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# Solvent effects on carbohydrate transformation: insights into chemical pathway modulation

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Carbohydrate utilization is a crucial aspect of sustainable resource development and offers a promising avenue for replacing fossil fuels. In carbohydrate reaction systems, solvent effects influence the interactions among carbohydrates, catalysts, and solvents. These can affect the reaction trajectory and selectivity, making them a crucial tool for cost-effectively regulating reactions. This review summarizes the primary types of carbohydrate chemical transformation and commonly used solvent systems, providing an overview of solvent effects in these reactions and an insight into solvent effects from a microscopic perspective. Additionally, it provides insights into the current state of solvent engineering and the challenges limiting the development of solvent-based carbohydrate transformation systems.

## Introduction

Recently, the impacts of fossil fuels on the environment have prompted concerted efforts to reduce reliance on them and to investigate renewable natural carbon resources. Carbohydrates, as renewable natural carbon resources in all types of biomass, play an important role in numerous biological processes, including energy storage and transportation, as well as serving as structural elements of living organisms, making them a powerful alternative to traditional fossil energy sources. Regenerative and abundant carbohydrates have become the main raw materials for the development of the sugar platform, which converts carbohydrates into high value-added products such as fuels, chemical raw materials, and biomaterials through chemical and biological technologies.[1] As a result, the sugar platform has become an important way to realize green chemistry and sustainable development.

Carbohydrates offer a compelling substitute for traditional fossil energy sources and exist as monomers, oligomers, polymers, or as part of biopolymers and other natural substances.[2] The simplest forms of carbohydrates are naturally occurring monosaccharides with five- and six-carbon atoms, including glucose, xylose, galactose, and fructose.[3] Oligosaccharides and polysaccharides, such as sucrose, maltose, cellulose, hemicellulose, and starch, are composed of different monosaccharides linked by glycosidic bonds with varying degrees of polymerization. This structural variety gives carbohydrates a versatile range of bonding patterns, structural arrangements, and spatial conformations. Polysaccharides can be divided into two major groups, homogeneous and heterogeneous, based on the structural uniformity of their sugar units.

The multitude of carbon and hydroxyl groups in carbohydrates make them highly versatile and amenable to modification. By incorporating reactive functional groups and specific chemical molecules, carbohydrates can be manipulated to yield target chemicals with substantially improved physical, chemical, and biological properties, all while preserving the structure of their carbon backbone and functional characteristics. Carbohydrates provide a sustainable carbon source, which has spurred the investigation of carbohydrate conversion pathways through chemical reactions such as deoxygenation, dehydration, hydrogenation, and hydrolysis. These processes involve breaking or reconfiguring the carbon skeleton of carbohydrates, producing novel chemical molecules.[4]

Valorization of carbohydrates often involves catalytic reactions, and both homogeneous and heterogeneous catalytic processes are methods of modifying and converting carbohydrates with a focus on improving reaction efficiency and product selectivity. The solvent plays a significant role in the modulation of the reaction. Adding polar aprotic solvents such as γ-valerolactone (GVL), tetrahydrofuran (THF), and dioxane to acid-catalyzed fructose conversion reactions improves the reaction rate and selectivity compared with aqueous solvents.[5] Similarly, dimethyl sulphoxide (DMSO) is a favorable solvent for the dehydration of carbohydrates into 5-hydroxymethylfurfural (HMF) due to its superior solubilizing capacity and differentiating effect, which prevents the formation of by-products such as levulinic acid (LA) and humins.[6–8] Solvent effects are crucial for achieving these objectives. In another study by Zuo *et al.*, choline chloride (ChCl) stabilized HMF

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production in aqueous-natural deep eutectic solvents (DESs) for carbohydrate conversion. The presence of water facilitated the transformation of Sn atoms in the catalyst, which promoted HMF production.[9]

Although solvent effects can be assessed both directly and indirectly through chemical reactions, further investigation into their fundamental nature is crucial. Shuai *et al.*[10] categorized solvent effects during biomass conversion into two groups: (1) those that affect the solubility of biomass constituents, including lignin, hemicellulose, cellulose, and biomass-derived molecules, such as sugars and furans; (2) those that influence the thermodynamics of chemical reactions. Varghese *et al.*[11] analyzed solvent effects in catalytic reactions and outlined intrinsic factors capable of altering the reactivity or performance of catalytic reactions and product selectivity. In order to obtain sustainable and efficient utilization of carbohydrate resources, it is essential to investigate the principles governing solvent effects and understand interactions between solvents and other substances. Moreover, solvent properties should be utilized to optimize their impact, form an effective chemical reaction system based on carbohydrates, and promote the conversion of carbohydrates into high-value renewable carbon resources.

In this review, we explore various chemical transformations involving carbohydrates, examine the pivotal role of solvent systems in such transformations, and provide a comprehensive overview of how these solvents influence the chemical reactions of carbohydrates. The solvent-solute interactions within these reaction systems form the basis of solvent effects. By conducting simulations, this study offers microscopic insights into the solvent effects and contributes to a broader understanding of their mechanisms. The final section of this review highlights critical considerations for solvent engineering advancements and presents prospects for future research in this field.

## Chemical pathways of carbohydrates

### Functionalization of carbohydrates

Functionalization is a widely used method to alter the physicochemical properties and enable carbohydrates, especially polysaccharides, to perform various functions. This approach is rooted in structure–function relationships and typically involves introducing groups with diverse properties onto polysaccharide molecules. Common techniques for polysaccharide modification include sulfation, acetylation, phosphorylation, carboxymethylation, methylation, and selenylation. It may also involve more complex functionalization methods, such as synthesizing polymer-grafted polysaccharides and hyperbranched polysaccharides.[12] Table 1 summarizes relevant information regarding the functionalization of various carbohydrates.

The structural reconstruction strategies of polysaccharides include introducing appropriate chemical groups to manipulate their physicochemical properties, such as hydrophobicity, mechanical strength, and charge profile, and creating reactive sites for grafting drugs or functional ligands, leading to enhanced properties and bioactivity.[22] The solubility of polysaccharides is typically determined by their structural arrangement. Polysaccharides that contain tightly packed hydrogen bond networks and a high crystallinity tend to have poor water solubility, which can be overcome by chemical modification routes. For example, introducing charged groups can disrupt intermolecular associations and enhance solubility. The hydrophobicity of polysaccharides such as hemicelluloses can be enhanced by incorporating hydrophobic groups such as benzene rings, long alkyl chains, and acyl chlorides.[23] Acetylation is often applied to branched polysaccharides, which stretches the branches, changes their direction, and aligns them in a laterally ordered state. This modification exposes hydroxyl groups of the polysaccharide and facilitates their dissolution in water.[24,25] However, the relationship between the degree of acetyl substitution and polysaccharide solubility is not strictly linear.[26] Solubility improvements of acetylated polysaccharides are attributed to an appropriate degree of substitution (DS) and a random distribution of acetyl groups.[27] Rao *et al.*[28] prepared films based on dialdehyde xylan hemiacetal by oxidation and hydration of xylan, which had tunable high tensile strength, flexibility, and transparency properties. This study reflects the application of structure reconstruction strategies for the mechanical strength of carbohydrate materials.

Introducing charged groups and electrostatic interactions between polysaccharides to form polysaccharide-based complexes is an important method for modifying and developing polysaccharides for various applications. Similarly, incorporating the hydrophobic properties of polysaccharides and drugs to facilitate self-assembly is another crucial strategy for creating polysaccharide-based drug delivery materials. Ma *et al.* prepared positively-charged quaternized xylan using 2,3-epoxypropyltrimethyl ammonium chloride and then coated it with negatively-charged γ-$Fe_2O_3$ using a reverse microemulsion method. The resulting xylan/γ-$Fe_2O_3$ composite was further modified with polylysine or folic acid to generate nanocomposites with vast biomedical applications.[29] Shen and colleagues synthesized graft polymers based on hemicellulose with incorporated hydrophobic chain fatty acids ranging from C4 to C18 in a homogeneous solution. The hemicellulose chains' flexibility allowed for the resulting polymers to self-assemble into rigid, spherical micelles in aqueous solutions *via* hydrophobic interactions. These micelles exhibited outstanding curcumin loading efficiency and release characteristics. Intriguingly, the study also revealed that the fatty acid chain length was crucial in determining the grafted polymers' physical and chemical properties and drug release profiles.[30]

The incorporation of various groups and molecules within polysaccharides imparts them with distinct antibacterial, antioxidant, and antitumor properties.[31,32] To this end, Yang *et al.* developed polysaccharide-peptide conjugates utilizing a biphasic system containing water, *N*,*N*-dimethylformamide (DMF), and $CCl_4$ and correlated the solvent properties between the polysaccharide initiators and *N*-carboxyanhydrides. The experiment demonstrated the effect of solvents, wherein the

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**Table 1** Construction of carbohydrates derivatization systems

| Carbohydrate derivatization type | Carbohydrate | Solvent | Catalyst | Derivatization reagent | Yield | Substitution efficiency (DS) | Remarks | Ref. |
|---|---|---|---|---|---|---|---|---|
| Sulfonation | Starch | Sulfamic acid–urea (molar ratio = 1 : 2) | —[a] | Sulfamic acid | — | 0.027 | Starch participated in the reaction as substrate and a part of solvent DES. | 13 |
| Sulfation | Diethylaminoethyl-cellulose | 1,4-Dioxane | Urea | Sulfamic acid | — | Sulfur content (wt%): 10.1 | Basicity and permittivity of solvent affected the efficiency of sulfation. | 14 |
| Sulfation | Oligoguluronic acid | DMF | — | $SO_3$: pyridine | — | 0.29–1.03 | Modified carbohydrates showed remarkable immunomodulatory effects. | 15 |
| Sulfation | *Cyclocarya paliurus* polysaccharides | Formamide | — | 1 : 7 ratio of chlorosulfonic acid to pyridine | 86.33 ± 1.45% | 0.17 | Modified polysaccharides improved biological activity. | 16 |
| Carboxymethylation | *Cyclocarya paliurus* polysaccharides | Isopropanol | — | A mixture of 10 mL 20% NaOH, 3 g chloroacetic acid, and 20 mL isopropanol | 69.16% ± 2.65% | 0.29 | Modified polysaccharides improved biological activity. | 16 |
| Esterification | MCC | 1-Allyl-3-methylimidazolium chloride-DMSO | Imidazole | *N*-Acylimidazole | — | 2.43 | Favorable activation enthalpy; lower solution viscosity; larger empirical polarity and basicity, and stronger biopolymer-solvent interactions favored higher IL-DMSO reactivity. | 17 |
| Benzylamination | Carboxymethyl cellulose | Milli-Q water | 1-Ethyl-3-(3-(dimethylamino) propyl)carbodiimide hydrochloride | Benzylamine | — | 0.05 | Functionalization enhanced product hydrophobicity for subsequent self-assembly reactions. | 18 |
| Acetylation | *Millettia speciosa* Champ polysaccharide | NaOH aqueous solution | — | Acetic anhydride | — | — | Modification effectively improved the emulsification performance of polysaccharide. | 19 |
| Propionylation | MCC | [EMIM][OAc]/1-methylimidazole or DMSO | — | Propionic anhydride | — | — | A large amount of co-solvents and a small amount of IL (10%) of the reaction solvent environment improved the propionyl : acetyl ratio. | 20 |
| Other modification | MCC | DMSO/1,8-diazabicyclo[5.4.0]undec-7-ene/$CO_2$ | 1,8-diazabicyclo[5.4.0]undec-7-ene | Isothiocyanate | 51% to 81% | 0.52–2.16 | A switchable solvent system connected cellulose dissolution, isothiocyanate formation, and *O*-cellulose thiocarbamates formation in tandem. | 21 |

[a] Not mentioned.

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polymerization rates of the mixed-solvent systems decreased upon increasing the solubility parameters. This was because solvents with high dielectric constants and polarities hindered binding interactions between the polypeptides and *N*-carboxyanhydrides. These polysaccharide-peptide conjugates displayed promising antimicrobial properties.[33]

Solvents provide optimized pathways for enhancing the reaction efficiency of various carbohydrate modification systems. Ge *et al.*[34] demonstrated cellulose modification reactions in novel DESs and ionic liquids (ILs) solvent systems, which indicated the substantial potential of novel solvent systems to construct cellulose and other carbohydrate modification systems (Fig. 1 and 2).

### Carbohydrate conversion

Carbohydrate conversion generally disintegrates the original structure to produce novel and valuable products. This process encompasses the transformation of carbohydrates into both fuels and platform compounds. In developing the pathway from carbohydrates to fuels, the aqueous phase reforming (APR) process is an environmentally sound catalytic method for reducing the oxygen content of carbohydrate feedstocks by generating hydrogen *in situ* under high-pressure and low-temperature reaction conditions. This process transforms biomass-derived oxygenated compounds, such as sugars, glycerol, and sugar alcohols, into carbon oxides, methane, or hydrocarbon derivatives.[35] Since the APR process was proposed by Cortright *et al.* in 2002, fuel production from carbohydrates, alcohols, and other hydrocarbons has been explored in numerous studies.[36–38] Carbohydrate derivatives, including HMF,[39] furfural,[40] LA,[41] and GVL[42] have also demonstrated their importance as hydrogenation sources in biofuel production.

Various platform chemicals have been identified as precise targets for carbohydrate conversion. Polysaccharides such as cellulose and hemicellulose are hydrolyzed into monosaccharides, which are then converted into a range of platform compounds, including HMF, furfural, formic acid, LA, GVL, and succinic acid.[43] The main processes involved in these conversion reactions include polysaccharide hydrolysis, monosaccharide dehydration, hydrogenation, isomerization, and retro-aldol condensation (Fig. 3 and 4). However, these complex reaction pathways often produce numerous side reactions and by-products. Table 2 summarizes relevant studies on carbohydrate conversion and highlights solvents' essential roles in accelerating these reactions, suppressing by-product formation, and stabilizing products.

