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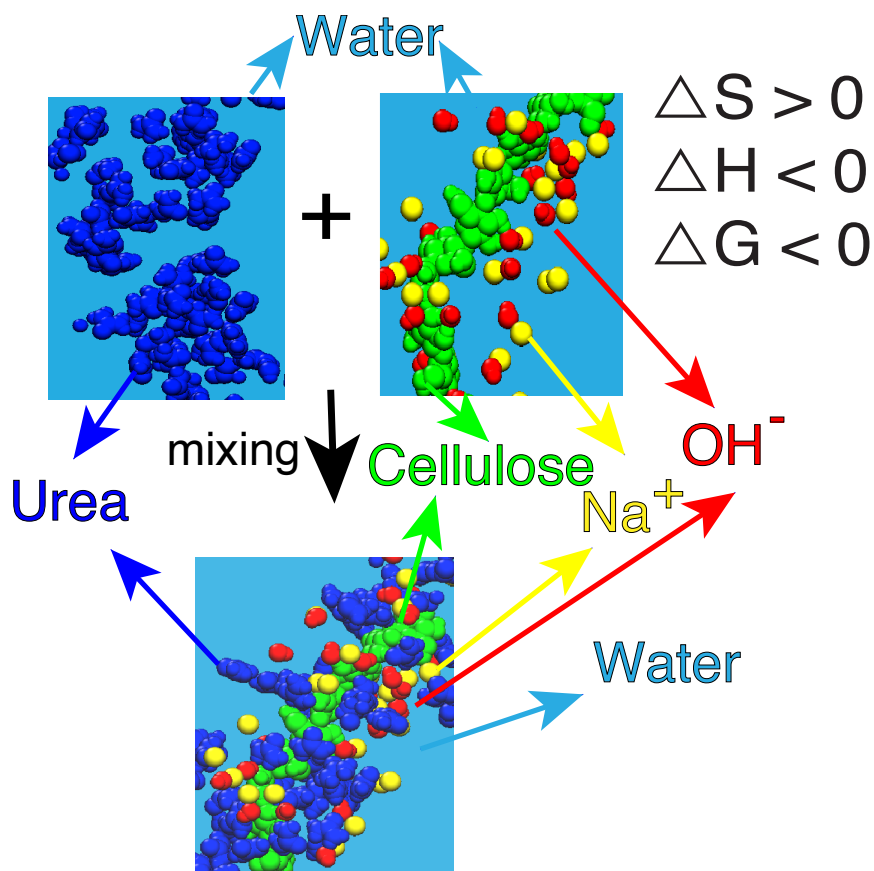
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Graphical Abstract

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Highlights

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- Urea accumulates to dissolved cellulose chain in NaOH solution.
- Entropy and enthalpy of mix promotes the dope stability of cellulose solution by urea.
- Dispersion energy and entropy both drive urea adsorption onto cellulose.

The Thermodynamics of Enhanced Dope Stability of Cellulose Solution in NaOH Solution by Urea

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ABSTRACT

The addition of urea in pre-cooled alkali aqueous solution is known to improve the dope stability of cellulose solution. However, its thermodynamic mechanism at a molecular level is not fully understood yet. By using molecular dynamics simulation of an aqueous NaOH/urea/cellulose system using an empirical force field, we found that urea was concentrated in the first solvation shell of the cellulose chain stabilized mainly by dispersion interaction. When adding a glucan chain into the solution, the total solvent entropy reduction is smaller if urea is present. Each urea molecule expelled an average of 2.3 water molecules away from the cellulose surface, releasing water entropy that over-compensates the entropy loss of urea and thus maximizing the total entropy. Scaling the Lennard-Jones parameter and atomistic partial charge of urea revealed that direct urea/cellulose interaction was also driven by dispersion energy. The mixing of urea solution and cellulose solution in the presence or absence of NaOH are both exothermic even after correcting for the contribution from dilution.

1. Introduction

Urea was first reported to promote cellulose dissolution in cold NaOH solution by Zhou et al. in 2000 (Zhou and Zhang, 2000). Later, Cai et al. further systematically explored the ratio of components in the ternary system and optimized the dissolution process (Cai and Zhang, 2005). This NaOH/Urea solvent and its analogs (LiOH/urea, KOH/urea, or LiOH/Thiourea) were also reported to dissolve chitin (Fang, Duan, Lu, Liu, Liu, Xu and Zhang, 2015a; Huang, Zhong, Zhang and Cai, 2017). Although the LiOH system dissolves cellulose better, the cost makes the NaOH system the most realistic (Budtova and Navard, 2016; Kamida, Okajima, Matsui and Kowsaka, 1984; Kamide, Saito and Kowsaka, 1987; Kamide, Yasuda, Matsui, Okajima and Yamashiki, 1990; Matsui, Sano, Yamane, Kamide and Okajima, 1995; Yamada, Kowsaka, Matsui, Okajima and Kamide, 1992; Yamane, Saito and Okajima, 1996a,c,d,b; Yamane, Abe, Satho and Miyamoto, 2015; Yamashiki, Kamide, Okajima, Kowsaka, Matsui and Fukase, 1988; Yamashiki, Matsui, Saitoh, Okajima, Kamide and Sawada, 1990a,b; Yamashiki, Saitoh, Yasuda, Okajima


and Kamide, 1990c; Yamashiki, Matsui, Kowsaka, Saitoh, Okajima and Kamide, 1992).

