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Molecular Guide for Selecting Green Deep Eutectic Solvents with High Monosaccharide Solubility for Food Applications

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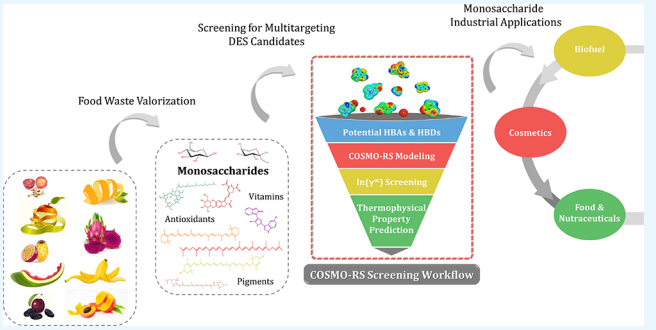
ABSTRACT: Monosaccharides play a vital role in the human diet due to their interesting biological activity and functional properties. Conventionally, sugars are extracted using volatile organic solvents (VOCs). Deep eutectic solvents (DESs) have recently emerged as a new green alternative to VOCs. Nonetheless, the selection criterion of an appropriate DES for a specific application is a very difficult task due to the designer nature of these solvents and the theoretically infinite number of combinations of their constituents and compositions. This paper presents a framework for screening a large number of DES constituents for monosaccharide extraction application using COSMO-RS. The framework employs the activity coefficients at infinite dilution (γ_i^{∞}) as a measure of glucose and fructose solubility. Moreover, the toxicity analysis of the constituents is considered to ensure that selected constituents are safe to work with. Finally, the obtained viscosity predictions were used to select DESs that are not transport-limited. To provide more insights into which functional groups are responsible for more effective monosaccharide extraction, a structure-solubility analysis was carried out. Based on an analysis of 212 DES constituents, the top-performing hydrogen bond acceptors were found to be carnitine, betaine, and choline chloride, while the top-performing hydrogen bond donors were oxalic acid, ethanolamine, and citric acid. A research initiative was presented in this paper to develop robust computational frameworks for selecting optimal DESs for a given application to develop an effective DES design strategy that can aid in the development of novel processes using DESs.



1. INTRODUCTION

The scientific community's interest in developing sustainable solvents has grown rapidly since the establishment of the 12 green engineering principles by Anastas and Warner.[1] These principles are considered grounds of recent research advancements and a guide to a future with chemical processes that do not generate or use any harmful solvents. Several breakthrough innovations have been achieved, including liquid polymers,[2] switchable solvents,[3] supercritical fluids,[4,5] ionic liquids,[6,7] and most recently, deep eutectic solvents (DESs).[8,9] DESs, green solvents that were first coined by Abbott and co-workers in 2003,[8] are emerging green solvents extensively studied for the extraction of various natural bioactive compounds, such as phenolic compounds, polysaccharides, proteins, and fatty acids.[10]

DESs are "mixtures of pure compounds for which the eutectic point temperature is far below that of an ideal liquid mixture".[11] They are generally formed by mixing one or more hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs), resulting in a liquid solvent at room temperature.[12] These solvents can be prepared to be biodegradable and sustainable by choosing the appropriate constituents.[8] They also have attractive characteristics, such as thermal and chemical stability, nonflammability, low volatility, high conductivity, and good solubilization capacity for several organic compounds.[9] These physical properties depend on the mixture's constituents and can be easily tailored for specific applications.[10] Attempts to understand the formation of naturally occurring DESs, such as honey, maple syrup, and sugar beet, led to the discovery of a new class of DESs called natural DESs (NADESs).[13] NADESs were first reported by Dai *et al.*,[13] where it was defined as supramolecular liquids composed of common metabolites in certain molar ratios, including water in some cases, which are characterized by extensive intermolecular interactions (hydrogen bonding). This class of DES has great potential as a green medium in many fields, such as food, nutraceutical, pharmaceutical, biomedical, and cosmetics due to the relatively low toxicity levels.[14]

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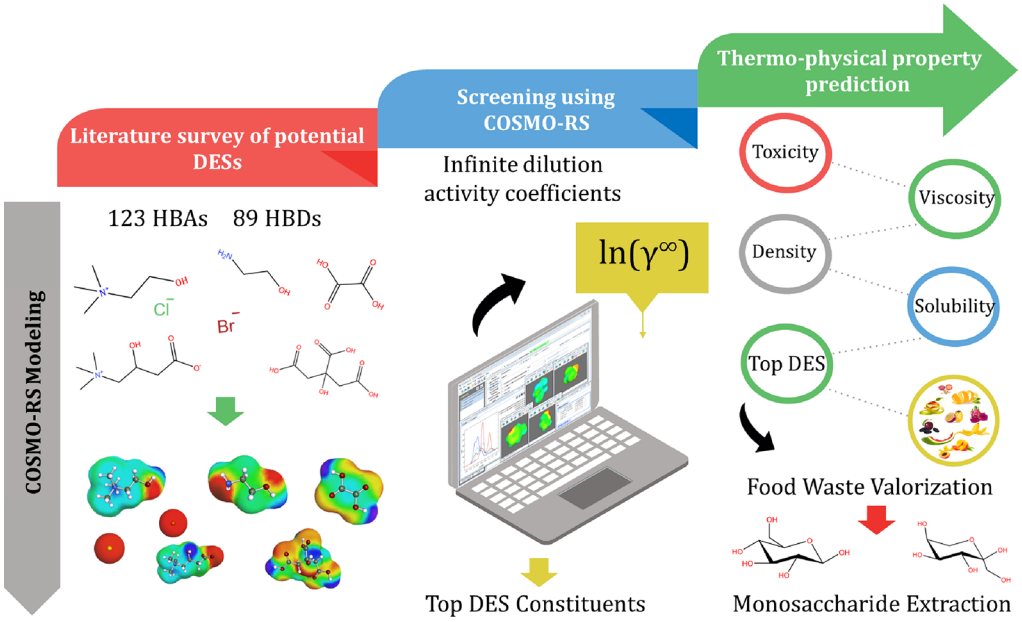

Figure 1. Schematic depicting the approach used in this study.