## Carbohydrate chemical reaction solvent systems

### Conventional solvents

Traditional solvents play a fundamental role in the upgrading process of carbohydrates, encompassing a wide range of organic solvents (hydrocarbons, alcohols, ketones, esters, ethers, nitrogen- and sulfur-containing compounds, *etc.*) as well as inorganic solvents (water, ammonia, strong acids, molten salts, *etc.*). Due to their versatility, diverse properties, low cost, and easy recovery, conventional solvents are widely used for polysaccharide modification and carbohydrate conver-

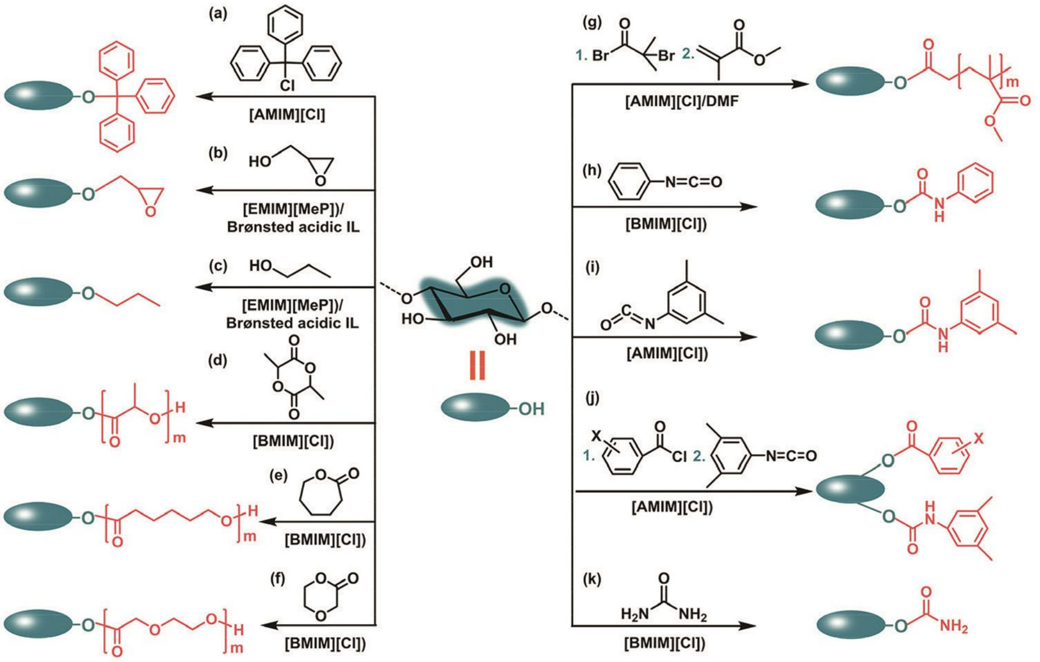

**Fig. 1** Etherification, grafting, and carbanilation reactions of cellulose for functionalization in ILs. Reproduced from ref. 34 with permission from [Royal Society of Chemistry], copyright [2021].

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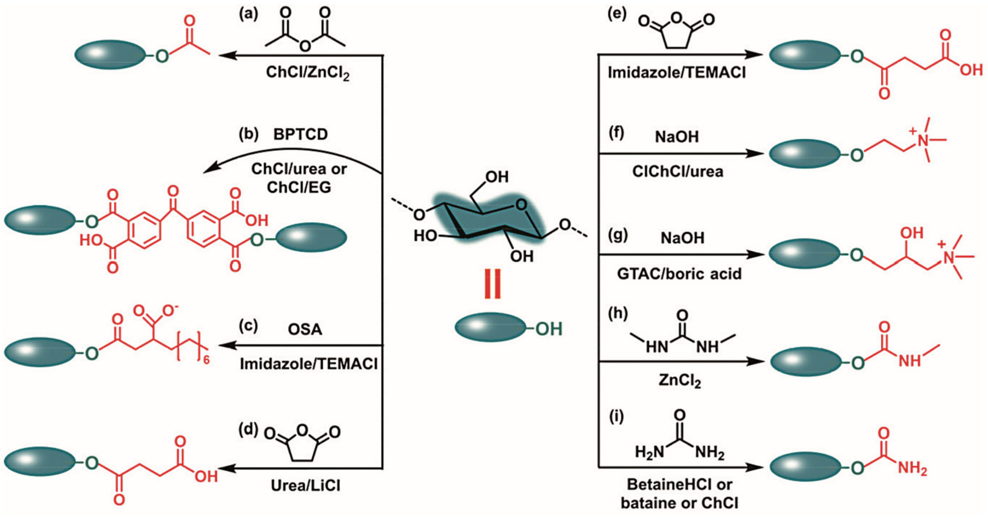

**Fig. 2** Functionalization of cellulose in DESs. Reproduced from ref. 34 with permission from [Royal Society of Chemistry], copyright [2021].

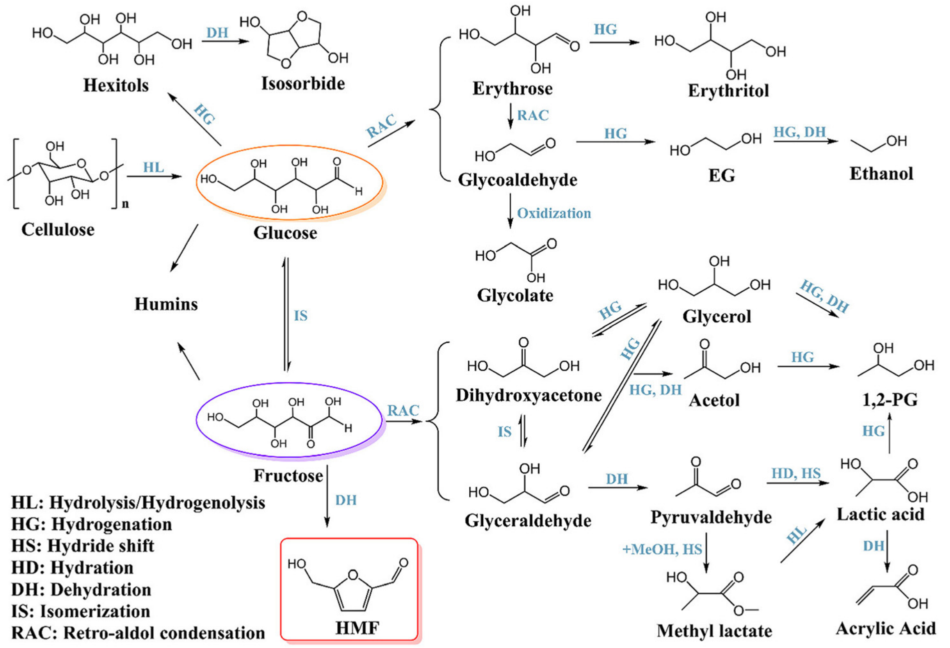

**Fig. 3** Cellulose conversion flowchart. Reproduced from ref. 43 with permission from [Royal Society of Chemistry], copyright [2023].

sion in traditional solvent systems. In inorganic solvents, molten salt hydrates can serve as an effective non-derivatization solvent to promote further conversion of carbohydrates represented by cellulose.[52] Similarly, acid solutions have a facilitating effect on the hydrolysis and dehydration of carbohydrates.[53] For organic solvents, they show advantages over water in the carboxymethylation of polysaccharides in terms of faster heat transfer, fewer side reactions, and a homogeneous environment.[54] Furthermore, several studies have highlighted that organic solvents increase the solubility, customizability, and conversion efficiency of carbohydrates.[55,56] GVL, a renewable lignocellulosic biomass derivative, has also been shown to enhance other reactions during the conversion of lignocellulosic materials.[57] Kinetic calculations revealed that the apparent activation energy for furfural production from polysaccharides was lower in GVL than in aqueous media, while the apparent activation energy for furfural degradation was higher. This suggests that GVL may promote furfural production while inhibiting furfural degradation.[58]

### Water

Water is an abundant, inexpensive, non-toxic, and harmless solvent with a high boiling point and polarity, making it an ideal green solvent. The physiological importance of water in

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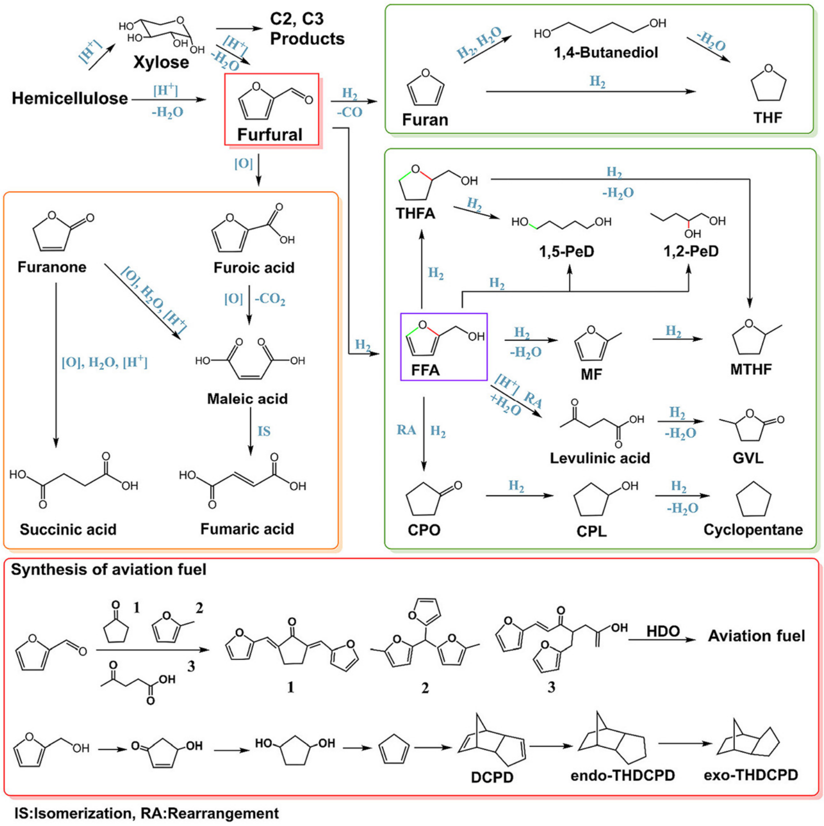

**Fig. 4** Hemicellulose conversion route map based on furfural. Reproduced from ref. 43 with permission from [Royal Society of Chemistry], copyright [2023].

the functioning of biological macromolecules, such as polysaccharides, proteins, and nucleic acids, is well-established. It facilitates a range of life-sustaining processes with the aid of various enzymes and cofactors. Although water shows excellent potential as a solvent for biotransformations involving biomolecules, chemical reactions in water that exclude organism catalytic effects require careful consideration of additional influential factors, especially when dealing with polysaccharides, a common form of carbohydrates.

Before delving into the core topic, it is crucial to consider the complex interplay between polysaccharides and water. Polysaccharides have abundant hydroxyl groups that offer numerous hydrogen bonding sites. In contrast, water is a simple yet versatile compound composed of hydrogen and oxygen atoms and can engage in a range of hydrogen bonds with polysaccharides. These hydrogen bonds help break down the hydrogen bond networks between polysaccharide molecules, thus dismantling and reconstructing polysaccharide hydrogen bond systems. As such, hydrogen bonding interactions are pivotal to the solvation process of polysaccharides in water.

Both carbohydrate hydrolysis and hydrothermal treatment are essential to the applications of carbohydrates in water-based systems. Cellulose contains hydrogen bond networks and β-1,4 glycosidic bonds with low reactivity, which impede water from penetrating crystalline regions and result in slow cellulose breakdown in aqueous media. Consequently, elevated temperatures and acid catalysis are generally necessary to enhance the breakdown efficiency. The acid-catalyzed hydrolysis of cellulose involves the protonation of glycosidic oxygen to produce water-soluble cellulose oligomers by cleaving the β-1,4-glycosidic bonds, ultimately generating glucose.[59] In this process, water competes with the hydroxyl groups of carbohydrates for protons, in which protonation is the rate-limiting step for carbohydrate degradation under acidic conditions. However, hydrogen bonding between water molecules and hydroxyl groups in carbohydrates disrupts the relative stability of C–C or C–O bonds to varying degrees, which then changes the subsequent reaction pathways.[60] One notable example of polysaccharide hydrolysis and subsequent process application is the conversion of polysaccharides to HMF, which involves the hydrolysis of polysaccharides such as starch and cellulose into glucose. This is followed by the isomerization of glucose to fructose and the dehydration of fructose to obtain HMF. In this process, water plays an essential role in determining the reaction efficiency. During cellulose conversion to HMF, the cellulose conversion initially increased after adding 5–10 mL of water but then decreased when more than 10 mL of water was added.[61] This was due to the diluting effect of excess water, which impeded the dissolution of cellulose and reduced

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**Table 2** Solvent effects in carbohydrates conversion systems

| Carbohydrate | Product | Solvent system | Catalyst | Yield | Remark | Ref. |
|---|---|---|---|---|---|---|
| Glucose | Humin-type polymers | Methanol–water (mass ratio: 0.22–10) | Amberlyst 70 | —[a] | Under different ratios of methanol/water solvent mixes, the water-rich medium favored polymer formation, while the methanol-rich medium significantly inhibited polymer formation. | 44 |
| Glucose | HMF | ChCl–water–acetone ternary solvent (mass ratio = 1 : 2 : 3) | $H_2SO_4$ | 73.3 mol% | Acetone contributed to the *in situ* extraction of the product HMF, promoting the swelling of the substrate and the transfer of acid protons. Water promoted the non-selective reaction but also reduced the viscosity of the solvent phase. | 45 |
| Xylose | Furfural | Polar aprotic organic solvents (water, GVL, dioxane or THF) | Various types of catalysts | — | Aprotic organic solvent altered the stability of the acidic proton relative to the protonated transition state, therefore affected carbohydrate conversion reaction kinetics. | 46 |
| Fructose | Furfural | γ-Butyrolactone | Hβ zeolite | 50.3% | Solvent inhibited product degradation. | 47 |
| Fructose | HMF | *N*-Methyl-pyrrolidone | Hβ zeolite | 81.1% | Solvent coordinated catalyst for selective catalysis. | 47 |
| Fructose | HMF | Acetone–water (volume ratio = 4 : 1) | HCl | 85.7% | Water helped intermolecular hydrogen transfer and speeded up the reaction, and acetone inhibited the degradation of HMF by preferentially solubilizing the reactive groups of HMF. | 48 |
| MCC | Reducing sugar | [BMIM][Cl] | Sulfonated carbon material | 72.7% | Water exhibited solvent effects that increased mass transfer, affected catalytic effects, and affected substrate solubility. | 49 |
| Hemicellulose | Furfural | Water-*p*-xylene | Zeolites: HUSY (Si/Al = 15; 0.3 g) | 56.0% | Water possessed polar proton properties that allowed it to form a solvent layer around the active site of the catalyst, affecting the catalytic efficiency. The biphasic solvent system facilitated product separation and protected the products from degradation. | 50 |
| Cellulose and xylan | LA | Water-dimethoxymethane | Amberlyst 15-$Al_2(SO_4)_3$ bifunctional catalyst | 52.5% | The biphasic solvent system facilitated the separation of products and promoted the reaction. Dimethoxymethane as an electrophilic reagent promoted the conversion of furfural to HMF and improved the yield of LA. Water facilitated the conversion of HMF to LA, and the yield of HMF was reduced. | 51 |

[a] Not mentioned.

the hydrolysis rate by hindering access to the active acid sites on the catalyst surface. Moreover, the high polarity and hydrogen bonding properties of water destabilized multiphase acid catalysts, particularly when the catalyst is exposed to high temperatures or prolonged heating in water. This will form undesired by-products such as LA and formic acid, consequently reducing the yield of HMF.[62]

Similarly, hydrothermal treatment is a common industrial process that involves interactions between polysaccharides and water. This process involves exposing water to high temperatures and pressures in either subcritical or supercritical states, which modifies its physical and chemical properties. These changes can include alterations to ionic products, density, viscosity, dielectric constant, *etc.*[63] Due to these modifications, water can become an optimal solvent for non-polar substances. Additionally, at high temperatures, the high ionic product of water promotes acid–base-catalyzed reactions, which may impact the kinetics and selectivity of chemical reactions.[64] It is worth noting that the crystallinity significantly affects cellulose dissolution and conversion in water. In supercritical water, microcrystalline cellulose (MCC) crystals may swell or dissolve at the surface layer and form amorphous-like cellulose molecules more easily hydrolyzed into low-degree polymerization cellulose and cellulose oligosaccharides. Hydrogen bond networks are cleaved to allow hydrolysis products to transition from the polymer to the aqueous phase.[65] Cantero *et al.*[66] demonstrated that the proton concentration in the reaction medium is crucial for the hydrothermal selective hydrolysis of cellulose. Glucose isomerization to fructose and dehydration to HMF are reactions that are highly dependent on the ion concentration. The retro-aldol condensation reaction pathway can be enhanced by controlling the temperature and pressure and increasing the pOH/pH, which weakens the isomerization/dehydration pathway. At 400 °C and a pressure of 25 MPa, cellulose produced sugar yields exceeding 95 wt%, with HMF yields remaining below 0.01 wt%.