The dissolution of cellulose in pre-cooled NaOH/urea takes place at low temperature (-12 °C) (Egal, Budtova and Navard, 2008) and was reported to show the best dissolution capacity at the proportion of 7% NaOH, 12% urea (Cai and Zhang, 2005), and 81% water that corresponded to a molar ratio of 1:1.1:26.

The 7% NaOH and the 81% water in a ternary solution of NaOH/urea/water are close to an 8% NaOH binary solution, known to swell extensively cellulose fibers at low temperature, reported as "Q" region (after Quellung = swelling in German) in the pseudo-phase diagram by Sobue et al. who investigated alkali-cellulose system at wide temperature range (Sobue, Kiessig and Hess, 1939).

The addition of urea is believed to promote dissolution, but the clearest effect is the enhancement of dope stability. The cellulose solution in NaOH/urea system was stable for weeks at room temperature, in comparison to the cellulose solution in pure NaOH solution that undergoes irreversible gelation within a few hours (Wang, Liu, Chen, Zhang and Lu, 2018; Wang, Lu and Zhang, 2016; Cai and Zhang, 2006). The increased solubility and delayed gelation allow for the development of various cellulose II based advanced functional materials through an aqueous system (Wang et al., 2016).

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The mechanism of dissolution enhancement by urea has been speculated in relation to both experimental and simulation approaches. The first hand-waving explanations tended to evoke hydrogen bonds (HBs). Since cellulose crystals show regular HB networks, the insolubility of cellulose in common solvents was often explained by intermolecular cohesion through this multiple hydrogen bonding that cannot be easily disrupted despite the limited cohesion energy of each bond. This would, however, not apply to the aqueous system, since the HBs among cellulose chains have the same strength as those between water molecules (Nishiyama, 2018; Wohlert, Bensselfelt, Wågberg, Furó, Berglund and Wohlert, 2022). Also, both urea and cellobiose dissolution in water are endothermic processes (Zhao, Chen, Jiang, Shang, Zhang, Gong, Zhang, Wang and Zhou, 2013; Pickering, 1987), which would suggest that the overall entropy gain rather than enthalpy drives the spontaneous dissolution.

Since about twenty years, there is a revival of recognition that cellulose is in fact amphiphilic (Glasser, Atalla, Blackwell, Malcolm Brown, Burchard, French, Klemm and Nishiyama, 2012; Bergensträhle, Wohlert, Himmel and Brady, 2010; Medronho, Romano, Miguel, Stigsson and Lindman, 2012; Biermann, Hädicke, Koltzenburg and Müller-Plathe, 2001), and more attention is paid to the hydrophobic character to explain the insolubility in aqueous system hypothesized the accumulation of urea on the hydrophobic surface to prevent association between cellulose molecules through hydrophobic interaction (Isobe, Noguchi, Nishiyama, Kimura, Wada and Kuga, 2013). There is more and more evidence for the co-localization of urea and cellulose in an aqueous solution. Molecular dynamics (MD) simulation from Wernersson et al. predicted the accumulation of urea at the proximity of the cellulose (Wernersson, Stenqvist and Lund, 2015), including the hydrophobic surface. They further analyzed the radial distribution function in Kirkwood-Buff theoretical framework, to explain the role of urea. The solution state NMR studies do not give indications on the interaction of urea with other components in the cellulose dissolution (Jiang, Fang, Xiang, Ma, Lu, Kang, Huang, Guo, Liu and Zhang, 2014), but when freeze-dried, the urea chemical shift was influenced by the presence of cellulose, which suggests their intimate interactions with cellulose (Song, Ge, Xu, Chen and Zhang, 2014). Also solution scattering of cellulose analog, trehalose suggests the co-localization of urea around the sugar (Qin, Ma, Gärtner, Headen, Zuo, Jiao, Han, Imberti, Han and Cheng, 2021).

Then what is driving the accumulation of urea around cellulose and why is it stabilizing the cellulose solution? Hydrophobic interaction is a term that sounds obvious but is still not answering the question. The term is a simple rephrasing of the observation that oily substances do not mix with water. Water cannot form HB with apolar moieties, and thus would tend to exclude to phase separation. The presence of a large solute can also diminish the water entropy by limiting its translational mobility at the interface. Many such factors can contribute to the penalty against dissolution,

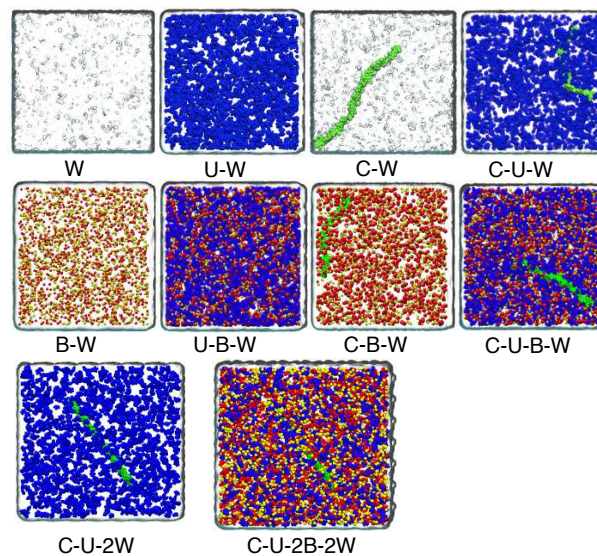


Figure 1: Snapshots of ten simulation boxes containing cellulose or pure solvents. Green stands for cellulose (C), white is water (W), 2W means twice the number of water molecules, blue is urea (U), yellow is sodium contour ion, and red is sodium hydroxide (B: NaOH).

and the temperature dependence of solubility or solution stability points to the importance of entropy. Here, we tried to quantify the enthalpy and entropy associated with the presence of urea in a cellulose aqueous solution system and to elucidate what thermodynamic factor contributes to the urea accumulation on cellulose surface, and what is the origin of enhanced dope stability.