Monosaccharides and sugars generally play a vital role in the human diet due to their interesting biological activity and functional properties.[15] Currently, sugars are commonly extracted using conventional organic solvents, such as ethanol or methanol aqueous solutions. However, organic solvents are characterized by high volatility, inflammability, and toxicity levels, which negatively impact the environment. At the industrial scale, sugar is produced from sugarcane and sugar beet through a water-based extraction that is heat intensive and involves several chemical-based treatments.[16] Thus, a green yet high-performing alternative solvent that can extract sugar and other heat-sensitive bioactive compounds under mild temperature conditions is needed. NADESs can provide excellent alternatives to water and other organic solvents. Recently, extraction of bioactive compounds using various techniques (ultrasound-assisted extraction, microwave-assisted extraction, pressurized liquid extraction, *etc.*) using green solvents such as NADES attracted the attention of researchers.[17] For example, Gómez *et al.*[18] investigated several NADESs for the extraction of soluble sugars from ripe bananas. Among the NADESs studied, malic acid:beta-alanine:water (1:1:3) with an additional 30 g water/100 g solvent was found to be the most effective in extracting the soluble sugars from banana puree. The solvent achieved a sugar recovery of 106.9 g/100 g of solvent (25 °C, 30 min), resulting in a much more effective extraction than traditional benchmark solvents, ethanol (79.7 g/100 g), and water (71.5 g/100 g).[18] Zhang and Wang[19] studied the ultrasound-assisted extraction of polysaccharides from *Dioscorea opposita Thunb* using several DESs, and ChCl:1,4-butanediol proved to be suitable for the extraction.

Moreover, DESs and NADESs were utilized for food waste biomass pretreatment to enhance sugar production through an enzymatic hydrolysis process. These derived sugars can then be used for biofuel production.[20] Although the results obtained in the literature seem to be very promising, there are some limitations that hinder the application of NADESs, such as their high viscosity and/or low polarity, which can lead to a reduction in the solute diffusivity into the extraction medium and a reduction in the solute dissolution capacity, resulting in a low yield. However, these issues could be altered by changing the constituents, composition, of DESs and the operating temperature.[10] The controllable addition of water can also be another promising solution as it can help weaken the NADES interactions, causing a decrease in viscosity and increase in its polarizability. Dai *et al.*[21] proved that the addition of 50% (v/v) water caused the complete disappearance of hydrogen bonding interactions between the two components of NADESs. Other researchers reported the preservation of the molecular-level NADES structure under certain water content conditions of 50 wt % or below.[18,22] Therefore, the dilution of NADES with water should be carefully controlled to avoid any adverse impact on NADES performance.

Despite the promising characteristics of NADES, research investigating the extraction of monosaccharides using NADESs is very scarce and limited. Therefore, more studies are needed to find an optimal NADES capable of effectively replacing conventional solvents. However, considering the high versatility and "designer" nature of NADES, there is a theoretically infinite number of possible NADES mixtures based on the choice of HBA, HBD, and their molar ratio. In that sense, relying only on experimental measurements for designing NADES is ineffective, and thus, using molecular-based modeling and simulation tools for pre-screening the NADES constituents that are effective for specific applications would save both investigation time and resources. The Conductor-like Screening Model for Real Solvents (COSMO-RS) has been successfully used in the literature to screen solvents for various separation processes, such as fuel purification,[23] CO_2 capture,[24] and the valorization of volatile fatty acids from wastewater.[25] The application of COSMO-RS screening for saccharide extraction has only been reported in a paper by Mohan *et al.*,[26] where they screened 64 ionic liquids (ILs) for their glucose, fructose, xylose, and galactose solubilities. The results indicated that imidazolium [Im^+]-, ammonium [N^+]-, and phosphonium [P^+]-based cations, especially those with lower chain lengths, showed promising performance. On the other hand, the best investigated anions were thiocyanate [SCN^-] and methylsulfate [$CH_3SO_4^-$].

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According to the author's knowledge, a methodical COSMO-RS evaluation for the utilization of sugar extraction via DESs or NADESs has not been reported up to this point.

Therefore, herein, we present the screening of 212 DES constituents, including 89 HBAs and 123 HBDs, for the extraction of glucose and fructose using COSMO-RS. The screening framework initially considers the infinite dilution activity coefficients (γ_i^{∞}) as a quantitative assessment of the monosaccharide's solubility, and then a toxicity analysis of the best constituents is conducted to confirm that the selected components are non-toxic and appropriate for use in food applications. Finally, viscosity predictions are applied to select NADESs that are not transport- or diffusion-limited. Additionally, a structure-solubility analysis was also conducted to offer molecular insights into how the structure of the NADES influences their attraction toward monosaccharides. A schematic summarizing the applied approach is shown in Figure 1. The results of this work can be used as a molecular-based guide and database for the design of new NADESs that are non-toxic, having low viscosity, and with relatively high monosaccharide solubility, which can be used in a plethora of food applications, such as the extraction of sugars from fruits with high sugar content (such as dates) and from food bio-wastes.