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### Ionic liquids (ILs)

ILs are molten salts composed entirely of organic cations and organic/inorganic anions that remain in the liquid state at or below 100 °C.[67] Due to their low vapor pressure, excellent thermal and chemical stability, remarkable solubilizing capability, high ionic conductivity, and superior designability,[68,69] ILs have demonstrated outstanding potential in carbohydrate biomass pretreatment, solubilizing, chemical reaction media to enable carbohydrate chemistry. In addition, IL-based carbohydrate materials have been developed with desirable properties. These advantages make ILs promising materials in carbohydrate science and technology.[70–77] ILs engage in complex interactions involving Coulomb forces, hydrogen bonds, and van der Waals forces.[78] These facilitate interactions with polysaccharides, resulting in successful solubilization. In particular, cellulose is a significant target for IL solubilizing, and numerous studies have shown that strong hydrogen bonds between IL anions and the equatorial hydroxyl groups of cellulose act as a key driving factor in solubilizing molecules.[79]

The extent to which cations contribute to the solubilizing capacity of ILs is still a matter of debate. Zhang *et al.* investigated the dissolution mechanism of 1-ethyl-3-methylimidazolium acetate ([EMIM][OAc]) in cellobiose using nuclear magnetic resonance (NMR) spectroscopy.[80] The study concluded that the relatively small free acetate anions initially targeted the hydrogen atoms of the cellobiose hydroxyl groups. This was followed by the rapid binding of the aromatic protons of the bulky cation $[EMIM]^+$, particularly H2, to the oxygen atoms of the cellobiose hydroxyl groups. Other research has confirmed the role of cations in solubilizing cellulose.[81]

Along with their adaptable design, ILs present significant potential for exploring their mechanism of action and establishing regularity conditions, which enables targeted modifications directed towards specific applications to create customized solvents. One crucial parameter that determines an IL's ability to dissolve cellulose is the hydrogen bond basicity of its anion, as noted by Wang *et al.*[82] Xu *et al.* further supported this by finding a direct correlation between cellulose solubility in ILs and the hydrogen bond acceptability of anion.[83] Additionally, the acidic protons of the cation can bind with cellulose's hydroxyl and ether oxygen atoms to form hydrogen bonds and promote cellulose solubilization. The existence of highly electronegative atoms, such as oxygen or nitrogen in the cationic backbone, as well as larger phenyl groups in the alkyl chain, can lead to competition or steric hindrance of the anions. Upon increasing the cationic alkyl chain length or symmetry, the rate of cellulose dissolution in an IL decreases due to increased IL viscosity and reduced hydrogen bond acidity.[84] Therefore, when selecting appropriate IL solvents for cellulose solubilization, anions with strong hydrogen bond basicity and asymmetric cations with short alkyl chains are preferred. Acidic protons on the main chain should be considered, while highly electronegative atoms and larger groups should be avoided. There is a fundamental correlation between the structure and dissolution capability of ILs. However, the specific dissolution performance of cellulose is determined by the ionic interactions between cations and anions within ILs, as well as other contributing factors.

In systems containing ILs and polysaccharides, it is crucial to assess the modulating effect of water. When the concentration of water added to the IL exceeds 1 wt% (approximately 0.5 mole fraction water), it can influence the interactions occurring in the system. Water may establish strong hydrogen bonds with the anions of the IL or compete with the IL and bond with cellulose, thus inhibiting interactions between anions in the IL and cellulose and decreasing its solubilization capacity. In either scenario, the IL's ability to dissolve cellulose is affected by weak anion-cellulose hydrogen bonding.[79] On the other hand, this can be exploited to promote cellulose precipitation by water in IL, and the contact mode between water and IL likewise regulates the morphological characteristics of the regenerated cellulose.[72]

Further, due to the complex interactions and natural ionic properties within ILs, ILs are endowed with mass transfer and catalytic properties in addition to solubilization. The specific chemical structures of the anions and cations in proton ILs make them acidic, and the catalytic activity of ILs is closely related to their acidity. The high proton acidity of *N*-methylmorpholinium methyl sulfonate $[NMM][CH_3SO_3]$ was positively correlated with its catalytic activity, yielding 74.8% of HMF from fructose. In addition, under the condition of similar acidity, the catalytic activity of *N*-methylmorpholinium hydrogen sulfate $[NMM][HSO_4]$ (23.4% HMF yield) was much higher than that of 1-methylimidazolium methyl sulfonate $[MIM][CH_3SO_3]$ (12.5% HMF yield), which could be attributed to the steric effects and nucleophilic effects of the $[NMM]^+$ in the dehydration reaction.[85] The above studies confirmed the excellent moldability of ILs as green solvents and catalysts.

### Deep eutectic solvents (DESs)

Since they were initially proposed by Abbott *et al.* in 2003, DESs have garnered significant attention as eco-friendly solvents.[86] The formation of DESs is typically facilitated through hydrogen bonding, whereby one component serves as a hydrogen bond donor (HBD), and the other serves as a hydrogen bond acceptor (HBA). The low lattice energy of asymmetric ions and charge delocalization between HBA and HBD molecules through hydrogen bonding gives DESs lower melting points than their individual components.[87,88]

Some studies have suggested that DESs are analogs of ILs, possibly due to the presence of salts or solids in room-temperature ILs, particularly those based on choline cations.[89,90] However, this is not strictly accurate because ILs comprise discrete anions and cations, while DESs consist of non-ideal mixtures of two or more compounds. As a result, the properties of DESs are influenced by their constituent substances and their mutual molar ratios. DESs may also possess properties beyond their individual constituent components.[91] Owing to their remarkable hydrogen bonding properties and ease of preparation and design, DESs can interact with polyhydroxy compounds through hydrogen bonding, thus increasing their solu-

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bility in DESs. DESs with excellent solubilization capacity have been widely utilized as solvents, reaction media, and materials. More recently, natural deep eutectic solvents have been introduced, which are produced from components such as organic acids, amino acids, sugars, choline, or urea, sourced from the primary metabolites of various organisms. Natural deep eutectic solvents hold immense promise as high-quality solvents for metabolites with low-to-medium polarity and biological macromolecules such as DNA, proteins, and polysaccharides.[92] They may also act as more environmentally friendly non-aqueous platforms for biosynthetic applications compared with organic solvents.

As solvents, DESs are featured for their ability to form hydrogen bonds. The highly electronegative anions in HBAs and HBDs can establish hydrogen bonds with polysaccharides and tune hydrogen bond networks between DESs and polysaccharides to facilitate polysaccharide solubilization.[93,94] DES has been shown to be highly effective in the pretreatment of lignocellulosic biomass due to this characteristic. Yu *et al.*[95] achieved fractionation and refining conversion of the three major components in lignocellulose by utilizing diol-based DESs to obtain high-quality cellulose, hemicellulose-derived xylose and furfural, and lignin polyols. The long-chain diol molecules enabled the lignins to be alkoxylated to have hydroxyl tails, which enhanced the steric hindrance and inhibited the competitive adsorption of lignin. Meanwhile, the high dissolving capacity of DES for lignin contributed to the optimal separation of lignin from carbohydrates. These effectively inhibited the lignin condensation and also facilitated further cellulose conversion. Lou *et al.*[96] demonstrated the effective separation of carbohydrates and protolignin from lignocellulose by ChCl/urea. ChCl/urea served a dual function during treatment, utilizing the hydrogen bonding capacity to promote lignocellulose deconstruction and lignin solubilization. Further, the decomposition of urea to $NH_3$ at 150 °C provided a nucleophilic reagent to break lignin-carbohydrate esters.

Prior researches focused on evaluating the polysaccharide solubilization capacity of ChCl-based DESs.[97,98] ChCl can act as a hydrogen bond acceptor due to the presence of $Cl^-$, making ChCl-based DESs the most common type of DESs. Various investigations have been carried out to improve the solubilizing capability of DES and broaden their range of applications by modulating their structure–property relationship. Due to the vital effect of anions on the solubilization ability, substituting $Cl^-$ with $OAc^-$, choline acetate/imidazole increased hemicellulose's solubility to 35 wt%.[99] For example, ChCl/urea (1 : 2) could not dissolve MCC, even after being heated at 110 °C for 12 h, while choline acetate in conjunction with 15 wt% tributylmethylammonium chloride achieved 6 wt% solubility of MCC in just 10 min under the same conditions.[100]

The outstanding ability of DESs to dissolve carbohydrates gives them great potential for the modification and conversion of such compounds. In a recent study, Azougagh *et al.*[101] prepared acylated hydroxyethylcellulose based on the homogeneous solubilization of benzyltriethylammonium bromide/urea without needing a catalyst. A DES composed of $FeCl_3$-$6H_2O$/ethylene glycol was used to convert cellulose to gluconic acid by providing a homogeneous environment and acidic properties that enabled the hydrolysis of the dissolved cellulose to glucose. Subsequently, glucose was oxidized to gluconic acid by $FeCl_3$ in a yield of 52.7%. Gluconic acid could be conveniently separated from the reaction system *via* self-precipitation.[102]

Water plays a crucial role in facilitating hydrogen bond formation in DESs containing hydrated metal salts by affecting the interactions between DESs and cellulose. A recent study by Tong *et al.*[103] demonstrated that water reduced the acidity of the solvent, thereby inhibiting cellulose degradation. However, excessive water reduced cellulose's solubility and prolonged its dissolution time. The authors found that a DES comprised of $ZnCl_2$, water, and formic acid (1 : 1 : 4 molar ratio) exhibited superior solubility toward MCC (16.33 wt%) and better solubilized other biomasses containing a high cellulose content.

In a separate investigation, Zhong *et al.* developed choline hydroxide (ChOH)-based DESs by manipulating the basicity of HBA to evaluate its effect on cellulose's solubility. Given the challenges associated with removing water molecules from aqueous ChOH solutions, the authors conducted experiments using a water gradient to investigate the impact of water content on solvents for cellulose. The results of these experiments showed that ChOH/urea, containing approximately 11 wt% water, exhibited the optimal solubilization of MCC (9.51 wt%). Furthermore, the hydrogen bond basicity parameter of ChOH/urea was 1.88, which is significantly higher than the corresponding parameter of other DES based on ChCl or ChOH (<0.6). This highlights the importance of hydrogen bond basicity in improving the solubilization capacity. Zhong *et al.* observed that ChOH/urea showed a maximum solubilization capacity towards MCC at a water content of approximately 11 wt%, which decreased as the water content increased.[104] Compared with ILs, ChOH/urea showed better water-resisting property. However, it should be noted that both ILs and DESs are sensitive to water content with varying interactions and hydration processes, leading to significant physicochemical differences according to structural characteristics.[105] Thus, further research is required to investigate the potential advantages and disadvantages of water on the solubilization capacity of IL and DES.

### Supercritical fluid

Supercritical fluids (SCFs) are liquids with temperature and pressure above critical values and no obvious gas–liquid boundary. SCFs differ from both gases and liquids and have many unique physicochemical properties. SCFs have densities close to those of liquids, two orders of magnitude greater than those of gases, and thus have solvation capacities comparable to those of conventional liquid solvents. On the other hand, the viscosities of SCFs are close to those of gases, which favors an increase in the diffusion coefficient and provides superior mass transfer rates and separation effects. Near the critical

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value, small changes in pressure and temperature will cause significant changes in the properties of SCFs, such as density, viscosity, diffusion coefficient, and dielectric constant. Therefore, the thermodynamic properties, heat and mass transfer coefficients, and reaction rates can be controlled by adjusting the pressure and temperature within a specific range. The excellent physical and chemical properties of SCFs make this kind of green solvent exhibit promising application prospects in many fields, such as extraction and separation, chromatography, chemical reaction, material synthesis, environmental protection, and cleaning.[106]

Common SCFs include supercritical $CO_2$, water, ethane, propane, ethylene, propylene, ethanol, and butanol, but the first two are the most widely used. The utilization of supercritical $CO_2$ and supercritical water in the carbohydrate industry mainly focuses on solubilization, extraction, fractionation, reaction media and bio-based materials preparation. The fractionation of carbohydrates in supercritical $CO_2$ is based on solubility differences. This process can be modulated by using small amounts of polar organic co-solvents such as methanol, ethanol, or isopropanol to obtain carbohydrates with different degrees of polymerization.[107] Montañés *et al.*[108] used different ethanol/water mixtures as co-solvents in supercritical $CO_2$ to selectively separate galactooligosaccharides from dairy-based prebiotic ingredients by optimizing temperature, pressure and co-solvent flow rate. Barbosa *et al.*[109] successfully extracted polysaccharides with antioxidant properties from mushrooms using hot water combined with supercritical $CO_2$. Gong *et al.*[110] extracted polysaccharides with antioxidant and hypoglycemic properties from *Ginkgo* leaves by supercritical $CO_2$ extraction using ethanol as a co-solvent.

