of ZnCl2 increases, salt accumulation () around cellobiose decreases which leads to a weaker contribution to solubilization (ZnCl2 - Figure 4). Despite this, decreasing cellobiose hydration (increasing cellobiose dehydration) indicated by decreasing (Figure 4) shows that salts still interact preferentially with cellobiose, thereby increasing its solubility.

Furthermore, though KCl exhibits weak salt accumulation, this is not compensated for by the corresponding dehydration and accumulation continues to weaken as salt ion concentration increases (Figure 4), therefore leading to a solubility decrease, thus the salt’s effect on solubility is again caused by the interplay between the two affinities.

Note here that the classical water structure hypothesis focuses exclusively on the *increase* of solute hydration with increasing salt concentration, i.e., the *increase* of . The rigorous statistical thermodynamic theory not only shows that *decrease* in cellobiose hydration takes place but also the crucial role of , instead of on its own, that is the driving force for solubilization.

* 1. **Cellobiose solubilization and the Hofmeister effect**

The effect of salts on solubilization has long been related to the Hofmeister effect, in which the ionic charge density is considered to play a crucial role on solubilization.70 According to the classical hypothesis, ions with low charge density break the “water structure” thereby weakens the hydrophobic effect, while those with high charge density enhance it and fortify the hydrophobic effect70,71 Note that the water structure hypothesis has been developed to rationalize the effect of ions chiefly on the hydrophobic effect. Nevertheless, here, in the context of cellobiose solubilization, the order of solubility enhancement ability, with respect to changing the cation, coincides with an increase in ion charge density (Zn2+>>Li+>Na+>K+). So, what is the mechanism upon which the charge density increases solubilization? The KBIs calculated in this paper enable us to re-examine the true mechanism.

According to the water structure hypothesis, solubilization is caused by the breaking of water structure around the hydrophobic group. Cellobiose hydration behavior exhibits the opposite trend to this hypothesis (Section 3.3), hence the role of charge density should be reconsidered. What we have observed here (Figures 2 and 4) instead is the importance of increasing *preferential* cellobiose-salt affinity instead of the cellobiose-salt affinity *per se*. This is consistent with the previous identification of preferential interaction as the driving force of the Hofmeister effect.72

Having singled out preferential interaction as the driving force of the Hofmeister effect for proteins as well as cellobiose, the next step is to elucidate the mechanism of preferential interaction on a molecular basis. To undertake this challenging task, a recent computational approach,73,74 which has been based firmly on the theory of solutions and successful in quantifying different types of electrostatic and non-electrostatic interactions (including configurational and excluded volume effects) on the origin of the Hofmeister effect on protein stability, could be translated to use in polysaccharides to identify the molecular level interactions that make up preferential ion-cellulose affinity.

**4. Conclusion**

Elucidation of the mechanism of cellulose dissolution has been hampered by the lack of a theoretical framework that can explain solubility on a molecular scale, as well as lack of standard model systems that enable the direct experimental measurements of cellulose-solvent interactions in a reproducible manner. To overcome these hindrances, we identified and quantified the driving forces of solubilization using cellobiose as a model system whose solubility in the presence of Hofmeister salts have been reported recently in the literature. The rigorous statistical thermodynamic framework, which has a track record of clarifying the microscopic basis of solvation in wide-ranging fields, has been applied to reveal the solubilization mechanism at odds with many of the classical hypotheses.

The driving force for solubilization is the preferential accumulation of salt ions around the solute molecules, which is stronger than cellobiose hydration. Even though the salt accumulation weakens as the concentration of salts in solution, the increasing cellobiose *dehydration* keeps the cellobiose-salt interaction still preferential. This scenario has also been observed for coffee ingredient molecules in aqueous ionic liquid solutions.59 The increasing dehydration is at odds with the classical “water structure” hypothesis for chaotropic solubilization which predicts the increase in cellobiose *hydration*.

Hence the classical hypothesis regarding the role of ionic charge density on water structure breaking and making should be revised: the larger charge density leads to preferential interaction with cellobiose. That the concentration of ions around cellobiose is the key towards solubilization is consistent with the classical hypothesis that emphasized the importance of cellulose-ion binding as the driving force. However, in contrast to the classical hypothesis that invoked the favourable entropy of mixing between cellulose polyelectrolyte and small charged ions in solution as the driving force, our theory links the ion accumulation and solubilization directly; the approach based on entropy of mixing (or more accurately “entropy of assimilation”) suffers from entropy-enthalpy compensation that prevents us from directly linking solubility with solution structure.

Self-association of salts in bulk solution has been identified also as a minor contribution that reduces the efficiency of solubilization, which is consistent with our recent application of statistical thermodynamics in a number of biological and chemical systems.

Based on our identification of the roles of cellulose-salt and cellulose water interactions on solubilization, applying our insights to cellulose in a quantitative manner requires an investigation into the group additivity of solvation that requires the study of cellulose analogues of longer chain lengths. In addition, a molecular-based mechanism of the role of individual ions on KBIs and solubility requires an extensive molecular dynamics simulation.75,76 Nevertheless, our present study successfully paved a way towards identifying the basic driving forces for cellulose solubilization in a quantitative manner for the first time.

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