2. COMPUTATIONAL METHOD

COSMO-RS is a predictive molecular modeling approach devised by Eckert and Klamt. It uses quantum chemistry and statistical mechanics to predict the thermodynamic behavior of pure substances and their combinations, based on their three-dimensional structure and screening charge density. This model can predict the attributes of traditional organic solvents, ILs, and has more recently been used to predict the properties of DESs. More comprehensive information about the theories and applications of COSMO-RS can be found in other sources.[27,28]

In this work, a list of DES systems that are commonly used in extraction was compiled based on an extensive literature survey. The list consisted of 89 HBAs and 123 HBDs. The three-dimensional structures of each molecule were initially created using Turbomole software[29] (TmoleX19 4.5.1) by inputting the SMILES for each HBA and HBD as well as for glucose and fructose into the software. The density functional theory (DFT) optimizations were carried out using the def-TZVP "triple-zeta valence polarized" basis alongside the Becke−Perdew (BP86) exchange−correlation function.[30] This method was previously applied in the literature for modeling DES components.[31,32] The generated ".cosmo" files (depicted in Figure 2) are subsequently imported into the BIOVIA COSMOtherm (2022 version) for the execution of quantum chemical simulations.

In COSMO-RS, DESs can be depicted using three main strategies: (a) the ion-pair strategy, (b) the meta file strategy, and (c) the electroneutral strategy. For this study, we utilized the electroneutral strategy, where the DESs are treated as three separate dissociated entities—the salt cation, the salt anion, and the HBD, considering their molar proportions. For instance, ChCl:ethanolamine (1:6) is viewed as a mole of choline cation, a mole of chloride anion, and 6 moles of ethanolamine. The advantage of using this approach is its flexibility in modeling any combination of DESs as it enables the cation, the anion, the HBD, or their molar ratios to be easily changed. Furthermore, by this method, it is plausible to study as many variations as possible of cation-anion-HBD-monosaccharide permutations that can occur in solution.

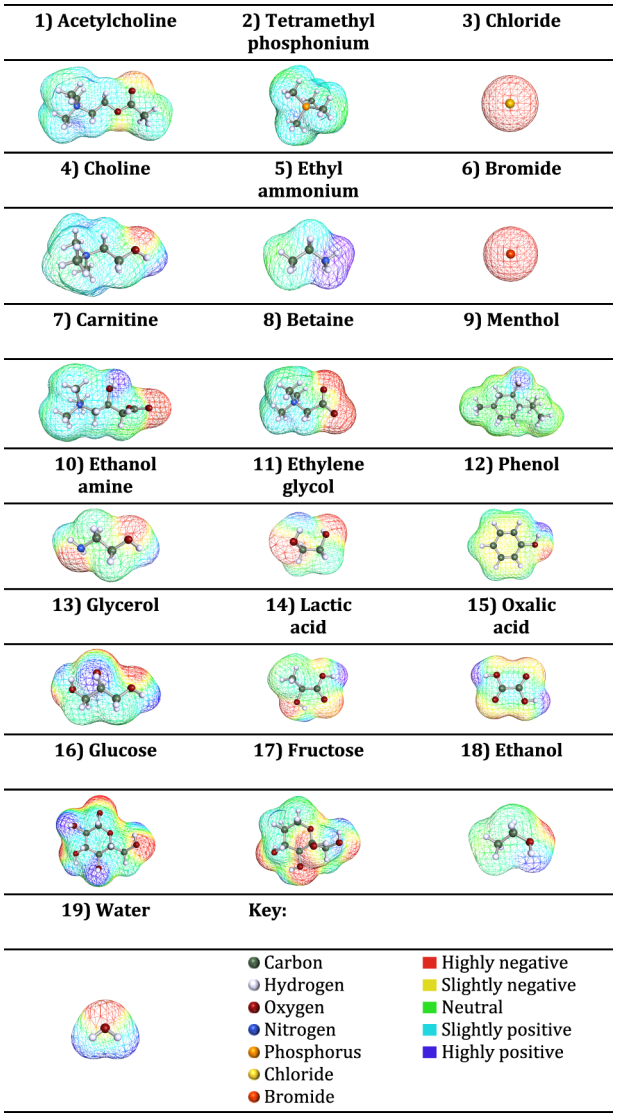

Figure 2. 3D COSMO-RS structures of typical examples of cations, anions, and HBDs along with the monosaccharides (glucose and fructose) and the benchmark solvents (ethanol and water).

To screen the best DES constituents for the extraction of monosaccharides, the activity coefficient at infinite dilution (γ_i^{∞}) method was used as an evaluation parameter, which is described as follows in COSMO-RS:[33]

$$\ln(\gamma_i^{\infty}) = \frac{\mu_S - \mu_i}{RT} \quad (1)$$

where μ_S and μ_i are the COSMO-RS predicted chemical potentials of the DES component and the monosaccharide (glucose or fructose), respectively. The solubility of a certain compound in a solvent is inversely proportional to its activity coefficient in the system. Thus, COSMO-RS was used to predict the activity coefficient of reducing sugars, namely, fructose and glucose, in the 212 constituents of DESs at 298.2 K.