2. Method

2.1. Modeling versus simulation

One single cellulose chain with a degree of polymerization (DP) 20 was immersed in four different aqueous solutions (Figure 1) either with NaOH or with urea, or both of them, denoted, NaOH/H₂O, H₂O, Urea/H₂O, NaOH/Urea/H₂O. Together with the four types of solution without cellulose, eight simulation boxes were constructed as shown in Figure 1. The number of water (32660), NaOH (1256), and urea (1452) molecules were kept constant throughout. The molar ratio corresponds to the reported values of the experimental optimum for the dissolution of cellulose (7.0 wt% NaOH, 12 wt% urea, and 0.44 wt% cellulose). Two additional systems, Cellulose/Urea/2*Water, and Cellulose/Urea/2*NaOH/2*Water were also created in order to calculate the enthalpy of dilution. In these two systems, the amount of water or NaOH/water is twice of Cellulose/Urea/H₂O or Cellulose/Urea/NaOH/H₂O systems. For simplicity, we use C, U, B, and W to represent cellulose, urea, NaOH, and Water, in the following.

The GROMOS 56A_{carbo} carbohydrate force field (Hansen and Hünenberger, 2011) together with the optimized Lennard-Jones (LJ) parameter (Chen, Nishiyama and Mazeau, 2014) for the CH united atom group was used for cellulose. The

urea model from Smith et al. (Smith, Berendsen and van Gunsteren, 2004) was used. The SPC water model was used for water (Fuhrmans, Sanders, Marrink and de Vries, 2010). The nonpolarizable model of the hydroxide ion, adapted from the polarizable one (Hub, Wolf, Caleman, van Maaren, Groenhof and van der Spoel, 2014), was optimized and validated in our previous study (Chen, Fu, Yu, Quan, Zhao, Shao, Ye, Qi and Chen, 2021).

MD simulations were performed using the GROMACS software package (Hess, Kutzner, Van Der Spoel and Lindahl, 2008), versions 2021.1 and 2016.3. The steepest descent and conjugate gradient methods are successively used for energy minimization. The production run was carried out under the NPT (constant number of particles, pressure, and temperature) ensemble. The velocity rescaling method is employed to regulate the temperature, and the Berendsen method for controlling the pressure (Bussi, Donadio and Parrinello, 2007; Berendsen, Postma, van Gunsteren, DiNola and Haak, 1984). Short-range electrostatic interactions and LJ interactions were calculated with a cutoff distance of 1.4 nm (Darden, York and Pedersen, 1993; Wennberg, Murtola, Hess and Lindahl, 2013). The Long-range electrostatic interactions were calculated by the particle mesh Ewald method (PME). The leapfrog algorithm was used to integrate Newton's equation of motion with an integration step size of 2 fs. LINCS algorithm is used to constrain the bond distance involved in the hydrogen atoms (Hess, Bekker, Berendsen and Fraaije, 1997). The equilibration run of systems containing NaOH lasted for 200 ns and that without NaOH was 100 ns. The production run last for 100 ns for all the systems.

During the entropy estimation, an equilibration of 10 ns was further carried out for each system in which 20 frames were selected at 0.5 ns intervals. These 20 frames of each system were used as starting points for another production run of 20 ps with both positions and velocities recorded every 3 fs to calculate the velocity auto-correlation function.

2.2. Distribution Functions

The radial distribution function (RDF) of urea, water, Na^+ , and OH^- around cellulose was calculated using *gmx trjorder* tool, by counting the number of molecules as a function of distance to the non-hydrogen atoms of cellulose. The spatial distribution function (SDF) is calculated by using *gmx sdf* tool and taking a single anhydrous glucose residue as the reference group (Kusalik and Svishchev, 1994).

2.3. Two-Phase Thermodynamics

In the Two-Phase Thermodynamics (2PT) method (Lin, Blanco and Goddard III, 2003) the translational and rotational modes of the density of states (DoS) are partitioned into two contributions: an ideal gas component (with 3N degrees of freedom) and a non-diffusive solid component. From this, the gas-like component of the absolute entropy is calculated using the entropy of a hard-sphere gas for the translational part and a rigid rotor approximation for the rotational part, while the solid-like contribution is calculated by integrating the entropy of a quantum-mechanical harmonic