The supercritical environment provides favorable conditions for chemical reactions. SCFs provide large diffusion coefficients and low viscosities, which overcome the mass transfer resistance in general fluids and allow reactant molecules or ions to make rapid and adequate contact. The solubilities of reactants and products in SCFs vary with molecular weight, temperature, and pressure changes. The modulation of solubilities facilitates the reaction conversion and forward reaction. In recent years, supercritical water gasification catalyzed biomass hydrogen production has developed rapidly, and the conversion of waste biomass into hydrogen-rich syngas under high temperature and pressure has emerged as a promising direction for biorefinery. The entire process includes water–gas shift, methanation, steam reforming, hydrogenation, dehydration, decarbonylation, decarboxylation, and Boudouard reactions.[111] Gökkaya *et al.*[112] applied hydrothermal gasification of xylose under supercritical conditions, and the gasification efficiency reached a maximum of 86% at 20 MPa and 600 °C with the addition of the catalyst $K_2CO_3$.

In supercritical hydrothermal gasification, temperature and pressure are the most important regulatory parameters that affect the reaction mechanism, product yield, and gasification efficiency. Based on different temperature conditions, the reaction mechanism may be either an ionic or a free radical effect. Under subcritical conditions, when the reaction temperature and pressure are below critical values, the dissociation of water releases a large amount of $OH^-$ and hydronium hydrate ions, which provide sufficient hydronium hydrate ions for carbohydrate acid-catalyzed reactions.[113] Therefore, the ionic reaction pathway is favored at low temperatures when the ionic concentration of water is high. When the temperature exceeds the critical point, hydrated hydrogen ions outnumber $OH^-$, which can lead to a decrease in the ionic concentration and pH of supercritical water, leading to the generation of free radicals in the water, triggering the reaction of the free radicals and accelerating the decomposition process of the biomass.[114] The ionic mechanism promotes hydrogenation and methanation reactions to produce $CH_4$, while the radical mechanism benefits hydrolysis and aqueous gas transfer, resulting in higher $H_2$ yields and improved gasification efficiency.[115] The mechanistic effects of pressure on hydrothermal gasification reactions are still being investigated. Under critical temperature conditions, high-pressure conditions result in supercritical water with higher water density compared to low-pressure conditions.[106] Higher water density increases the ionic products and favors the ionic mechanism over the free radical mechanism. The unique characteristics of supercritical water can only be expressed beyond the saturation pressure, so the pressure plays a vital role in regulating the supercritical state of water. However, beyond the saturation pressure, increasing the pressure did not significantly improve but instead affected the $H_2$ yield.[111] In summary, temperature and pressure have essential effects on the conversion of carbohydrates in SCFs and need to be regulated with a focus on optimizing the reaction system.

### Mixed-solvent systems

Due to the inherent limitations of single-solvent properties, mixed-solvent systems are becoming increasingly popular for developing novel solvents. These systems typically consist of two or more components that form complex solvent–solvent and solvent–solute interactions. In particular, polar aprotic solvents exhibit specific interactions with water, as shown in Fig. 5a. Hydrophilic reactants contribute to forming local solvent domains around hydroxyl groups, resulting in a higher density of water molecules near reactants compared with the overall water molecule density in the solvent. In a mixed solvent, the apparent free energy barrier of a reaction can be reduced compared with that of the overall solvent by stabilizing protons and transition states (TSs) in the water-rich local domain, as depicted in Fig. 5b.[116] The mixed-solvent approach seeks to decrease solvent viscosity, enhance mass transfer, improve solvent effectiveness, reduce expenses, and simplify recovery. This concept has propelled numerous researchers to examine the process of material interactions and modifications to the physicochemical properties in mixed-solvent systems. This approach offers new avenues for boosting industrial production efficiency and maximizing solvent efficacy.

The complexity of mixed solvents calls for a comprehensive examination of interactions occurring in these solvent systems. To this end, Zhao *et al.* used quantum chemical calculations

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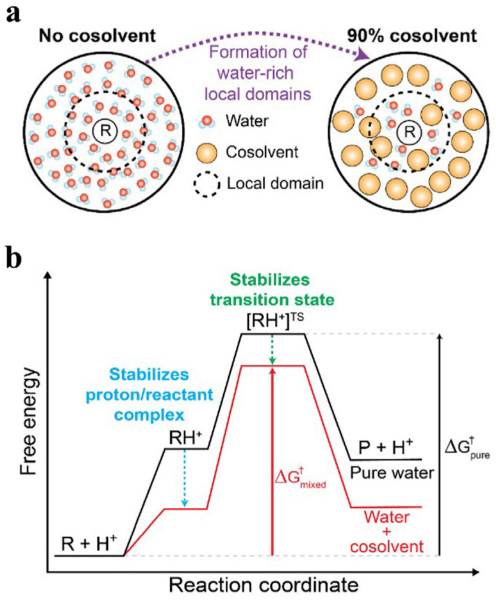

**Fig. 5** Effect of cosolvent molecules on (a) the distribution of solvent molecules and (b) the free energy distribution of the reaction. Reproduced from ref. 116 with permission from [Royal Society of Chemistry], copyright [2018].

and molecular dynamics simulations to investigate the impact of mixed solvents consisting of 1-butyl-3-methylimidazolium acetate ([BMIM][OAc]) with protic solvents ($CH_3OH$ and water) and aprotic solvents such as DMSO and DMF on the dissolution of cellulose. The results indicated that protic and aprotic solvents contributed differently to the solubilization process. The cellulose solubilization in the IL/co-solvent system was primarily driven by hydrogen bonding between the anion $[OAc]^-$ and hydroxyl proton of cellulose. Specifically, the anion-cellulose interactions were enhanced after adding DMSO or DMF to the ILs but decreased after adding $CH_3OH$ or water to the system. Within an appropriate range of co-solvent ratios, the mixed-solvent system displayed an enhanced solubilizing ability due to the presence of aprotic solvents. It was suggested that aprotic solvents disrupted interactions between IL anions and cations, allowing more anions to interact with cellulose. Conversely, protic solvents competed with cellulose for anions, preferentially solubilizing IL anions and reducing anion–cellulose interactions, resulting in decreased solubility. Hence, aprotic solvents with larger molar volumes increased the anion concentration through solvation and provided the optimal co-solvent for improving cellulose solubility.[117] Similarly, the solubilizing effect of many protic solvents such as DMSO, DMF, dimethylacetamide (DMAc), and 1,3-dimethyl-2-imidazolidinone on cellulose has also been experimentally demonstrated.[118–121]

Mixed-solvent systems are extensively used as reaction media because of their unique properties and economic advantages. A mixed solvent comprised of 1-butyl-3-methylimidazolium chloride ([BMIM][Cl])/DMSO was suitable for preparing fatty acid starch esters, resulting in starch laurates with a higher DS compared with those prepared in [BMIM][Cl] and [EMIM][OAc].[122] Furthermore, the chemical conversion efficiency of carbohydrates is influenced by the ratio of components in the solvent mixture. For example, a study revealed that the highest LA yield (72 mol%) for fructose was obtained in a water/GVL (1 : 1) solvent mixture. Excessive (70%, 90%) or insufficient amounts of GVL (10%, 30%) reduced the LA yield and increased the formation of undesired solid products.[123] Pires and colleagues investigated the impact of utilizing IL in conjunction with DMAc, DMSO, and sulfolane as reaction solvents on the efficiency of MCC esterification. Their findings indicated that several factors contributed to the higher reactivity of IL-DMSO, including a favorable activation enthalpy, lower solution viscosity, greater empirical polarity and basicity, and stronger biopolymer-solvent interactions.[17]

The utilization of mixed-solvent systems offers a unique approach to tailoring the applications of solvents by combining individual solvents to generate new intra-solvent interactions that give rise to novel physicochemical properties. However, it is crucial to consider the retrieval of such solvents and products when employing two or more solvents. Thus, the design process must consider the boiling point, polarity, and volatility of different solvents and products to optimize the separation process. Moreover, developing biphasic mixed-solvent systems can facilitate product separation based on biphasic partition coefficients, improve product yields, and efficiently recycle solvents. Numerous biphasic mixed-solvent systems are currently utilized to explore carbohydrate extraction, modification, and transformation.[51,124]

## Solvent effects in carbohydrate chemical transformations

Solvent effects refer to solvents' impact on chemical reactivity and molecular association. Solvent effects can be classified as either static or dynamic. Static effects involve the impact of the solvent on the stability of reactants, TSs, and products and can be extended to how a solvent affects their free energy and activation energy.[125] Dynamic solvent effects are derived from the coupling of reaction kinetics with solvent fluctuations and ultimately from the direct involvement of the solvent in reaction coordinates.[126] The rate constant in this state depends on the solvent dynamics and varies with parameters such as density, internal pressure, and viscosity.[10] In carbohydrate-based reaction systems, the solution contains the carbohydrate substrate and derivatization reagents, catalysts, and various product-related substances, including TSs, intermediates, byproducts, and end-products. These substances can fully contact and interact with each other, providing an impetus for solvent effects. Solvents play a critical role in improving the mass transfer and heat transfer of the reaction substrate and altering the solubility, thermodynamic state, TS, activation energy, and products. In summary, solvents can be utilized to modulate the reaction rate, reaction pathway, product distribution, yield,

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and other factors by interacting with solvents, solutes, and other substances.[10,127]

### Solubilization

Polysaccharides are carbohydrate polymers with a complex structure and numerous hydroxyl groups. The structure of polysaccharides makes them prone to form complicated hydrogen bonding interactions that can affect their solubility. Consequently, the solubilization of polysaccharides is necessary for their subsequent processing and applications. Cellulose, the most abundant natural polymer, requires thoroughly exploring its solubilization scheme and mechanism for further development. Depending on the dissolution mechanism, solvents for cellulose are typically classified as either derivatization solvents or non-derivatization solvents. Derivatization solvents such as $CS_2$/NaOH and orthophosphoric acid involve covalently modifying cellulose to generate ethers, esters, or acetal intermediates, which enhance solubility. Then the resulting products are processed to obtain regenerated cellulose. Non-derivatized solvents act on cellulose through physical means, including *N*-methylmorpholine *N*-oxide, DMAc/LiCl, tetrabutylammonium fluoride trihydrate/DMSO, aqueous NaOH solutions, ILs, and DESs.

Interactions between solvents and polysaccharides involve dynamic processes. For instance, when polysaccharides dissolve in water, they bind with other polysaccharides, and this binding can be transferred to water through a series of hydration processes. These events give rise to changes in entropy. The key to solubilizing polysaccharides lies in achieving a dynamic balance between molecule-molecule and molecule–solvent interactions. In the solid state, polysaccharide molecules or chain segments contain disordered regions in which intermolecular hydrogen bonds and other interactions are partially balanced due to the random spatial arrangement of the molecules. However, some unbalanced hydrogen bonding sites exist in these amorphous regions and can interact with the solvent. When water-soluble polysaccharides are added to water, the amorphous regions are quickly infiltrated by water molecules, which surround the polymer interaction sites and gradually break down other intermolecular bonds until they become negligibly weak. Subsequently, the sections of the polysaccharide chain dissolve entirely and enter the solution, further breaking the bonds between other polysaccharide molecules and causing them to dissolve gradually. As the degree of hydration increases, partially-immobilized water molecules surround polysaccharide molecules and form a solvent layer. The polysaccharide molecules then move into the solution and remain in their monodisperse state, displaying low-energy states and conformations.[128]

Similarly, the process of solubilizing carbohydrates in different solvents involves the permeation of solvent clusters, disruption of the hydrogen bond networks of the carbohydrates, and subsequent reassembly of the hydrogen bond networks between the carbohydrates and the solvents. Fig. 6 depicts the solubilization mechanism of carbohydrates in different solvents, emphasizing the essential role of solvent-carbohydrate interactions.[121,129–131] Tong *et al.*[129] demonstrated that DES comprised of $ZnCl_2/H_2O$/formic acid formed multiple coordination bonds and anionic/neutral hydrogen bonds with biopolymers and acted as molecular scissor to break the hydrogen bond networks of a wide range of biopolymers, such as cellulose, starch, chitin, and silk, to achieve effective solubilization (Fig. 6a). Tomimatsu *et al.*[121] modulated the ratio and species of ILs/DMSO and found that IL with a higher hydrogen bond basicity exhibited the greatest cellulose solubilization at relatively low concentrations. The solvent effect of solubilization was also modulated by ion mobility in the mixed solvent (Fig. 6d).