The liquid viscosities of the DESs in COSMO-RS were computed based on (1) the Grunberg−Nissan equation, (2) the surface area as read from the ".cosmo" file (a_i), (3) the

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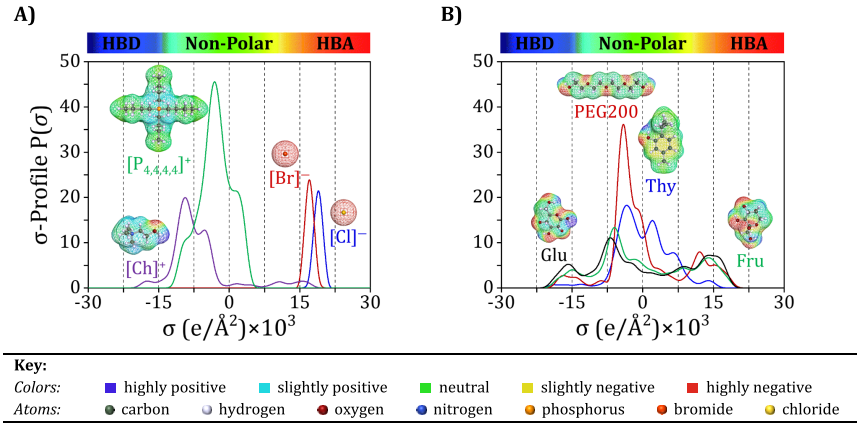

Figure 3. σ-profiles of (A) bromide, chloride, tetrabutylphosphonium, choline, and (B) polyethylene glycol 200, and thymol as representative examples of anions, cations, and HBDs, respectively, with glucose and fructose.

second σ-moment (M_i^2), (4) the number of ring atoms (N_i^{Ring}), and (5) the multiplication of temperature and entropy (TS_i) that is calculated from the enthalpy (H_i) and the chemical potential [$TS_i = -(H_i - \mu_i)$].[34]

The COSMO-RS solubility predictions were made in the "Multiple Solvents" panel with the selected options of (i) absolute values and (ii) SLE (best quality, slow). The predictions require the melting temperature and the enthalpy of fusion of the solutes (glucose and fructose), which were obtained from the NIST Chemistry Database as T_m = 414 K; ΔH_{fus} = 31.42 kJ/mol for glucose, and T_m = 376 K; ΔH_{fus} = 30.30 kJ/mol for fructose. The IDs of glucose and fructose in the NIST Database are C50997 and C57487, respectively. The fusion entropy was also fed into the COSMO-RS software, which was determined as given below:

$$\Delta S_{fus} = \frac{\Delta H_{fus}}{T_m} \quad (2)$$

where ΔS_{fus} is in units of kJ·K^{-1}·mol^{-1} and is calculated to be 0.0759 and 0.0806 kj·K^{-1}·mol^{-1} for glucose and fructose, respectively. Using the COSMO-RS SLE panel, predictions of the DES density and viscosity are also provided as an output, which are also reported in this work.

3. RESULTS AND DISCUSSION

3.1. σ-Profiles: Their Practical Significance and Contribution to the Predictions. The predictions of COSMO-RS are based on two main factors, (i) the geometrically optimized DFT structures of the molecules and (ii) their σ-profiles $P_s(\sigma)$. The σ-profile of a molecule is a probability distribution that denotes the relative likelihood of a molecular surface segment having a specific surface charge, σ, which could be positive, neutral, or negative.[35] As a result, the position, height, and breadth of the peaks in the σ-profile carry the necessary structural and energy-related data required to forecast its dominant intermolecular interactions, such as hydrogen bonding, electrostatic, and polar inducing interactions. Figure 3 shows eight representative examples of the σ-profiles of two cations, two anions, two HBDs, and the monosaccharides (glucose and fructose). The σ-profiles of the rest of the molecules are available in Figures S1 and S2 of the Supporting Information. In Figure 3, the profile can be divided into three separate areas. Negative charge densities ($\sigma < -0.008$ e/Å^2) indicate positive polarity surfaces with a hydrogen "donating" trait (shown by blue molecular surfaces), whereas positive charge densities ($\sigma > +0.008$ e/Å^2) indicate negative polarity surfaces with a hydrogen "accepting" trait (represented by red molecular surfaces). Charge densities within the range of ($-0.008 \leq \sigma \leq +0.008$ e/Å^2) signify neutral surfaces within the molecule.

When contrasting the ions in Figure 3A, it is apparent that cations are skewed to the left in their profile, whereas anions have a right-side skewness, reflecting their positive and negative charges, respectively. When different anions are compared, it can be observed that chloride is slightly more negative than bromide (more toward the right) because chloride has a higher electronegativity than bromide. However, bromide has a peak higher than chloride because the atomic weight of bromide is higher. In the same sense, it can also be observed that the tetrabutylphosphonium cation exhibits a peak (particularly in the neutral region) that is significantly higher than that of the choline cation as it encompasses more non-polar surfaces. Conversely, it can be observed that the choline cation possesses a more localized charge (to the left). This occurs because the impact of the N^+ is more evident as fewer carbons are available for charge stabilization and due to the H^+ part of the hydroxy functional group.[36] Moving on to Figure 3B, it can be observed that tetraethylene glycol, glucose, and fructose showcase relatively large peaks in both the HBA and the HBD regions, suggesting that these molecules can function as both an HBA and an HBD. In addition, it can be observed that the sizes of the glucose and fructose profiles are very similar due to their similarity in nature and molecular weight. On the other hand, thymol has more pronounced peaks in the HBA region than in the HBD region. It can also be observed that the charges in thymol are spread over a wide peak, a characteristic resulting from its resonance structures and charge delocalization of the lone electron pairs from the oxygen through the aromatic ring.[37]