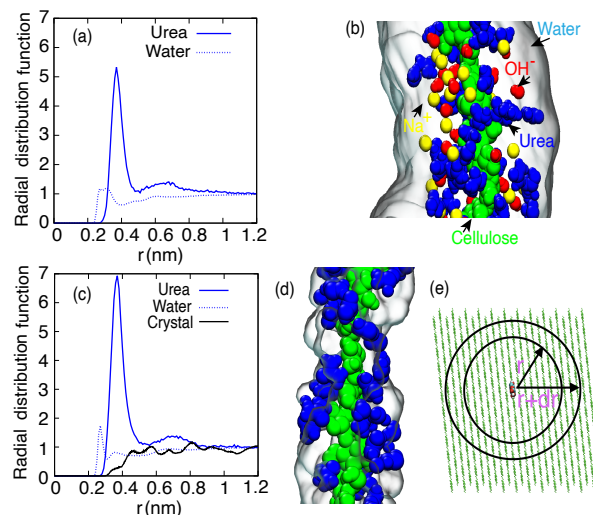


Figure 2: RDF of solvent molecules around cellulose in the presence (a) and absence (c) of NaOH. The glucose-glucose RDF in native cellulose is added in (c). The snapshots of cellulose solvation in U/W are shown in (b) and in U/B/W shown in (d) as well as that of crystalline cellulose β shown in (e).

oscillator over the solid-like DoS partition, thus approximating all modes as being purely harmonic. In addition, for non-rigid molecules, there is also a vibrational contribution to the entropy coming from internal degrees of freedom. These are treated purely within a harmonic approximation. A detailed description of the 2PT method is presented in the supporting information (SI). A modified version of the *gmx traj* tool in GROMACS was used to extract different velocity components, and *gmx dos* was used to calculate the velocity density of state as in our previous study (Chen, Nishiyama, Wohler, Lu, Mazeau and Ismail, 2017).

3. Result and Discussion

3.1. Accumulation of Urea around Cellulose Chain

Figure 2 shows the snapshots of cellulose solvation in U/B/W and U/W systems, and the corresponding surface RDF as well as the glucose-glucose RDF in crystals. The Na^+ , OH^- , and urea in the figure are all those in the first solvation shell (defined as less than 0.9 nm to the heavy atom of glucose) of cellulose (green), and they are colored in yellow, red, and blue, respectively. The RDF profiles (Figure 2a and c) show that urea has a much higher density than in bulk (normalized to 1), while the water has a first solvation peak above 1 followed by a depression valley below 1 with little change in the average density. The first solvation peak of the urea to glucose ring is at 0.4 nm, larger than to water molecule (0.25 nm), but similar to the glucose-glucose distance in native cellulose crystals (Figure 2c and e). Tables S2 & S3 list the number of different types of HBs within 0.5 nm of the solvation shell. On average, there are 18.3 water and 2.2 urea per glucose residue that forms 4.4 and 1.4 HBs with water and urea respectively in the absence

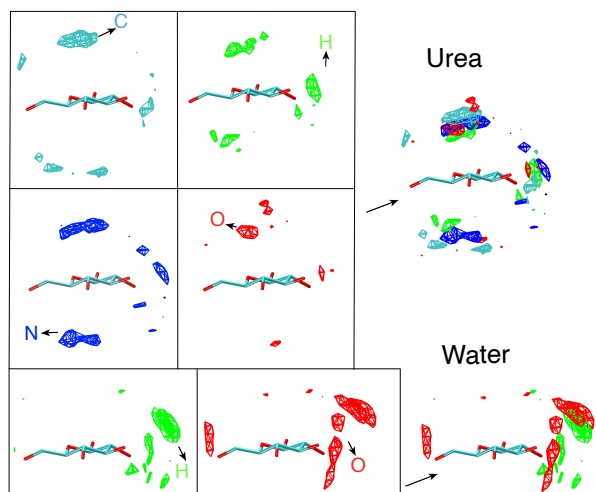


Figure 3: Spatial distribution function (SDF) of urea/glucose and water/glucose (cyan:C,red:O,blue:N,lime:H).

of NaOH. The number ratio of water to urea in this first solvation shell is 8.2 compared to 22.5 in the whole system, indicating more than the two-fold concentration of urea in the proximity of cellulose. In the presence of NaOH, there are 14.8 water and 1.6 urea per glucose in the proximity and forming 2.8 and 0.93 HBs, with the water to urea ratio of 9.5. Furthermore, the number of HBs between cellulose-water is only three times that of cellulose-urea despite its abundance in this solvation shell, further suggesting the affinity of urea to cellulose. The SDF analysis (Figure 3), also visually confirms the presence of urea near cellulose molecules. Furthermore, the SDF illustrates that the non-hydrogen atoms in urea, (carbon, oxygen, and nitrogen) all contact preferentially the axial backbone of the glucose ring than the equatorial hydroxyl groups, whereas hydrogen atoms in urea distributed around both the axial and equatorial directions of glucose. The water molecules tend to locate near the equatorial direction of the glucose ring.

As urea is in short contact with glucose, we do observe the U/C HBs, in which urea acts more frequently as a donor through N-H groups and cellulose more as an acceptor, as shown in Table S2 & S3. Would it be the driving factor that leads to the urea enrichment around the cellulose (Cai, Liu and Liang, 2012)?