The type of structure found within the repeat units of polysaccharides significantly impacts their interactions with solvents. These features include branching, ionizing groups, bonding, and the non-uniformity of repeat units. The branching structure of polysaccharide macromolecules disrupts intermolecular associations, which aids solvation. Incorporating charged groups into polysaccharides is a common strategy for increasing their interactions with solvents. For instance, ionic groups such as carboxylate, sulfonate, and sulfate are easily solubilized by solvents. These groups contribute to disrupting hydrogen bond networks in polysaccharides by inhibiting intermolecular associations through electrostatic repulsion. Different glycosidic bonds exhibit unique solvation properties due to their different spatial structures. The presence of β-1,4-glycosidic bonds leads to polysaccharides with elongated and nearly flat macromolecular conformations that promote both intramolecular and intermolecular hydrogen bonding, forming insoluble microcrystals. On the other hand, α-1,6 bonds provide greater rotational flexibility compared with cyclic hydroxyl groups, and the C-6 position increases the distance between glucopyranosyl units, ultimately improving the solubility. Notably, increasing the heterogeneity of polysaccharides enhances the entropy of the system and facilitates the solvation process. This heterogeneity is primarily reflected in factors such as glycosidic bonds and the type and conformation of monomer units.[132,133]

Solvents exhibit diverse physicochemical properties determined by their unique structures, which can affect their dissolving capacities. Further research into solvent properties has identified various parameters to measure solvent effects. Hammett acidity function ($H_0$), a class of solvent acidity indicators, is often investigated in relation to solvent solubility and catalytic properties.[134] Polysaccharides exhibit an affinity for more polar substances due to the polar nature induced by poly-hydrogen bonding. $E_T(30)$ and the normalization parameter $E_T^N$ are often applied to measure the polarity to probe solvent-polysaccharide interactions.[135] Hydrogen bonding is the primary interaction mode of solvents with polysaccharides, making it crucial to evaluate the hydrogen bonding capability of a solvent. The Kamlet–Taft parameters include hydrogen bond acidity ($\alpha$), which signifies their ability to form hydrogen bonds as a HBD, hydrogen bond basicity ($\beta$), which indicates their ability to form hydrogen bonds as a HBA, and dipolarity/polarizability ($\pi^*$). The Kamlet–Taft parameters address the

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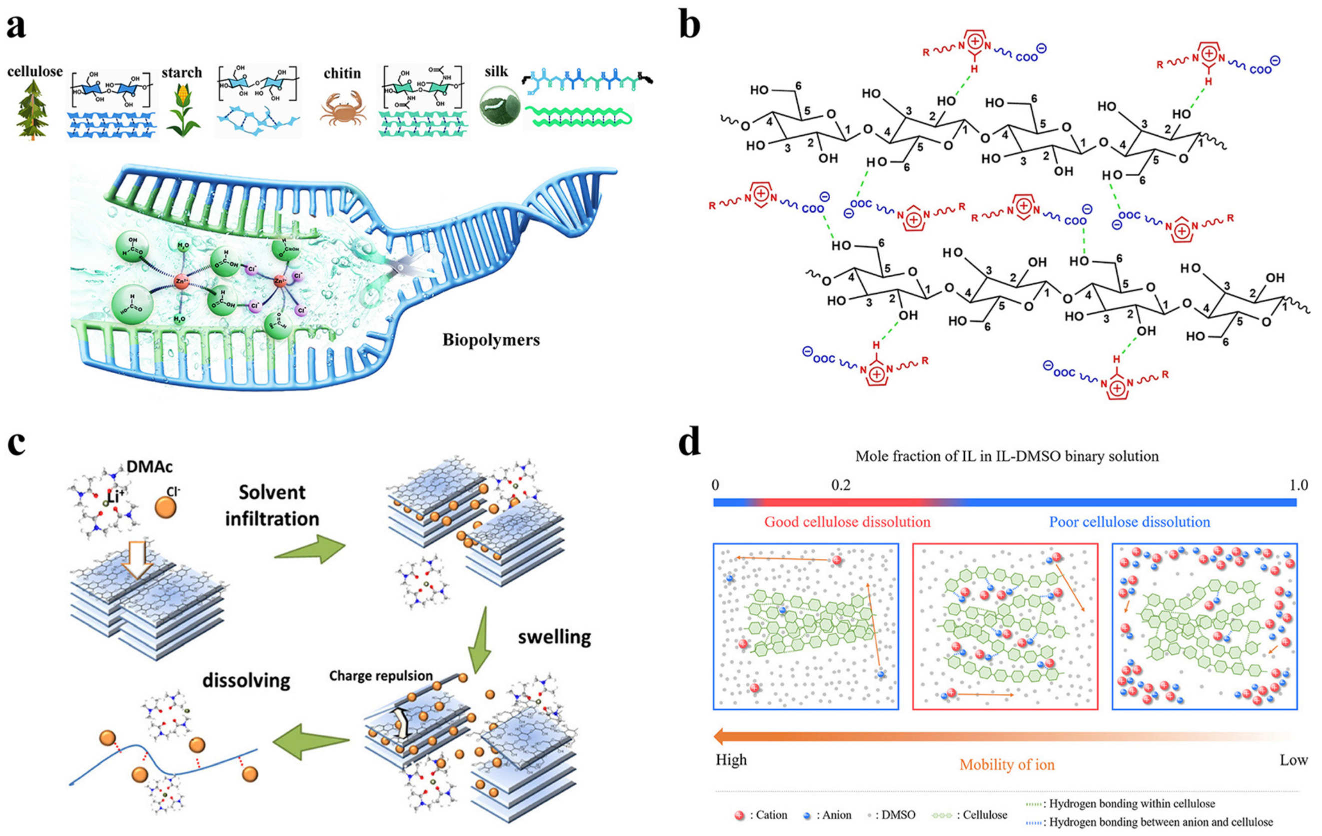

**Fig. 6** Solubilization mechanism of cellulose in various solvent systems. (a) $ZnCl_2/H_2O$/formic acid, reproduced from ref. 129 with permission from [Royal Society of Chemistry], copyright [2023]. (b) *N*-Oxyethylene substituted imidazolium-based zwitterions, reproduced from ref. 130 with permission from [Springer Nature], copyright [2022]. (c) LiCl/DMAc, reproduced from ref. 131 with permission from [Springer Nature], copyright [2019]. (d) IL/DMSO, reproduced from ref. 121 with permission from [Elsevier], copyright [2019].

limitations of single-parameter polarity scales by providing more information about solvent polarity, which is essential for capturing the complex interactions that change a solvent's polarity.[136]

Numerous studies have highlighted the crucial role of hydrogen bond basicity in promoting the solvent solubilizing capacity.[83,137] Researchers have also suggested that the net basicity ($\beta$–$\alpha$) of ILs is also significant. By comparing several ILs, it has been proposed that the empirical "solubility window" ranges from $\beta$ values of 0.80–1.20 at high $\pi^*$ values. The net basicity should lie within the range of 0.35–0.90. Achieving a balance between hydrogen bond acidity and basicity is essential for obtaining good hydrogen bonding properties and solubility.[138]

The Hansen solubility parameters (HSP) are also utilized to predict solubility in solvents, which was an improvement upon the preceding work of Hildebrand.[139] According to HSP, the cohesive energy ($E$) contains three components that correspond to different types of interactions: nonpolar (dispersion) interactions ($E_d$), polar (dipole–dipole and dipole–induced-dipole) interactions ($E_p$), and hydrogen-bonding or other specific association interactions ($E_h$). These components ($\delta_d$, $\delta_p$, and $\delta_h$) of the total solubility parameter correspond to the interactions mentioned earlier.[140] In order to predict the solubility of a polymer in a given solvent, it is necessary to determine and compare the similarity between the HSPs of a polymer and solvent.[141] Additionally, Klamt *et al.*[142] developed the conductor-like screening model for real solvents (COSMO-RS) by combining quantum chemistry and statistical mechanics methods to enable the quantitative calculation of solvation phenomena. This model can predict the physicochemical properties and solubilization performance of solvents and is particularly useful for screening the optimal solvent for polysaccharide solubilization and conversion processes.[143,144]

It is crucial to understand that in addition to the solvent parameters mentioned above, molecular weight, temperature, and viscosity also play significant roles in the solvation process by affecting the movement of polysaccharide macromolecules within a solvent, requiring a comprehensive consideration of optimal dissolution conditions. Table 3 summarizes the solubility of different carbohydrates in various solvents and the associated solvent parameters. Further, adequate solubilization of the carbohydrates in the solvents facilitates subsequent conversion. Higher solubility usually leads to a higher concentration of substrate in the reaction mixture, which can

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**Table 3** Solubility of carbohydrates in various solvents

| Substrate | Solvent | Solubility (g per 100 g) | Solvent viscosity (mPa·s) | *α* | *β* | π* | Ref. |
|---|---|---|---|---|---|---|---|
| Pulp cellulose | $ZnCl_2$–water–formic acid (molar ratio = 1 : 1 : 4) | 10.12 (23–33 °C) | *ca.* 50 | 1.850 | 0.470 | 1.320 | 103 and 129 |
| Pulp cellulose | ChCl–imidazole (molar ratio = 3 : 7) | 2.48 (110 °C, 1.5 h) | Below 10 | —[a] | 0.864 | 0.382 | 145 |
| Pulp cellulose | ChCl–urea (molar ratio = 1 : 2) | 1.43 (110 °C, 2 h) | Below 10 | — | 0.821 | 0.319 | 145 |
| Pulp cellulose | [AMIM][Cl] | 1.89 | — | — | 0.830 | 0.298 | 145 |
| Avicel | [EMIM][OAc] | 23.40 | — | 0.468 | 1.106 | 1.048 | 121 |
| Avicel | [EMIM][OAc]–DMSO (mass ratio = 3 : 2) | 28.00 | — | *ca.* 0.400 | *ca.* 1.105 | *ca.* 1.046 | 121 |
| Avicel | [EMIM][DEP] | 8.90 | — | — | 1.085 | 0.986 | 121 |
| Avicel | [EMIM][DEP]–DMSO (mass ratio = 3 : 2) | 17.30 | — | — | *ca.* 1.077 | *ca.* 0.997 | 121 |
| Starch | ChCl–formic acid (mass ratio = 1 : 4) | 52.80 | 10.85 | 1.130 | 0.550 | 1.080 | 146 |
| Starch | $ZnCl_2$–water–formic acid (molar ratio = 1 : 1 : 4) | 42.79 (23–33 °C) | *ca.* 50 | 1.850 | 0.470 | 1.320 | 103 and 129 |
| Chitin | $ZnCl_2$–water–formic acid (molar ratio = 1 : 1 : 4) | 20.81 (23–33°C) | *ca.* 50 | 1.850 | 0.470 | 1.320 | 103 and 129 |
| Chitosan | [BMIM][OAc] | 13.40 (130 °C) | *ca.* 20 | 0.470 | 1.156 | 0.970 | 147 |
| Xylan | ChCl–monoethanolamine (molar ratio = 1: 6) | 95.00 (75 °C, 3 h) | *ca.* 10 | — | 1.876 | 1.084 | 148 |
| Xylan | [AMIM]Cl | 23.70 (70 °C) | *ca.* 61 | 0.460 | 0.830 | 1.170 | 137, 149 and 150 |
| Xylan | [AMIM]Cl–ethylene glycol (molar ratio = 2 : 1) | 40.40 (70 °C) | Below 12.273 | 0.935 | 1.284 | 0.700 | 150 |

[a] Not mentioned.

increase the reaction rate according to the principles of chemical kinetics. In the process of converting fructose into HMF, under the same catalyst conditions, DMSO with greater fructose solubility (1260 g $L^{-1}$) can result in HMF with a yield of 88.3%, while the yield was only about 12% in acetone with lower solubilization capacity (0.5 g $L^{-1}$).[48] Meanwhile, the high partition coefficient of the product in the solvent, combined with an effective product transfer strategy, could enhance the product selectivity. The higher partition coefficient of HMF in the mixed methyl isobutyl ketone/water biphasic solvent (1.10) resulted in a higher HMF yield compared to the partition coefficient of HMF in the methyl isobutyl ether/water biphasic solvent (0.23). The organic phase was able to extract the HMF formed in the aqueous medium and promote the reaction in the forward direction, thus increasing the selectivity for HMF.[151]

## System stability effect

In chemical reactions involving polysaccharides, the solvent system contains the polysaccharide substrate as a solute and also the TS, catalyst, and reaction products.[10] The interaction between solvents, solutes, and solvation of kinetic-related species (*e.g.*, adsorbed species, intermediates, and activated complexes) can change the reaction rate, thereby altering the reaction efficiency and pathways.[11,152] Controlling the solvent environment makes it possible to regulate the types of products and production paths to facilitate the selective regulation of the target products.

Mellmer *et al.*[46] reported that strong Brønsted acid catalysts exhibited remarkable reactivity in the polar aprotic solvent, GVL. They conducted reaction kinetics experiments and established that GVL impacted the stabilization of acidic protons and protonated TSs, thereby enhancing the reaction rate of acid-catalyzed carbohydrate conversion reactions (Fig. 7). In addition, under a high temperature and water content, the release of protons accelerated the furfural degradation reactions, resulting in undesired side reactions, including fragmentation, resinification, and condensation.[153] Previous studies have shown that these reactions increase the production of humin-type polymers.[154,155] One of the ideas to address this is to introduce organic solvents into the aqueous phase to establish mixed-solvent systems. For example, Hu *et al.*[44] found that after incorporating methanol into an

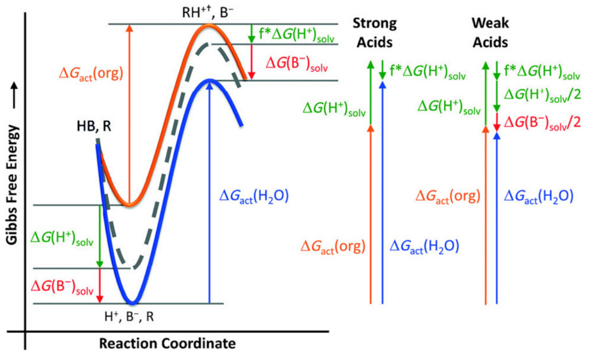

**Fig. 7** The Gibbs free energy surface of the Brønsted acid-catalyzed reaction that converts reactant (R) into product (P) in $H_2O$ and polar aprotic organic solvents. Reproduced from ref. 46 with permission from [John Wiley and Sons], copyright [2014].

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aqueous reaction medium during the gluconic acid-catalyzed process, glucose tended to convert to methyl glucoside in the methanol-rich environment. The shielding effect of the active C1-site of the hydroxyl groups of methyl glucoside prevented the conversion of methyl glucoside to glucose or the active form containing reactive carbocations. This decreased its polymerization tendency. Furthermore, a series of derivative intermediates, such as ethers or acetals of HMF and furfural, were produced and eventually converted to the leading products, methyl formate and methyl levulinate. This modification blocked the reactive hydroxyl and carbonyl groups, hindering isomerization and ring fusion. This increased the stability and decreased the polymerization tendency of these compounds.

Previous studies have demonstrated the effectiveness of aprotic organic solvents, such as DMSO, in stabilizing reaction intermediates and preventing unwanted side reactions. Mushrif *et al.*[156] investigated the effects of DMSO in DMSO/water mixtures. Their findings highlighted that DMSO preferentially solvated fructose, with water and DMSO competing for HBD and HBA roles near the hydroxyl group's oxygen and hydrogen atoms, respectively. The DMSO sulfonyl-oxygen's hydrogen bonding was stronger and hindered the formation of fructose reversion and polymerization products. The researchers also observed that DMSO's preferential alignment near the C1 carbon of HMF stabilized HMF, which prevented the production of humins and inhibited C1–C2 cleavage and subsequent production of LA and formic acid *via* HMF rehydration. Tsilomelekis *et al.* also supported this observation by revealing that DMSO had stronger binding interactions with HMF, particularly with its hydroxyl groups, compared with only water. In a mixed DMSO/water solvent, DMSO preferentially solubilized the C=O group of HMF.[157] Furthermore, the conversion of fructose to HMF *via* the nucleophilic attack of DMSO on the intermediate (fructopyranosil oxocarbenium ion) formed a crucial intermediate, 2-(hydroxydimethylsulfinyloxy)-β-D-fructofuranose. This intermediate readily converted to HMF instead of oligomers and humins, which facilitated and directed the reaction toward the desired product.[158] A theoretical investigation suggested that a Brønsted acid in the system facilitated interactions between $H^+$ and DMSO, leading to the formation of $[DMSOH]^+$, accelerating the dehydration of fructose and generating trimolecular water.[159] Nonetheless, the high boiling point of DMSO may cause elevated energy consumption and poor economic feasibility compared with solvents with lower boiling points, such as methyl isobutyl ketone.[160] Thus, it is crucial to thoroughly evaluate the solvent's performance at different reaction stages and its suitability for carbohydrate chemistry.