3.2. COSMO-RS Evaluation: Screening the Influence of HBAs and HBDs. For selecting the DES components with the highest capacity to extract glucose and fructose, the activity coefficient at infinite dilution (γ_i^∞) of each DES constituent was determined at 298.2 K with COSMO-RS. The γ_i^∞ describes the behavior of the monosaccharide molecules when they are fully surrounded by the molecules of the DES constituent (*i.e.*, $x_i \approx 0$). The lower the value of γ_i^∞, the higher the solubility of the solute in the DES constituent (stronger interactions). The predicted averaged γ_i^∞ values of both solutes

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Table 1. Predicted Activity Coefficients at Infinite Dilution (γ_i^{∞}) of the Targeted Monosaccharides in the 212 DES Constituents at 298.2 K and 1.01 Bar

#	constituent	$\ln(\gamma^{\infty}{}_{Fru})$	$\ln(\gamma^{\infty}{}_{Glu})$	#	constituent	$\ln(\gamma^{\infty}{}_{Fru})$	$\ln(\gamma^{\infty}{}_{Glu})$
	hydrogen bond acceptors (HBAs)			D17	hydroquinone[38]	−3.534	−1.812
A1	ammonium chloride	−76.380	−76.020	D18	maleic acid[39]	−3.165	−2.097
A2	ammonium bromide	−68.513	−66.997	D19	urea[40]	−1.935	−3.001
A3	tetramethylammonium chloride	−15.282	−17.604	D20	phenol[41]	−3.446	−1.118
A4	carnitine[42]	−13.710	−16.525	D21	3-salicylic acid[43]	−2.978	−1.486
A5	tetramethyl phosphonium chloride	−13.725	−16.151	D22	tartaric acid[44]	−2.672	−1.692
A6	betaine[42]	−12.899	−15.610	D23	malonic acid[45]	−2.565	−1.765
A7	tetraethylammonium chloride	−12.540	−15.047	D24	lidocaine[46]	−1.549	−2.761
A8	tetraethylphosphonium chloride	−12.514	−15.030	D25	diethylene glycol[47]	−1.566	−2.727
A9	choline chloride[8]	−11.912	−14.189	D26	methanol[48]	−1.460	−2.700
A10	tetramethylammonium bromide	−11.796	−13.654	D27	formic acid[49]	−2.446	−1.601
A11	tetrapropylammonium chloride	−11.001	−13.526	D28	diethanolamine[50]	−1.364	−2.611
A12	tetrapropylphosphonium chloride	−10.838	−13.354	D29	1,4-butanediol[19]	−1.152	−2.522
A13	benzyltriethylammonium chloride[51]	−10.543	−12.955	D30	2-salicylic acid[52]	−2.637	−0.669
A14	benzyltriethylphosphonium chloride[51]	−10.466	−12.882	D31	1,3-propanediol[53]	−0.985	−2.150
A15	dimethylethylethanolammonium chloride	−10.472	−12.833	D32	3-cresol[50]	−2.619	−0.479
A16	diethylethanolammonium chloride	−10.393	−12.849	D33	bisphenol Z[54]	−2.499	−0.452
A17	tetrabutylammonium chloride[55]	−10.244	−12.752	D34	2-methylpentanediol[56]	−0.793	−2.142
A18	tetrabutylphosphonium chloride[57]	−10.065	−12.566	D35	4-phenyl phenol[38]	−2.741	−0.058
A19	tetramethyl phosphonium bromide	−10.284	−12.182	D36	ethanol[58]	−0.785	−1.948
A20	tetrapentylammonium chloride	−9.795	−12.289	D37	4-cresol[50]	−2.400	−0.157
A21	benzyl trimethylammonium chloride	−9.698	−12.040	D38	2-cresol[50]	−2.510	−0.033
A22	benzyl trimethyl phosphonium chloride	−9.689	−12.039	D39	sesamol[43]	−2.121	−0.188
A23	tetrapentylphosphonium chloride	−9.510	−11.995	D40	ethylene glycol[53]	−0.649	−1.644
A24	acetylcholine chloride	−9.435	−11.704	D41	malic acid[44]	−1.431	−0.646