If HBs were the driving force, increasing the atomic partial charge of urea in MD simulation would facilitate the formation of U/C HBs, and thus would lead to increased urea adsorption around cellulose. However, the scaling up of the partial atomic charge of urea by 4/3 did not change the accumulation of urea at the surface, as shown in Figure 4. In contrast, the scaling down of the charge to 2/3, which means that less polar, and thus more "hydrophobic" urea preferentially interacts with cellulose. Alternatively, we varied the energy well of the LJ parameter of urea and observed that increasing the attractive term promotes the U/C interaction. This is in line with the urea adsorption on the cellulose bundle (Chen et al., 2017) and confirmed that

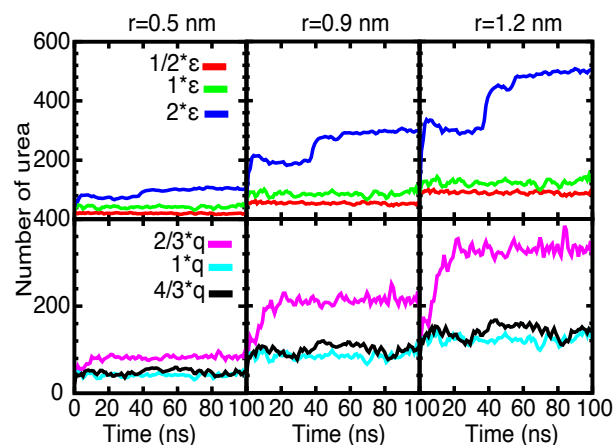


Figure 4: Variation of the number of urea molecules in different solvation shells of cellulose (0.5 nm, 0.9 nm, and 1.2 nm) when scaling up/down either the partial atomic charge or energy well of LJ parameters of urea, respectively. (ϵ : energy well of LJ parameters of C, O, N in urea, q : partial atomic charge of all atoms in urea molecules)

it is the dispersion energy rather than HBs that drives the accumulation of urea onto the cellulose chain.

Using standard criteria of HBs formation, each glucose within cellulose was only forming 1.4/0.93 HBs to urea, in the C/U/W or the C/U/B/W system, respectively (Table S2 & S3). By modulating the HB criteria, each glucose can form 3.2/2.1 HBs to urea (Table S2 & S3). The energy decomposition analysis from the MD trajectory showed the electrostatic interaction between glucose and urea to be -34.2 kJ/mol and dispersion energy of -21.5 kJ/mol per glucose in the absence of NaOH (Table S4). These interactions varied to -13.9 and -16.6 kJ/mol per glucose in the presence of NaOH (Table S4). Such cellulose/urea (C-U) interaction is a combination of both electrostatic and dispersion terms rather than only HBs. Therefore, urea can be stabilized considerably by dispersion interaction with cellulose and is one of the physical origins that drives the accumulation. In the following, we further analyze the contribution of entropy in a different form.

3.2. Solvent Entropy

The dissolution of a substance is associated with a change in entropy, which can be viewed as a combination of several terms of different origins: the entropy of mixing, which is related to the concentration of the solution; the conformational entropy, which is related to changes in conformational freedom of the solute; and the entropy of the solvent. The two former terms are generally increasing upon dissolution, while the latter is decreasing due to excluded volume and increasing solvent order close to a solute. The dissolution of glucose and cellobiose in water has in both cases been shown to be endothermic (Zhao et al., 2013), which means the total entropy has to increase to allow dissolution. However, for a given number of glucose monomers, the entropy of mixing (per glucose) decreases

with increasing chain length, while the other terms remain approximately constant (Bergensträhle-Wohlert, d'Ortoli, Sjöberg, Widmalm and Wohlert, 2016). This means that there is a critical DP above which the reduction of water entropy becomes the dominating term, thus barring dissolution.

For studying the effect of different solvent systems on the dissolution of cellulose, we assume that the composition of the solvent has little effect on either the entropy of mixing or the conformational entropy of the cellulose chain because cellulose has little conformational freedom even in a solution state due to the ring structure and the rigidity of glycosidic linkage. Thus we focus on the entropy of the solvent (and co-solvent) molecules. The variation in solvent entropy with different conditions was systematically investigated using the 2PT method. The total entropies per solvent (or co-solvent) molecule are shown in Table 1. Pure water has an entropy of $S_w^W = 64.922 \pm 0.010$ J/mol/K per water molecule at 300 K, which is close to both experimental values (65.09 ± 0.13) and previous calculations using the same water model and method (Lin, Maiti and Goddard III, 2010). This indicates that 20 ps trajectories are sufficient for this purpose.

From Table 1 S(tot) values, and the components S(trn/rot/vib) in SI, one finds that adding one DP 20 cellulose chain in pure water induces an entropy reduction of the water of -0.006 J/mol/K per water molecule. In NaOH solution (B/W system) the corresponding reduction is -0.017 J/mol/K per water molecule. Figure 5a-d shows the variation of solvent/co-solvent entropy as a function of distance from the solute. Na^+ , OH^- , urea, and water all show similar decreasing trends close to the cellulose chain. Thus, the observed decrease of solvent entropy when cellulose is added to the solution is ascribed to constrained translational and/or rotational degrees of freedom in the vicinity of cellulose.

Interestingly, in the presence of urea, the reduction of water entropy was to some extent inhibited: ± 0.0 J/mol/K (U/W) and -0.008 J/mol/K (U/B/W) respectively (Table 1). The relatively smaller reduction of water entropy in the presence of urea can be explained by the enrichment of urea around the cellulose chain, which partially expels water to the bulk (2.3 water molecules per urea on average), leading to a translational entropy gain of the released water. This means that having urea in the solution increases the solubility of cellulose if only water entropy is considered. However, both Table 1 and Figure 5 show that also the entropy of urea is reduced upon the addition of cellulose. From the simulations, the reduction in entropy per urea molecule is calculated to be -0.035 J/mol/K (without NaOH) and -0.034 J/mol/K (with NaOH), respectively.