In addition to the stabilizing role in carbohydrate conversion, stabilization strategies in biomass pretreatment processes are often adopted. Due to the typically acidic conditions of most pretreatment systems, carbohydrates tend to dehydrate into furfural and related derivatives. The incorporation of stabilizers such as methanol can protect the functional groups in hemicellulose and cellulose. This approach converts carbohydrates into diformylxylose or diformylglucose and stabilizes them in a form resistant to subsequent dehydration and degradation. This approach has been shown to improve the utilization of carbohydrates in downstream processes.[161]

### Catalyst synergy

Catalysts are classified into homogeneous and heterogeneous catalysts based on their homogeneity with the reactants' phase states. In homogeneous catalyzed reactions, the catalyst is in the same phase as the reactants and products. The catalyst of a heterogeneous catalyzed reaction is in a different phase from the reactants, which also facilitates the recovery of the catalyst.[162] The synergies between solvent and catalyst can also be discussed in homogeneous and heterogeneous cases. For carbohydrate transformations, homogeneous catalyzed reactions often occur in the liquid phase, so the discussion here will focus on this category. In homogeneous catalysis of carbohydrates, the catalyst and reactants are uniformly dispersed in a solvent, which serves as a bridge connecting the reactants and the catalyst for free contact and reaction. Therefore, the interaction of the solvent with the catalyst and the reactants deserves further investigation. The high solubility of the reactants in the solvent positively promotes the reaction, which is particularly important for homogeneous reactions. This was discussed in detail in the prior section on solubilizing effects of solvents. Similarly, the solvation of the catalyst can affect its concentration in the solvent and the reaction rate. Moreover, the solvent needs to be compatible with the catalyst and not react with it unnecessarily. Wang *et al.* demonstrated a strong domain-restricting effect of the solvent aggregates structure present in the 3-hexanol solvent on the distribution and mobility of catalyst $CuCl_2$. As the concentration of $CuCl_2$ in 3-hexanol increased, the electron paramagnetic resonance showed that the $CuCl_2$ nuclearity shifted from mononuclear to multinuclear, and the aerobic oxidation of 2,3,6-trimethylphenol changed from aerobic oxidative coupling to oxygenation, affecting the reaction paths of the reactants and the selectivity of the final products.[163] Further, the activity, selectivity, and stability of a catalyst can be affected by interactions or coordination with a solvent.[164] EXAFS (extended X-ray absorption fine structure) characterization of $CrCl_3 \cdot 6H_2O$ showed that the coordination number of Cr–O decreases and that of Cr–Cl increases as the solvent changes from water[165,166] to isopropanol[167] and then to 1-ethyl-3-methylimidazolium chloride [EMIM][Cl],[168] which affected important properties such as catalyst activity and stability.[169] The physicochemical properties of the solvent, such as polarity and protonation, likewise strongly influence the catalytic effect. The presence of chloride ions in [EMIM][Cl] was demonstrated to play a key role in the conversion of hexoses to HMF, and the protonated methylimidazolium chloride [MIM][Cl] could inhibit the formation of fructose-catalyst complexes and reduce the yield of HMF.[170] In addition, solvents can also participate in reactions as catalysts, acting as proton donors or acceptors in homogeneous acid-catalyzed reactions.[171]

In heterogeneous systems, the solvent usually does not directly influence the reaction mechanism as it does in homo-

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geneous systems because the active sites are on the surface of the solid catalyst rather than in solution. The solvent can act as a medium for the reactants to reach the catalyst surface, which involves solvation, transport, and adsorption of the reactants on the catalyst surface. On the other hand, solvent-catalyst interactions still influence the dispersion, activity, selectivity, and stability of the catalyst. In heterogeneous reactions, the solvent may influence the active form of the catalyst. Wang *et al.*[47] found that when *N*-methyl-pyrrolidone was used in a heterogeneous environment, it interacted with the Hβ zeolite active site, resulting in the high-selectivity fructose conversion to HMF. The solvent modulation of the coordination environment of aluminum shifted the catalyst's active state from the 6-fold state to the aluminum species of the tetrahedral coordination state. This affected Hβ zeolite's selective catalytic effect. Moreover, fructose exhibited a higher conversion turnover frequency in the non-lactam solvent γ-butyrolactone. Furfural degradation was negligible, which resulted in a higher furfural selectivity in γ-butyrolactone.

Adsorption between the solvent and catalyst provides a clear indication of their interactions. As shown in Fig. 8, the typical hydration reaction occurring in a zeolite involves several stages, including the solvation of the reactant and catalyst, catalyst hydration to an acid, adsorption between reactant and catalyst, and acid catalysis *via* a TS. The initial step of a liquid-phase reaction involves the adsorption of a reactant from the solvent onto the catalyst surface. During this process, the preferential adsorption of a solvent molecule onto the catalyst surface may hinder reactant molecule migration to the active sites, thereby decreasing the catalytic performance.[172] Deng and colleagues[173] investigated the catalytic influence of α-MoC on the hydrogenation of furfural derived from carbohydrates. They identified that the catalytic activity of α-MoC on furfural hydrogenation depended on the supply of alcohol solvents. Alcohol solvents worked in conjunction with the catalyst to promote the hydrogenation reaction. Utilizing the Lewis acid-mediated Meerwein–Ponndorf–Verley mechanism illustrated in Fig. 9, the catalytic transfer hydrogenation reaction occurs as the β-H atom of the alcohol solvent transfers to the carbonyl C atom of furfural *via* a concerted six-membered ring TS at the Lewis acid site, ultimately achieving hydrogenation. It was observed that methanol demonstrated exceptional selectivity towards furfuryl alcohol (>95%) due to the favorable adsorption–desorption equilibrium between alcohols and MoC, which covered the catalyst surface. The size of the alcohol molecule significantly affected the accessibility of the active site and the steric hindrance for forming reaction TSs on catalytic surfaces. This manifested as a high energy potential for the hydrogenolysis of furfuryl alcohol in methanol, ultimately resulting in a high selectivity for furfuryl alcohol.

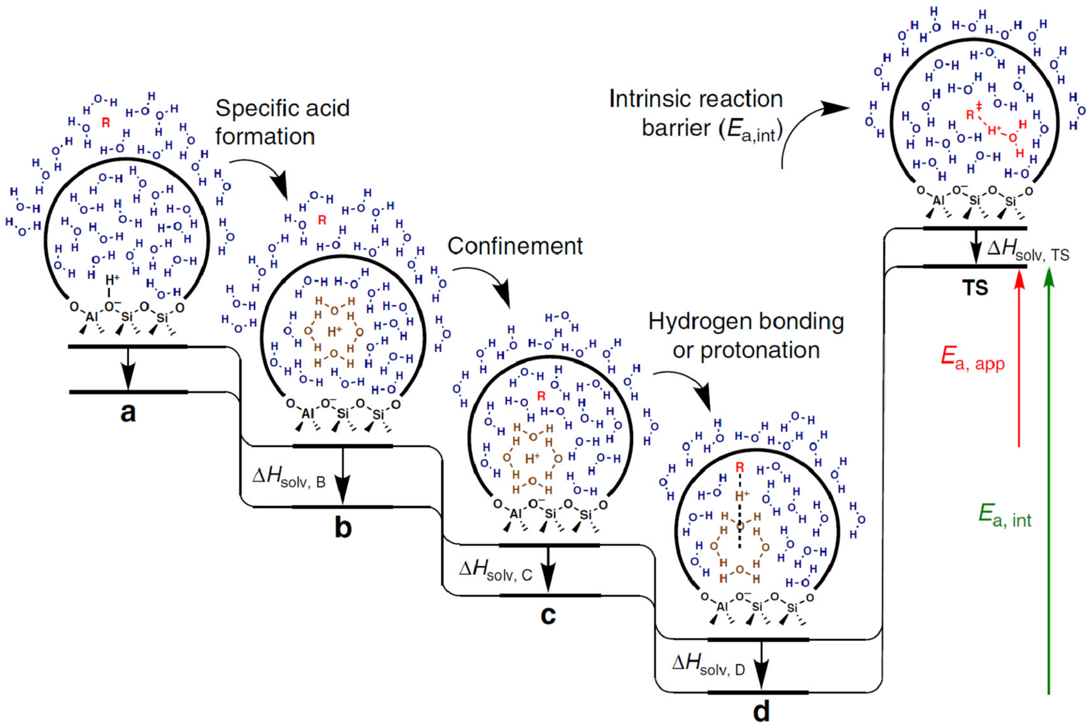

**Fig. 8** Typical zeolite-catalyzed aqueous-phase reaction coordinate diagram. (a) Initially, the liquid phase outside the porous catalyst dissolves the reactant (R), and the proton in the catalyst is not hydrated. (b) The hydration of the proton forms the acid, (c) followed by the adsorption of R into the catalyst pores. (d) The hydrogen bonding or protonation of R in the catalyst pore occurs together with partial or complete de-solvation of the proton, followed by an acid-catalyzed chemical conversion that passes through a TS. Water molecules (brown and red) are involved in the specific acid solvation sphere and the TS, respectively. The zeolite pore walls are shown by the solid curved lines. Interactions with the solvent environment affect enthalpy changes (Δ*H*), apparent activation energy ($E_{a,\ app}$), and intrinsic activation energy ($E_{a,\ int}$). Reproduced from ref. 172 with permission from [Springer Nature], copyright [2020].

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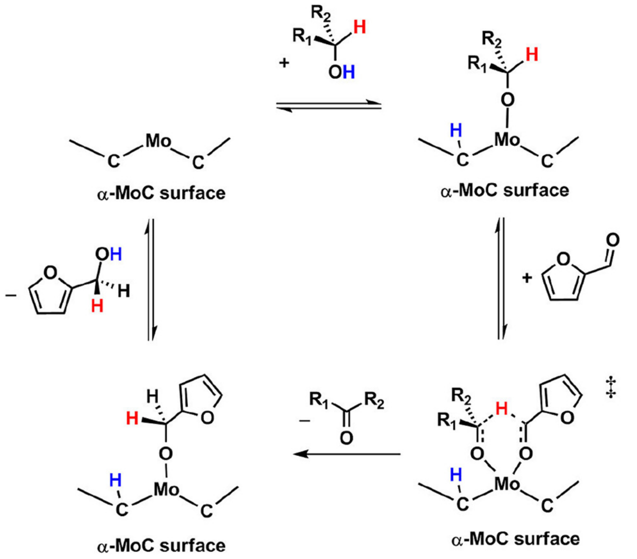

**Fig. 9** Possible pathway of alcohol transfer hydrogenation to furfural on α-MoC surface. Reproduced from ref. 173 with permission from [American Chemical Society], copyright [2018].

Researchers have also investigated furfural hydrogenation using Co/CoO$_x$ catalysts supported on N-doped carbon nanotubes which showed significant solvent selectivity in the synthesized products. In water, a high selectivity was achieved during the synthesis of cyclopentanone/cyclopentanol *via* the Piancatelli rearrangement. The catalyst maintained its Brønsted acid sites, while the four hydrogen atoms in the water molecule participated in furfural conversion *via* the cyclopentanone pathway. In contrast, a lack of Brønsted acid sites and the involvement of only three hydrogen atoms in the ethanol molecule resulted in the preferential use of the tetrahydrofurfuryl alcohol pathway. Notably, the reactants' solubility and the catalyst powder dispersion, which were influenced by solvent polarity, played a crucial role in the adsorption and catalytic activity of the catalyst.[174]

## Mass and heat transfer

Biomass-based feedstocks typically possess low volatilities and are highly oxygenated, which necessitates using solvents during biomass upgrading reactions to enhance the mass and heat transfer from the substrate to the catalyst surface.[175] A recent investigation by Zhou and colleagues[176] demonstrated that incorporated carboxylic acid anions displayed a tunneling effect with acylation reagents in imidazole-derived ILs, which promoted rapid and efficient homogeneous acylation of cellulose *via* dynamic hydrogen bonding. In another study, Gomes *et al.*[73] employed a taurine-based IL, [TauIm][HSO$_4$], as both solvent and catalyst under microwave-assisted conditions (190 °C, 60 min, 10 eq. of IL) and achieved 81% yield of ethyl levulinate *via* the conversion of MCC as the feedstock.

A similar selective reaction pathway exists in the hydrogenation of furfural, where the hydrogenation of C═O bonds mainly involves solvent-mediated reactions. Surface charge separation allows a hydrogen atom to be taken up as a proton and then transferred by water. Moreover, hydrogen bypasses direct surface reactions *via* hydrogen-bonded water networks. Water directly participates in the kinetically-relevant reaction steps, providing an extra channel for aldehyde hydrogenation and reducing the activation barrier for C═O hydrogenation. In contrast, the hydrogenation of C═C bonds is primarily facilitated by surface reactions due to the hydrophobic nature and the lack of hydrogen bonding channels at the C atom.[177] Zhu *et al.*[48] investigated the mechanism of the dehydration of fructose to HMF in an acetone-water mixed solvent. The authors found that hydronium ions attacked the C2-ether oxygen bond and generated the by-products LA and formic acid. The removal of the second and third water molecules presented a significant energy barrier due to intermolecular H transfer. The study also revealed that water played a crucial role in reducing the hydrogen transfer barrier through water-assisted H transfer, thereby accelerating the reaction rate. These results challenge the traditional view that water has a detrimental effect on the dehydration of fructose, highlighting its critical role in this process.