A25	tetrahexylammonium chloride	−9.248	−11.730	D42	4-ethylphenol[59]	−2.183	0.121
A26	1-butyl-3-methylimidazolium chloride[52]	−9.183	−11.654	D43	*N*-methyl diethanolamine[60]	−0.465	−1.366
A27	butyltriphenylphosphonium chloride	−9.146	−11.499	D44	propylene glycol[61]	−0.442	−1.343
A28	tetra hexyl phosphonium chloride	−9.062	−11.535	D45	4-cyanophenol[38]	−1.474	0.042
A29	tetraheptylammonium chloride[62]	−8.826	−11.297	D46	acetic acid[63]	−0.884	−0.515
A30	allyl triphenylphosphonium chloride	−8.826	−11.145	D47	4-propyl phenol[59]	−1.876	0.484
A31	methyl triphenylphosphonium chloride	−8.743	−11.058	D48	xylitol[40]	−0.286	−0.903
A32	tetraheptylphosphonium chloride[62]	−8.624	−11.085	D49	1,6-hexanediol[19]	−0.091	−1.093
A33	tetraethylammonium bromide	−8.908	−10.794	D50	glycerol[64]	−0.211	−0.950
A34	tetraethylphosphonium bromide	−8.849	−10.713	D51	thiourea[65]	−1.073	−0.050
A35	tetraoctylammonium chloride[66]	−8.506	−10.968	D52	ascorbic acid[67]	−0.806	−0.221
A36	methyl triphenyl ammonium chloride	−8.546	−10.866	D53	1,2-butanediol[53]	−0.065	−0.831
A37	1-hexyl-3-methylimidazolium chloride[52]	−8.420	−10.879	D54	lactic acid[68]	−0.585	−0.216
A38	choline bromide	−8.715	−10.581	D55	levulinic acid[69]	−0.426	−0.363
A39	methyltrioctylphosphonium chloride[70]	−8.418	−10.870	D56	polyethylene glycol 200[71]	−0.085	−0.695
A40	benzyltriphenylphosphonium chloride[72]	−8.464	−10.750	D57	thymol[56]	−1.754	0.998
A41	benzyltriphenylammonium chloride[72]	−8.413	−10.698	D58	1-propanol[53]	0.096	−0.850
A42	methyltrioctylammonium chloride[70]	−8.299	−10.753	D59	propionic acid[73]	−0.570	−0.028
A43	tetraoctylphosphonium chloride[66]	−8.298	−10.749	D60	glycolic acid[74]	−0.414	−0.157
A44	hexadecyltrimethylphosphonium chloride	−7.831	−10.248	D61	mequinol[59]	−1.143	0.602
A45	dodecyldimethylbenzylphosphonium chloride[75]	−7.678	−10.029	D62	1,2-decanediol[76]	0.348	−0.865
A46	dodecyldimethylbenzylammonium chloride[75]	−7.595	−9.948	D63	maltitol[40]	0.214	−0.730
A47	tetrapropylammonium bromide	−7.586	−9.414	D64	maltose[61]	−0.034	−0.450
A48	hexadecyltrimethylammonium chloride	−7.304	−9.695	D65	mandelic acid[73]	−0.780	0.442
A49	tetrapropylphosphonium bromide	−7.456	−9.272	D66	pyruvic acid[68]	−0.804	0.570
A50	dimethylethylethanolammonium bromide	−7.395	−9.289	D67	1,8-octanediol[77]	0.355	−0.572
A51	diethylethanolammonium bromide	−7.048	−8.952	D68	diclofenac[78]	−1.321	1.212
A52	benzyltriethylammonium bromide[51]	−7.107	−8.871	D69	sorbitol[40]	0.087	−0.171
A53	benzyltriethylphosphonium bromide[51]	−7.054	−8.806	D70	1-butanol[53]	0.475	−0.450
A54	tetrabutylammonium bromide[55]	−6.864	−8.647	D71	atropine[76]	0.354	−0.299
A55	tetrabutylphosphonium bromide[57]	−6.721	−8.495	D72	benzoic acid[52]	−0.619	0.766
A56	benzethonium chloride	−6.482	−8.613	D73	cyclohexanol[53]	0.584	−0.424
A57	benzyl trimethyl phosphonium bromide	−6.602	−8.363	D74	trioctylphosphine[79]	1.058	−0.725
A58	benzyl trimethylammonium bromide	−6.536	−8.305	D75	phenylacetic acid[73]	−0.456	0.848
A59	tetrapentylammonium bromide	−6.385	−8.137	D76	trifluoroacetamide[80]	−0.323	0.832