Although this reduction (per molecule) is larger than for water, the fact that the urea molecule is larger and thus fewer molecules in total are affected is important. By multiplying the calculated numbers by the total number of molecules of each species (see Methods), the total entropy changes are calculated. The total entropy change when adding one DP 20 cellulose chain to the solution becomes, for the different

systems: $\Delta S^W = -196$ J/mol/K, $\Delta S^{U/W} = -51$ J/mol/K, $\Delta S^{B/W} = -761$ J/mol/K, and $\Delta S^{U/B/W} = -503$ J/mol/K. This shows that the total entropy reduction is always smaller with urea present, meaning that the relative increase of water entropy from not having to be as tightly bound to the cellulose overcompensates the entropy reduction of associated urea.

Another way to view this is to consider the solvent entropy change upon mixing. From Table 1 one sees that using pure water as the reference state, the entropy change per water in the C/W system is $\Delta S_w^{C/W} = -0.006$ J/mol/K, which is within the error estimates of water entropy. Similarly, the entropy change due to urea is $S_w^{U/W} - S_w^w = -0.453$ J/mol/K. If no specific interactions existed between cellulose and urea, the entropy change for the C/U/W system would be the sum of the two, i.e., -0.459 J/mol/K. However, in the mixed system, this reduction was $S_w^{C/U/W} - S_w^w = -0.453$ J/mol/K, which is smaller than expected, but the difference is anyway within the estimated errors of the order of 0.01 J/mol/K. The excess entropy of water by mixing urea in the cellulose/water system can be temporally calculated as 0.006 J/mol/K. At the same time, urea loses 0.035 J/mol/K due to the presence of cellulose. Due to the much larger number of water molecules, the addition of the two contributions leads to a net increase. This effect is shown graphically in Figure 5 both without (e) and with (f) NaOH present in the solution.

The excess entropy of the box of having urea in the solution is $\Delta \Delta S^{C/U/B/W} = 258$ J/mol/K and $\Delta \Delta S^{C/U/W} = 145$ J/mol/K. This gives a free energy gain ($-T \Delta \Delta S$) of -77 and -44 kJ/mol at 300 K, respectively, which corresponds to -2.2 and -3.9 kJ/mol per glucose residue. Although the effect of urea is positive in terms of entropy, the total change in solvent entropy upon cellulose dissolution is still large and negative, thus lowering the temperature would increase the net entropy gain (Bergensträhle-Wohlert et al., 2016).

The excess entropy of combining urea in cellulose/water system we evaluated here is small compared to the standard error of the water entropy, and for a definitive answer, more calculation is needed to lower the error estimates. The concentration of cellulose in our simulation is only 0.44% which is much lower than standard experimental conditions. This was imposed by our choice of using a relatively long cellulose chain. We preferred to use a cello-oligomer with DP over 10 to represent the cellulose chain in our simulation and have decided to use DP 20 whose chain length is nearly 10 nm in a fully extended conformation. If a simulation box with a box size of less than 10 nm is used, the chain might interact with its mirror due to periodic boundary conditions. This consideration leads to a relatively large simulation box ($10 \times 10 \times 10$ nm³). However, due to the dilute concentration of cellulose, the effect of the presence of cellulose on the total entropy of water is small. Also, the estimation of entropy for such a large system is computationally expensive. Using a small simulation box and a smaller DP of cellulose (such as a box size of $4 \times 4 \times 4$ nm³ and DP 8), would increase the concentration of cellulose up to 3% leading to a larger effect, diminishing the water entropy fluctuation, so that the

Table 1

Absolute entropies per molecule of water, urea, Na⁺, and OH⁻ in the different solvent systems (W: water, U: urea, B: NaOH) with and without cellulose (C). "Diff" indicates the entropy change (per molecule) upon cellulose addition.

System	S_w (J/mol/K)	S_u (J/mol/K)	S_{Na} (J/mol/K)	S_{OH} (J/mol/K)
W	64.922±0.010	-	-	-
C/W	64.916±0.009	-	-	-
Diff.	-0.006	-	-	-
U/W	64.469±0.011	137.835±0.110	-	-
C/U/W	64.469±0.013	137.800±0.119	-	-
Diff.	0.0	-0.035	-	-
B/W	59.866±0.021	-	39.711±0.030	35.071±0.027
C/B/W	59.849±0.021	-	39.687±0.026	34.931±0.030
Diff.	-0.017	-	-0.024	-0.140
U/B/W	59.571±0.022	131.741±0.085	39.362±0.024	34.682±0.028
C/U/B/W	59.563±0.021	131.707±0.102	39.341±0.025	34.550±0.027
Diff.	-0.008	-0.034	-0.021	-0.132