In order to further improve the material and energy exchange in the reaction system, the mass transfer efficiency can be increased by regulating the temperature and pressure and using special solvents such as supercritical fluid or subcritical water. In addition, physical means such as microwaves and ultrasounds can improve mass transfer efficiency by increasing the mixing effect and contact area of substances. At the same time, the microenvironment of high temperature and high pressure generated by particle vibration and friction can promote the chemical reactions of carbohydrates.[178,179]

## Extraction and multiphase separation

During the chemical reactions of carbohydrates, the recovery of products can be optimized by using extractants with high partition coefficients to improve product yield and selectivity. Qing *et al.*[45] proposed the addition of extractants to an aqueous-ChCl solvent system to minimize HMF degradation in an acidic environment. With a higher O/C ratio that provided more hydrogen bond acceptor sites, acetone demonstrated greater extraction ability for HMF. The ideal extraction efficiency and partition coefficient were 70.4% and 3.52, respectively. Compared with other extractants, acetone provided the highest HMF yield of 54.7% and the best glucose conversion rate (ChCl–water–acetone ratio of 1 : 1 : 1).

A heterogeneous reaction system is developed to simplify the extraction pathway and increase the yield of target products, incorporating an aqueous phase and a nonpolar organic solvent phase. This innovative biphasic system leverages differences in solvent polarity and partition coefficients and shows greater product yields than a single organic solvent or pure water system. The system, composed of water and dimethoxymethane, capitalized on the polarity differences of target products to optimize extraction efficiency. Following the transformation of lignocellulosic polysaccharides to LA, LA was continuously separated into dimethoxymethane, while intermedi-

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ate products such as glucose and xylose were retained in the aqueous phase. This extraction methodology prevented LA polymerization and streamlined the collection process of LA.[51] Tong *et al.* prepared HMF by fructose dehydration *via* a THF-$H_2O$ biphasic solvent system. The experimental results showed that through solvent regulation, a higher HMF yield was obtained in the THF-$H_2O$ biphasic solvent (78.0%), exceeding the results using $H_2O$ (18.0%) or THF (31.0%) as the solvent alone. This result was attributed to the presence of the organic phase THF extracting HMF from the aqueous phase, thus preventing the rapid degradation of HMF into unwanted by-products under aqueous conditions.[180]

Li and colleagues introduced a multi-step cascade approach utilizing biphasic solvent systems to promote complex reactions.[181] This approach entailed explicit reaction steps and gradual product separation. The authors applied a three-stage, tandem reaction involving the acid-catalyzed conversion of carbohydrates to furfural and LA esters, aldol condensation of furfural and LA esters, and hydrodeoxygenation reactions to produce branched long-chain alkanes. The biphasic solvent system included toluene and water, which exploited the polarity difference between the solvents and facilitated the transfer and separation of products. This simplified the cascade reaction progress, as shown in Fig. 10. Moreover, solvent polarity can be influenced by multiple factors, and differences in solvent polarity through induced modulation can provide a force that promotes product separation. Research has shown that a temperature-induced two-phase aqueous solvent system can efficiently extract polysaccharides from *Camellia oleifera* Abel. Seed cake by employing thermosensitive polymers such as ethylene oxide-propylene oxide and DES.[182]

The concepts of product production, isolation, and transfer described above are critical for increasing a reaction's efficiency, particularly for promoting product transfer, which can lead to several advantages. Firstly, the continuous transfer of products can minimize product inhibition and shifts in the reaction equilibrium. Secondly, it can lower the probability of side reactions and enhance intermediate selectivity. Finally, it facilitates the optimization of experimental conditions by reducing energy consumption and the number of required reaction steps.[183]

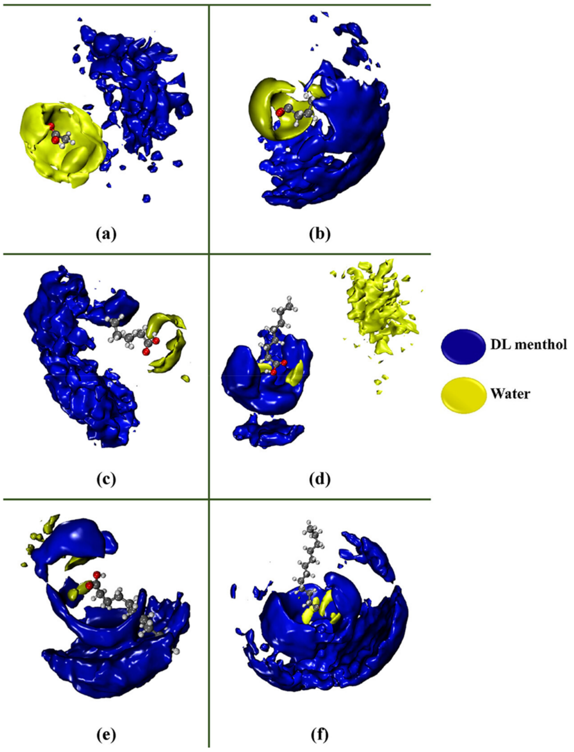

**Fig. 11** Molecular dynamics simulations of the DL-menthol-carboxylic acid (DES)-water system, in which the spatial distribution function of DL-menthol (HBA) and water molecules were calculated around the corresponding carboxylic acids (HBDs) of several DESs. Menthol and water around (a) acetic acid, (b) butanoic acid, (c) hexanoic acid, (d) octanoic acid, (e) decanoic acid, and (f) dodecanoic acid are indicated in blue and yellow, respectively. Menthol around the carboxylic acid and water around the carboxylic acid are shown with isovalue of 2.1 particles $nm^{-3}$ and 20 particles $nm^{-3}$, respectively. Reproduced from ref. 186 with permission from [American Chemical Society], copyright [2023].

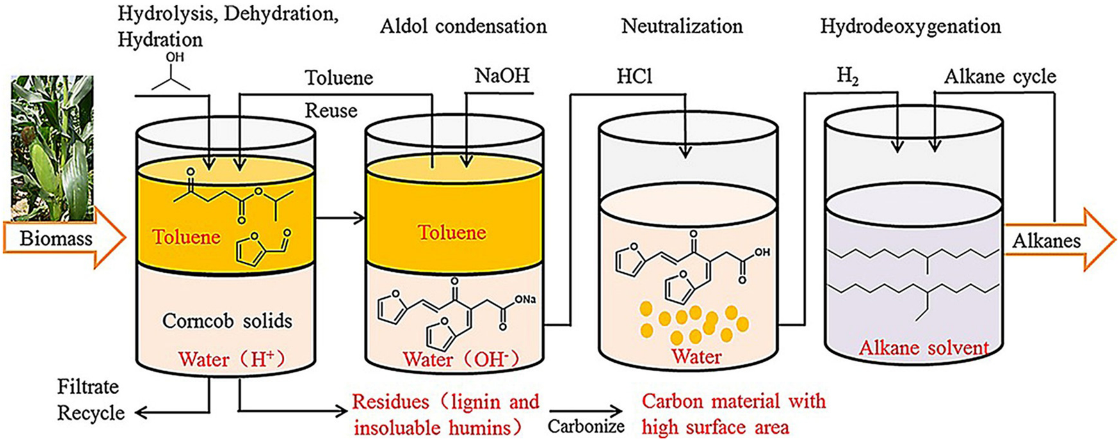

**Fig. 10** Conversion of carbohydrate-rich biomass (corncob) to branched-chain alkanes through tandem reactions. Reproduced from ref. 181 with permission from [John Wiley and Sons], copyright [2016].

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## Microscopic interpretation of solvent effects

Solvent effects in carbohydrate chemistry can be examined at a molecular level by investigating interactions between components within a reaction system. The physicochemical properties of solvents are primarily derived from their chemical structure and interactions within their respective systems. For intricate systems, such as novel or mixed solvents, molecular simulations provide valuable insights into structural information and physicochemical properties of solvents. These, in turn, facilitate the selection and design of molecules with superior performance.[184,185]

Paul *et al.*[186] conducted computational investigations on hydrophobic DES derived from DL-menthol and several carboxylic acids. Charges in the electrostatic potentials using a grid-based method and natural bonding orbital analyses were carried out to investigate the molecular structure and charge transfer resistance of acetic acid-based DES compared with DESs based on longer-chain fatty acids (C8 to C12). The results indicated that the DES based on acetic acid exhibited a more compact molecular structure and lower charge transfer resistance. Spatial distribution function analysis showed that the DES composed of fatty acids with a longer chain length (C8 to C12) demonstrated more excellent resistance to water permeation than those composed of fatty acids with shorter chains (C1 to C6) (Fig. 11). Additionally, Kalhor *et al.*[187] studied interactions in binary solvent mixtures of DES and acetonitrile and demonstrated the transition of acetonitrile in the mixed solvent. Fourier transform infrared (FTIR) spectroscopy coupled with quantum chemical calculations revealed that acetonitrile molecules in the co-solvent predominantly engaged in non-covalent hydrogen bonding with the DES core, particularly with the hydroxyl group of ethylene glycol/choline rather than with $Cl^-$.

The different physicochemical properties of solvents and solutes lead to specific interactions that may influence the con-

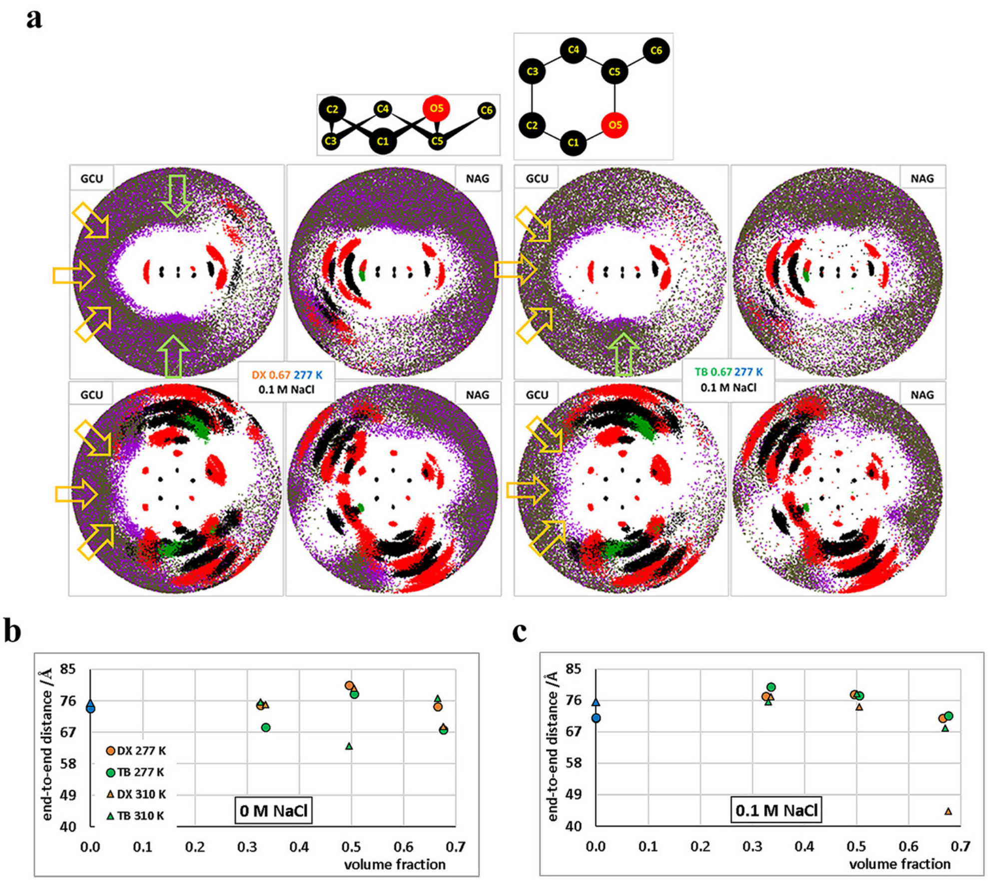

**Fig. 12** (a) Cumulative solvation-shell diagrams depicting the distribution of organic components (1,4-dioxane, DX, on the left; *tert*-butanol, TB, on the right) of the mixed solvents surrounding the HA residues. The orientation scheme of the monosaccharide ring is shown in the side view (upper images) and top view (lower images). The different atoms are represented by specific colors: black – carbon in HA, red – oxygen in HA, green – nitrogen in HA, brown – carbon in organic components, and violet – oxygen in organic components. Yellow arrows indicate regions of hydrogen-bonded organic molecules, while green arrows indicate organic molecules clustered in hydrophobic HA regions. (b) and (c) End-to-end distance of the HA oligosaccharide at different NaCl concentrations, temperatures, and mixed solvents. The aqueous solution is shown by blue dots. Reproduced from ref. 188 with permission from [Elsevier], copyright [2023].