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Table 1. continued

#	constituent	$\ln(\gamma^{\infty}_{Fru})$	$\ln(\gamma^{\infty}_{Glu})$	#	constituent	$\ln(\gamma^{\infty}_{Fru})$	$\ln(\gamma^{\infty}_{Glu})$
A60	acetylcholine bromide	−6.370	−8.139	D77	1,10-decanediol[75]	0.800	−0.043
A61	tetrapentylphosphonium bromide	−6.168	−7.912	D78	anise alcohol[81]	0.454	0.371
A62	1-butyl-3-methylimidazolium bromide[52]	−5.904	−7.755	D79	sobrerol[82]	0.655	0.248
A63	tetrahexylammonium bromide	−5.843	−7.574	D80	ethyl paraben[83]	−0.026	1.132
A64	butyltriphenylphosphonium bromide	−5.757	−7.408	D81	allantoic acid	0.808	0.575
A65	tetrahexylphosphonium bromide	−5.703	−7.425	D82	2-phenylethanol[84]	0.716	0.675
A66	allyl triphenylphosphonium bromide	−5.544	−7.178	D83	trimethyl-1,3-pentanediol[85]	1.073	0.340
A67	methyl triphenylphosphonium bromide[86]	−5.510	−7.151	D84	camphor[82]	0.982	0.627
A68	tetraheptylammonium bromide[62]	−5.407	−7.119	D85	hexanoic acid[87]	0.529	1.303
A69	1-hexyl-3-methylimidazolium bromide[52]	−5.271	−7.079	D86	phenyl salicylate[88]	0.562	1.450
A70	methyl triphenyl ammonium bromide	−5.336	−6.992	D87	1-hexanol[53]	1.421	0.688
A71	tetraheptylphosphonium bromide[62]	−5.264	−6.967	D88	coumarin[76]	1.013	1.257
A72	methyltrioctylphosphonium bromide[70]	−5.163	−6.868	D89	ketoprofen[89]	0.613	1.660
A73	benzyltriphenylphosphonium bromide[72]	−5.193	−6.785	D90	heptanoic acid[90]	0.779	1.659
A74	benzyltriphenylammonium bromide[72]	−5.155	−6.752	D91	ibuprofen[91]	0.438	2.069
A75	methyltrioctylammonium bromide[70]	−5.080	−6.788	D92	1-heptanol[90]	1.748	1.082
A76	tetraoctylammonium bromide[66]	−5.053	−6.750	D93	water[92−94]	2.128	0.856
A77	tetraoctylphosphonium bromide[66]	−4.910	−6.598	D94	octanoic acid[95]	1.026	1.969
A78	hexadecyltrimethylphosphonium bromide	−4.889	−6.591	D95	alpha-terpineol[96]	1.755	1.272
A79	dodecyldimethylbenzylphosphonium bromide[75]	−4.798	−6.443	D96	glycine[97]	2.830	0.403
A80	dodecyldimethylbenzylammonium bromide[75]	−4.697	−6.347	D97	nonanoic acid[95]	1.228	2.248
A81	hexadecyltrimethylammonium bromide	−4.490	−6.181	D98	2-dodecanol[72]	2.208	1.273
A82	beta-alanine[18]	−4.068	−6.547	D99	1-octanol[53]	2.045	1.444
A83	benzethonium bromide	−3.859	−5.310	D100	10-undecenoic acid[98]	1.161	2.371
A84	butylammonium chloride	−2.788	−5.550	D101	carvacrol[99]	0.807	2.771
A85	ethyl ammonium chloride	−2.723	−5.591	D102	decanoic acid[70]	1.444	2.496
A86	propylammonium chloride	−2.483	−5.312	D103	1-nonanol[100]	2.286	1.731
A87	butylammonium bromide	−0.806	−2.874	D104	menthol[101]	2.302	1.789
A88	propylammonium bromide	−0.173	−2.333	D105	undecanoic acid[102]	1.595	2.748
A89	ethyl ammonium bromide	0.563	−1.744	D106	1-decanol[53]	2.513	2.027
	hydrogen bond donors (HBDs)			D107	ricinoleic acid[103]	2.185	2.385
D1	perfluorodecanoic acid[104]	−11.536	−9.043	D108	dodecanoic acid[68]	1.791	2.970
D2	trioctylphosphine oxide[79]	−6.611	−9.218	D109	borneol[82]	2.463	2.308
D3	hexafluoroisopropanol[42]	−7.599	−4.814	D110	1-undecanol[105]	2.697	2.239
D4	dodecylmethylsulfoxide[54]	−5.123	−7.257	D111	carveol[76]	1.712	3.331
D5	oxalic acid[61]	−6.874	−5.407	D112	1,3-dihexylthiourea[54]	2.192	3.124
D6	5-sulfosalicylic acid[106]	−6.455	−5.022	D113	1-dodecanol[53]	2.911	2.527
D7	ethanolamine[50]	−4.586	−6.403	D114	tetradecanoic acid[107]	2.075	3.367
D8	polyethylene glycol 400[71]	−4.632	−6.327	D115	oleic acid[91]	2.240	3.731
D9	3,5-di-*tert*-butylcatechol[54]	−6.254	−3.195	D116	hexadecenoic acid[108]	2.326	3.691
D10	*p*-toluenesulfonic acid[109]	−4.734	−2.832	D117	1-tetradecanol[53]	3.200	2.869
D11	gallic acid[110]	−4.497	−3.023	D118	octadecanoic acid[107]	2.560	4.012
D12	4-chlorophenol[59]	−4.711	−2.094	D119	1-hexadecanol[54]	3.456	3.188
D13	citric acid[40]	−3.926	−2.866	D120	oleyl alcohol[111]	3.492	3.504
D14	1-naphthol[76]	−4.768	−1.824	D121	triphenyl phosphate[79]	3.737	5.175
D15	triethylene glycol[112]	−2.517	−3.766	D122	benzoyltrifluoroacetone[79]	3.775	6.082
D16	triethanolamine[50]	−2.140	−3.543	D123	thenoyltrifluoroacetone[79]	3.236	5.180

(fructose and glucose) are listed from lowest to highest in Table 1 and are visually represented in Figure 4 and compared to two commonly used benchmark solvents (ethanol and water) for extracting monosaccharides. The dashed lines in the figures correspond to four quadrants indicating the effectiveness of each DES component compared to ethanol, with Q1 corresponding to DES components performing worse than ethanol with respect to both monosaccharides, Q3 corresponds to DES constituents performing better than ethanol with respect to both monosaccharides, and Q2 and Q4 correspond to DES constituents that are better than ethanol for only fructose or glucose, respectively.