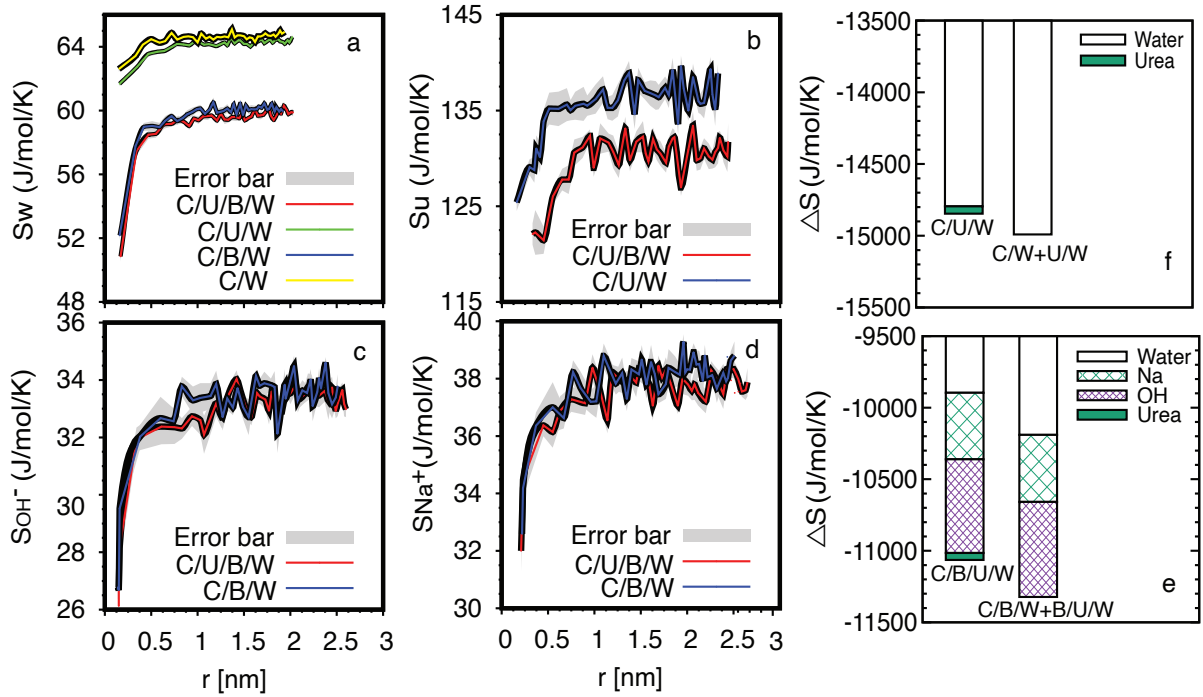


Figure 5: Entropy per molecule of water (a), urea (b), Na⁺ (c), OH⁻ (d) as a function of distance from the cellulose chain. (e): Total entropy variation in the U/B/C/W system in comparison to the sum of those from B/U/W and B/C/W. (f) Total entropy variation in the U/C/W system in comparison to the sum of those from C/W and U/W systems.

excess entropy would be higher than the error estimate in a reasonable simulation time.

3.3. Enthalpy of Mixing

In addition to the entropy change, the enthalpy of solvation also changes in the presence of urea and NaOH. The enthalpy is more straightforward to calculate from an MD simulation than the entropy. It is well known that adding NaOH to water is an exothermic process while adding pure urea or cellooligomers to water are both endothermic processes. However, the nature of the reaction when mixing a urea solution with either a cellooligomer solution or a NaOH

solution is not known. From MD simulations the enthalpy of mixing (ΔH_{mix}) can be estimated as follows:

$$\Delta H_{mix}^{C/U/W} = H^{C/U/W} - H^W - H^C - H^U, \Delta H_{mix}^{C/W} = H^{C/W} - H^W - H^C, \text{ and } \Delta H_{mix}^{U/W} = H^{U/W} - H^W - H^U,$$

where H^x stands for the total enthalpy of each (either liquid or solid) system. From this we define the *excess* enthalpy of mixing, $\Delta H_{mix,ex}^{C/U/W} = \Delta H_{mix}^{C/U/W} - \Delta H_{mix}^{C/W} - \Delta H_{mix}^{U/W} = H^{C/U/W} - H^{C/W} - H^{U/W} + H^W$. This is the deviation from the ideal mixture of two pre-formed solutions of urea and cellulose without the effects of dilution. This can be seen by writing $\Delta H_{mix,ex}^{C/U/W} = H^{C/U/2W} - (H^{C/W} + H^{U/W}) - \Delta H_{dil}$, where 2W means the double amount

Table 2

The decomposition of potential energy variation upon mixing of C/W and U/W, as well as C/B/W and U/B/W. (ΔE of C/U/W equals to $E_{C/U/2W} - E_{U/W} - E_{C/W} - E_{dilution}$; ΔE of C/U/B/W stands for $E_{C/U/2B/2W} - E_{U/W/B} - E_{C/W/B} - E_{dilution}$).

Pair Items	C/U/W		C/U/B/W	
	Coul	LJ	Coul	LJ
C-C	-13±4	7±1	-87±8	1±1
C-U	-683±20	-429±14	-279±7	-332±3
C-W	794±15	130±4	-44±54	160±7
U-U	-58±13	8±5	39±20	22±7
U-W	767±28	140±3	419±48	110±5
W-W	-850±15	37±6	-410±133	-30±10
C-Na ⁺	-	-	375±48	-32±5
C-OH ⁻	-	-	352±79	-41±13
Na ⁺ -Na ⁺	-	-	-815±43	1±0
Na ⁺ -OH ⁻	-	-	-1974±355	74±16
Na ⁺ -U	-	-	-124±23	9±1
Na ⁺ -W	-	-	3203±305	9±12
OH ⁻ -OH ⁻	-	-	2140±158	-23±2
OH ⁻ -U	-	-	-161±19	-2±2
OH ⁻ -W	-	-	-2933±106	76±10
Sum	-43±7	-106±3	-300±36	-1±2
ΔE	-140±9		-240±13	

of water, and ΔH_{dil} is the enthalpy of dilution. Writing $\Delta H_{dil} = H^{C/U/2W} - (H^{C/U/W} + H^W)$ one finds that $\Delta H_{mix,ex}^{C/U/W} = H^{C/U/W} - H^{C/W} - H^{U/W} + H^W$, just as above.