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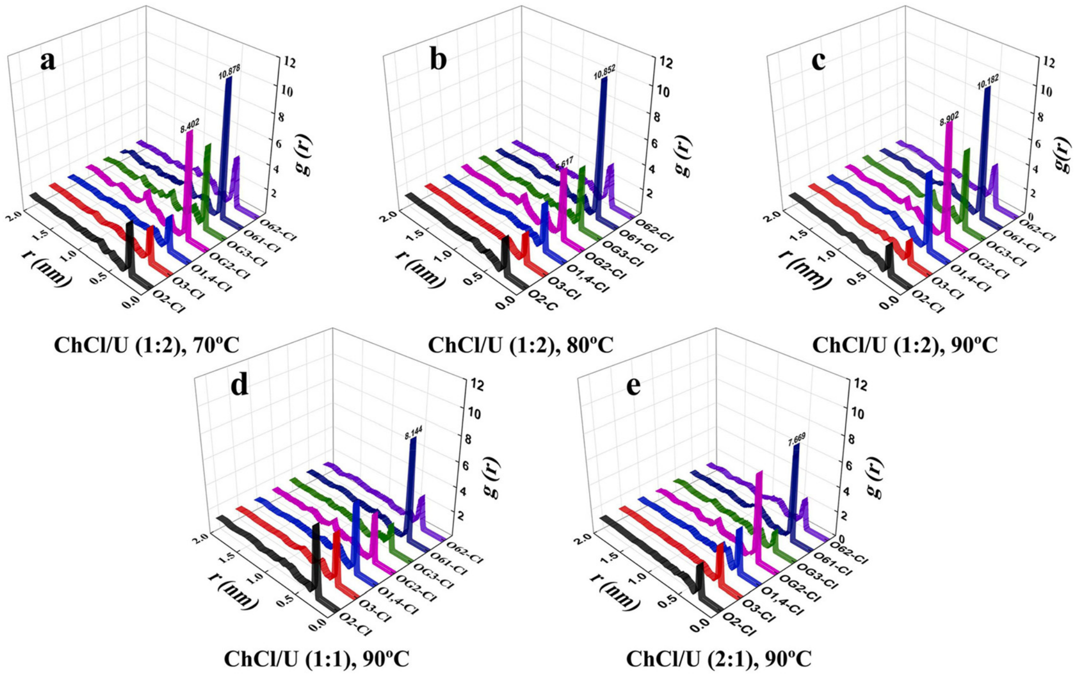
formation and solvation effect of carbohydrates in solutions. Computational simulations can be used to investigate these interactions, providing valuable information for subsequent carbohydrate reactions. The generalized approach to the theoretical description of solute-solvent interactions is mainly based on quantum-chemical continuum models, supramolecular models, and semicontinuum quantum-chemical models.[127] Fig. 12a depicts the cumulative solvation-shell diagrams of hyaluronan (HA) in a mixture of water and the organic solvents 1,4-dioxane and *tert*-butanol. These diagrams reveal that the organic solvent molecules competed with water to form hydrogen bonds with hyaluronan in the hydrophilic regions of O2 and O3 of glucuronic acid and O4 and O6 of *N*-acetyl-D-glucosamine (NAG). The aggregation of organic molecules *via* their oxygen atoms was observed beneath the glucuronic acid at the hydrophobic sites. 1,4-Dioxane demonstrated more aggregation than *tert*-butanol. Weaker aggregation was observed at NAG residues above the NAG ring structure. This may have been driven by hydrophobic interactions that pushed less-polar organic molecules toward the nonpolar part of the carbohydrate rings, while hydrophilic oxygen atoms were located towards the hydrophobic part of the carbohydrate residues due to spatial factors. Solvent effects changed the carbohydrate conformation with the HA chains, which were rigid in water and formed a large, loosely-packed state of random coils. As the salt concentration in the solvent increased, dynamic changes in the HA chains were induced by cations, resulting in the flipping of glycosidic dihedral angles and the temporary formation of hairpin-like kinks. These changes led to the partial shrinkage of the random coils and decreased the rigidity of the HA chains. Based on observations in Fig. 12b and c obtained by monitoring the average end-to-end distances of the chains, changes in chain rigidity in the mixed solvents at a lower temperature of 277 K were insignificant and independent of the solvent composition. However, as temperature increased to 310 K in the presence of 0.1 M NaCl, the end-to-end distances exhibited an overall tendency to decrease upon increasing the fraction of the organic component. This was attributed to more frequent interactions between HA and $Na^+$ cations, resulting in repeated shortening of the chains.[188]

Wang *et al.*[189] investigated interactions between the 4-*O*-methyl glucuronic acid xylan (Gxyl) atoms and DES at various temperatures and HBA/HBD ratios using molecular dynamics simulations. The radial distribution function plot in Fig. 13 illustrates that the ChCl/urea (1 : 2) exhibited higher peak values at 70 °C and 90 °C, indicating a superior solubilization potential. Moreover, at the same temperature (90 °C), the ChCl/urea (1 : 2) showed enhanced solubilization capabilities compared with other ratios of ChCl/urea. The spatial distribution function plot (Fig. 14) revealed that water molecules and $Cl^-$ ions surrounded the hydroxyl groups of xylan with both 4-*O*-methyl glucuronic acid and arabinofuranose residues (Xyl) in the DES-water mixtures containing 50 wt% or 80 wt% DES, and water molecules were located closer to Xyl. Water molecules and $Cl^-$ ions synergistically promoted the dissolution of Xyl, with choline and urea playing secondary roles. Adding water decreased the interaction energy between $Cl^-$



ChCl/U (1:2), 70ºC ChCl/U (1:2), 80ºC ChCl/U (1:2), 90ºC

ChCl/U (1:1), 90ºC ChCl/U (2:1), 90ºC

**Fig. 13** Radial distribution function diagrams of Gxyl-DES with different solvent compositions and temperatures: (a) ChCl/urea (1 : 2), 70 °C; (b) ChCl/urea (1 : 2), 80 °C; (c) ChCl/urea (1 : 2), 90 °C; (d) ChCl/urea (1 : 1), 90 °C; (e) ChCl/urea (2 : 1), 90 °C. Reproduced from ref. 189 with permission from [Elsevier], copyright [2022].

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and Gxyl, but the interaction energy (absolute value) between Gxyl and water molecules increased from 48.302 kJ $mol^{-1}$ to 568.420 kJ $mol^{-1}$. The authors speculated that the added water reduced the hydrogen bond strength in ChCl/urea (1 : 2), and ChCl, urea, and water formed new hydrogen bond networks that exerted a solubilizing effect.

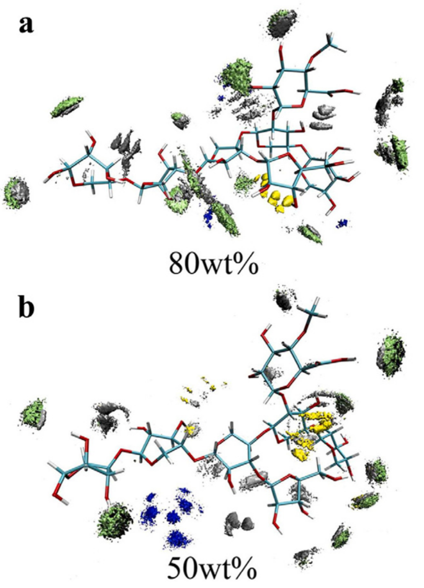

**Fig. 14** Spatial distribution function diagrams for different DES ratios and Xyl systems: (a) 80 wt% DES and (b) 50 wt% DES. Different substances are indicated by different colors: $Cl^-$: green, $H_2O$: grey, choline: blue, and urea: yellow. Reproduced from ref. 189 with permission from [Elsevier], copyright [2022].

Chew *et al.* conducted molecular dynamics simulations to determine the solvation free energy and evaluate the free energy difference between reactants and products relative to water within a mixed solvent. Their results revealed the primary trend in the acid-catalyzed dehydration conversion of 1,2-propanediol (PDO) to malondialdehyde in a 90 wt% 1,4-dioxane aqueous solution. They identified the predominant conversion mechanism of acetone in 90 wt% DMSO aqueous solution. The study also provided spatial distribution maps (Fig. 15a and b) that combined the distribution of pure water, a 90 wt% 1,4-dioxane solution, and a 90 wt% DMSO solution around PDO in the *trans* and *gauche* conformations. The observations suggested that DMSO prevented propanal formation by inhibiting the hydronium ion from entering the hydroxyl groups of the reactants. The authors also postulated that DMSO acted as a base to eliminate the primary hydroxyl group in the form of water. Fig. 15c shows the mechanism responsible for the DMSO-mediated production of acetone, which suggests that the process was initiated by the addition of an acidic proton, which was stabilized by the DMSO–water cluster or the DMSO molecule itself, to the primary hydroxyl group of PDO. The intermediate, DMSO–water-PDO, generated the final product through the semipinacol rearrangement. These findings were further corroborated by the energy difference ($\Delta E$) observed between the protonated primary and secondary hydroxyl groups of PDO in the *trans* and *gauche* conformations (Fig. 15d and e). These results reveal the preferential primary hydroxyl group protonation in DMSO–water mixtures.[190] Hence, the simulations offer valuable microscale insights into the solvent effect mechanism, which can help understand and manipulate interactions within solutions and provide a more comprehensive understanding of solvation and catalytic reac-

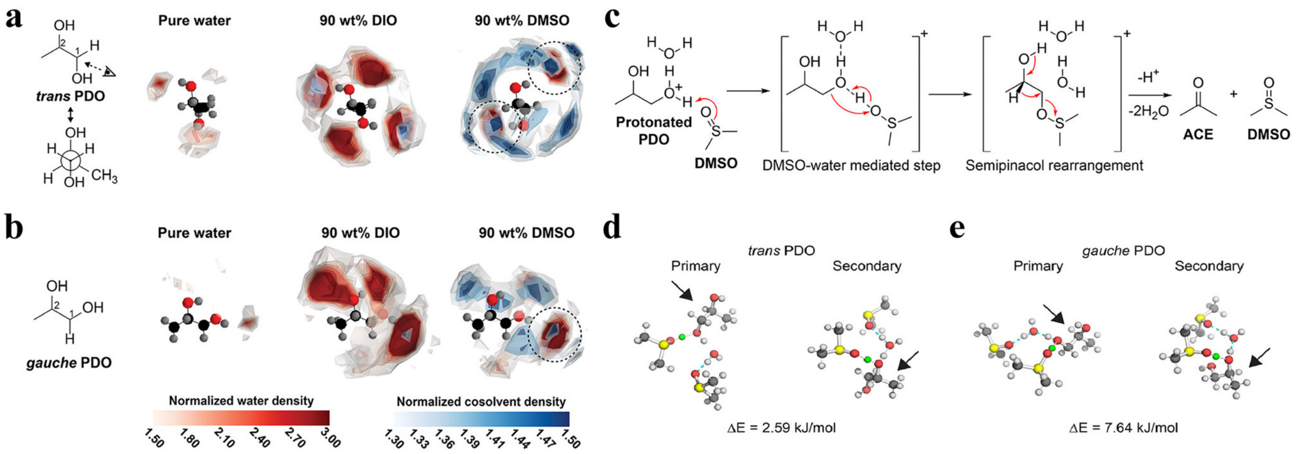

**Fig. 15** Spatial distribution maps of PDO in pure water, 90 wt% 1,4-dioxane, DIO, and 90 wt% DMSO in (a) *trans*-vicinal diol conformation and (b) *gauche*-vicinal diol conformation. Normalized density isovalues for water between 1.5 and 3.0 are presented in red, while cosolvent isovalues between 1.3 and 1.5 are shown in blue. Dashed lines highlight regions that remained water-enriched in DMSO–water mixtures, while other water-enriched regions are absent. (c) PDO dehydration is thought to provide acetone, ACE, in DMSO–water mixtures. The transfer of electrons is indicated by red arrows. Relaxed structures of two DMSO molecules and one water and protonated primary or secondary hydroxyl groups of PDO in the (d) *trans*-vicinal diol conformation or (e) *gauche*-vicinal diol conformation. Black arrows are depicted in panels (d) and (e) as a visual guide to distinguish PDO. The green atoms represent protons, and hydrogen bonds are shown by the cyan dashed lines. Reproduced from ref. 190 with permission from [American Chemical Society], copyright [2020].

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tions in mixed-solvent systems. Combining experimental data and computational models can enable a thorough examination of the complexities of solvent effects, ultimately guiding the development of efficient solvents and solvent mixtures.

## Conclusions and outlook

Solvents are essential to chemical reactions involving carbohydrates and exhibit unique physicochemical properties during their interactions with solutes and catalysts. This review offers an overview of the main pathways for modifying and transforming carbohydrates, and designing solvent systems to facilitate these chemical reactions. The effects of solvents on solubilization, solution stability, catalysis, mass transfer, and product separation efficiency were discussed to highlight their roles in the success of chemical reactions. These solvent effects are universal in reaction systems with substrates other than carbohydrates.

The solvent system plays a crucial role in linking reaction substrates, products, and catalysts, which showcases the unity of the reaction system. Therefore, separating products while recovering solvents and catalysts from the system is a significant challenge in chemical reactions. Developing solvent systems requires comprehensively understanding the physicochemical properties of potential solvents. This involves assessing solvent-substrate interactions and mass production-related properties, such as toxicity, stability, and recoverability, to identify suitable solvents. Theoretical calculations also provide valuable insights into the type, extent, and variations of interactions occurring within solvents or solution systems under specific or extreme conditions. This information supports the fundamental study of solvent effects at the microscopic scale and facilitates the screening and development of solvents.

Carbohydrate-based DESs and ILs designed using various monosaccharides and modified charged carbohydrate ions fully exploit the structural tuning properties of green solvents. These solvents can also act as substrates, resulting in high substrate loading and achieving an *in situ* and self-sufficient substrate supply. Carbohydrate-based DESs and ILs are known for their superior chiral catalytic and extraction properties. They also possess high biocompatibility, making them suitable for biomacromolecule reaction systems and biomedical engineering applications. The structural properties of these solvents also contribute to their sustainability, further enhancing their potential applications. In addition to modulating the solvent structure, researchers continue to explore solvent form regulation. For example, porous materials that can function as both solvents and load catalytic centers are being developed to create porous solid solvents that provide both solvation and catalytic environments. Moreover, the emergence of solvent-free reaction systems has opened up new avenues for modifying and converting biomolecules.

The future development of the sugar platform revolves around the realization of efficient, low-cost and diversified saccharification of lignocellulose and the conversion of carbohydrates into high-value-added and multifunctional products. The sugar platform aims at building a sustainable, green economic system founded on biomass-based carbohydrates. The solvent effects in carbohydrate conversion serve as a key regulatory step in the specific implementation program of the sugar platform. Further research should be undertaken to investigate the development of new solvent systems, optimization of solvent structure and form, improvement of solvent recovery, studying the microscopic mechanisms and macroscopic laws of solvent effects, and providing theoretical guidance and experimental basis for the implementation of the specific plan of the sugar platform. Overall, solvent engineering with solvent performance regulation as the starting point provides new opportunities and thoughts for carbohydrate transformation and sugar platform development.

## Abbreviations

| | |
|---|---|
| APR | Aqueous phase reforming; |
| ChCl | Choline chloride |
| ChOH | Choline hydroxide |
| DESs | Deep eutectic solvents |
| DMAc | Dimethylacetamizde |
| DMSO | Dimethyl sulphoxide |
| DMF | *N*,*N*-Dimethylformamide |
| DS | Degree of substitution |
| GVL | γ-Valerolactone |
| Gxyl | 4-*O*-methyl glucuronic acid xylan |
| HA | Hyaluronan |
| HBA | Hydrogen bond acceptor |
| HBD | Hydrogen bond donor |
| HMF | 5-Hydroxymethylfurfural |
| HSP | Hansen solubility parameters |
| ILs | Ionic liquids |
| LA | Levulinic acid |
| MCC | Microcrystalline cellulose |
| NAG | *N*-Acetyl-D-glucosamine |
| PDO | 1,2-Propanediol |
| SCFs | Supercritical fluids |
| THF | Tetrahydrofuran |
| TSs | Transition states |
| Xyl | Xylan with both 4-*O*-methyl glucuronic acid and arabinofuranose residues. |

## Author contributions

H. Y. supervised the project and proposed the concept. Y. S. organized the literature and wrote the text. Z. T., Y. Y., and W. C. participated in the design of the framework for this review. Y. L., S. Z., and Y. L. were involved in collecting topic literature and organizing table data. H. Y., Y. L., and Q. X. made several guidance amendments to the pictures and text. All authors read and approved the final submitted manuscript.

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## Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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