Using data from simulations we find that $\Delta H_{mix,ex}^{C/U/W}$ is -140 ± 9 kJ/mol, equalling to -7 kJ/mol per glucose (Table 2). Thus mixing of C/W and U/W is exothermic after correction for the effect of dilution. As shown in Table 2, energy decomposition analysis shows that this net enthalpy decrease is dominated by two terms: new cellulose/urea (C-U) interactions at short range due to accumulation of urea onto cellulose, and improved water/water (W-W) interactions as water molecules being expelled into bulk, reducing U-W interactions and increasing W-W interactions. Among the net enthalpy gain is 71% is due to LJ interactions (Table 2), most of which from interactions between cellulose and urea.

The mixing of C/B/W and U/B/W is also exothermic with $\Delta H_{mix,ex}^{C/U/B/W} = -240 \pm 13$ kJ/mol (Table 2), corresponding to -12 kJ/mol per glucose. The main contributions are Na⁺/Na⁺, cellulose/urea (C-U), OH⁻/W, and Na⁺/W interactions. In contrast to the C/U/W system, here the LJ energy change is zero. The net C-U energy change is negative, but is canceled by increased C-W and U-W LJ energies. The net energy change is thus dominated by decreased Coulomb energy, mainly from Na⁺/OH⁻ and OH⁻/W interactions.

Mixing of C/W and B/W is also exothermic with $\Delta H_{mix,ex}^{C/B/W} = -540 \pm 13$ kJ/mol (Table S5). Here, the enthalpy reduction is mainly due to favorable Coulomb energies from C/OH⁻, C/Na⁺, and W/W interactions, accompanying the accumulation of Na⁺ and OH⁻ onto cellulose.

The mixing of U/W and B/W is even more exothermic ($\Delta H_{mix,ex}^{U/B/W} = -1220 \pm 13$ kJ/mol), with the main contribution from LJ energy of U/OH⁻, Na⁺/W, U/W, and U/U terms. The interaction between NaOH and urea was also

suggested by the upfield shift of the ¹³C band of urea in NMR induced by the presence of the NaOH (Fang, Duan, Lu, Liu, Liu, Xu and Zhang, 2015b). However, RDF (Figure S4) shows no special coordination between urea/Na⁺ or urea/OH⁻. Experimental measurements of the enthalpy of this mixture would be interesting for comparison with our MD results.

The C/U/B/W system can be achieved by mixing of several different systems, such as B/W and C/U/W, or C/W and B/U/W. Energy decomposition analysis shows that both these mixing processes are exothermic (-1860 ± 13 and -780 ± 11 kJ/mol, respectively), as shown in Table S5. The mixing of C/W and B/U/W is fully Coulomb interaction dominated, and that of B/W and C/U/W is dominated by both Coulomb interactions and LJ interactions.

3.4. Excess Free Energy from Mixing

From the perspective of free energy, the mixing of C/W and U/W and the mixing of C/B/W and U/B/W are both enthalpically and entropically favorable, respectively, as shown above. The excess Gibbs free energy of mixing becomes

$$\Delta G_{mix,ex}^{C/U/W} = \Delta H_{mix,ex}^{C/U/W} - T\Delta\Delta S^{C/U/W} = -184 \text{ kJ/mol}$$

$$\Delta G_{mix,ex}^{C/B/U/W} = \Delta H_{mix,ex}^{C/B/U/W} - T\Delta\Delta S^{C/B/U/W} = -318 \text{ kJ/mol}$$

Adding urea corresponds to a free energy gain of -9.2 kJ/mol and -15.9 kJ/mol per glucose in the absence and presence of NaOH at 300 K, respectively, and thus favors the dope stability of cellulose. Its influence on enthalpy is relatively larger (-7.0 and -12 kJ/mol per glucose) than entropy (-2.2 and -3.9 kJ/mol per glucose).

4. Conclusion

By using MD simulations, we investigated the mechanism of urea-promoted dope stability of cellulose solution in water and alkali solution on the molecular level. From the perspective of thermodynamics, the improved stability of dope is due to a more favorable free energy of solvation, originating in both increased solvent entropy and decreased enthalpy. Upon dissolution, the reduction of water entropy induced by the solute (cellulose) was smaller in the presence of urea and this effect is enhanced in the presence of NaOH. The main mechanism behind the increased solvent entropy is that when urea adsorbs to cellulose, water molecules are expelled into the bulk. The translational entropy gain of the released water over-compensates the entropy loss of adsorbed urea because the urea molecule is relatively large. The enrichment of urea around the cellulose chain is driven by urea-cellulose dispersion interaction and maximization of solvent entropy rather than urea/cellulose hydrogen bonds. Besides, mixing C/B/W and U/B/W, C/W and B/W, B/W, C/U/W, or C/W and B/U/W are all exothermic and the enthalpy change is larger with urea present. Among the contributions to the free energy changes, the enthalpy change by adding urea is more important than the entropy change. This study provides a new fundamental understanding of the urea-induced dope stability of cellulose solution in concentrated alkali.

5. Declaration of competing interest

There are no conflicts of interest to declare.

6. Acknowledgments

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