3.2.1. Effect of Varying HBA. As can be seen in Table 1, hundreds of DES constituents have been reported in the literature. However, a systematic analysis that determines which types of DES constituents have high potential to extract monosaccharides has not yet been reported. In Figure 4, it can be observed that the performance of HBAs is generally better than the performance of HBDs as they correspond to lower γ_i^{∞} of glucose and fructose. Focusing specifically on HBAs, it can be deduced that chloride anions result in much higher solubility compared to bromide anions, as shown in Figure 5A [*e.g.*, TBACl (A17) > TBABr (A54) with a 49% increase in $\ln(\gamma^{\infty}_{Glu})$]. This is likely due to chloride's smaller anionic

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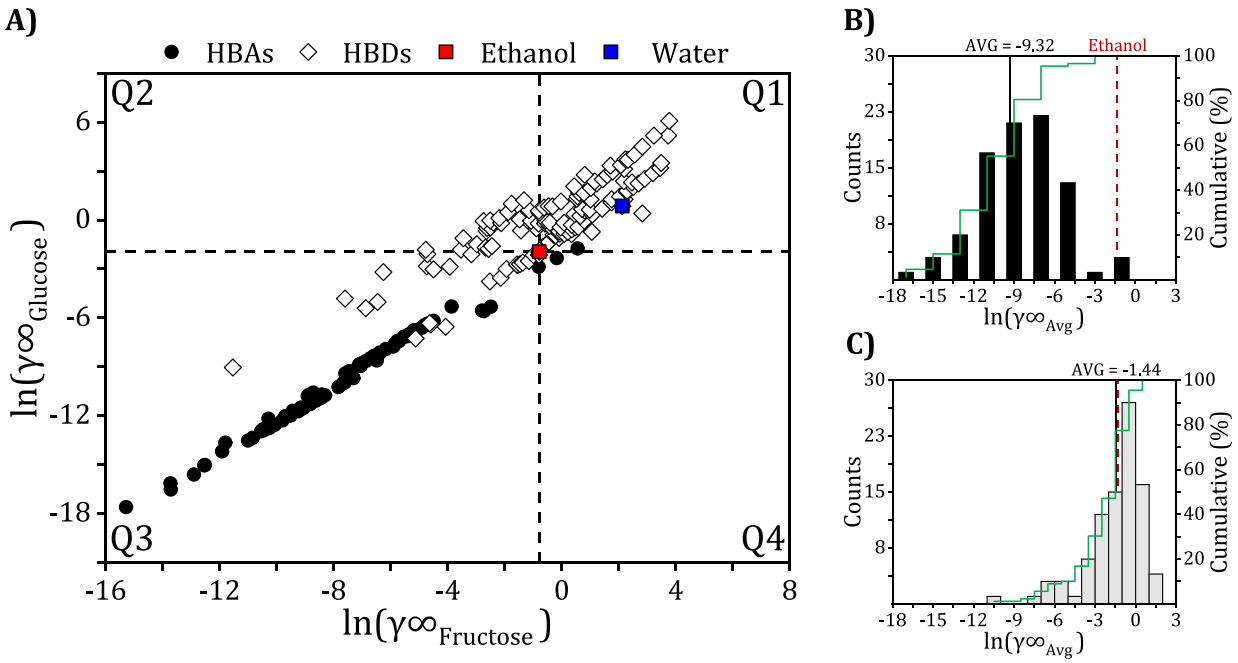

Figure 4. (A) Predicted activity coefficients (γ_i^{∞}) of glucose versus those of fructose and the histogram distributions of the averaged γ_i^{∞} of (B) HBAs and (C) HBDs. The average γ_i^{∞} of all HBAs and all HBDs is shown as a black solid line, and the cumulative count is in green according to the right axis.

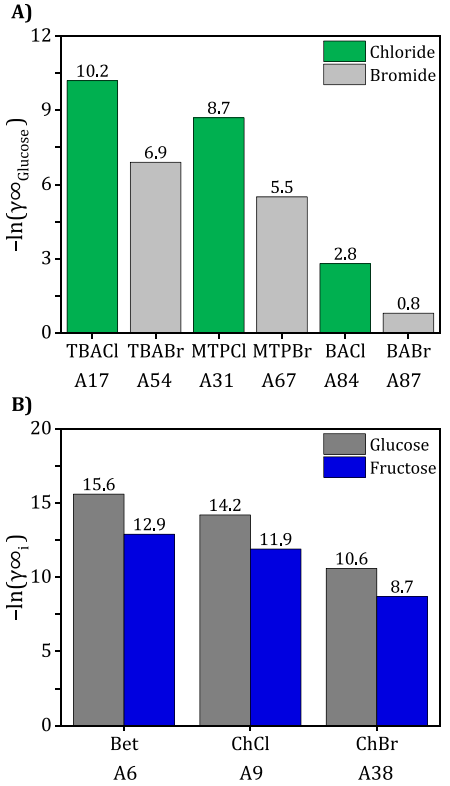

Figure 5. (A) Effect of Cl^- and Br^- on γ_{Glu}^{∞} for similar cationic cores [A17, A54, A31, A67, A84, and A87]. (B) Comparison of the γ_{Glu}^{∞} and γ_{Fru}^{∞} on betaine (with O^-) and choline (with Cl^-/Br^-) [A6, A9, and A38].

volume and greater electronegativity in comparison to bromide. Therefore, chloride anions are more likely to form stronger supramolecular clusters with cations,[113,114] which may facilitate interactions between the HBA and the extracted monosaccharides due to the formation of an even stronger hydrogen bonding network. Additionally, it can also be noticed that HBAs with oxygen anions (carboxylate groups) tend to perform very well, such as carnitine (A4) and betaine (A6). This can be specifically noticed when comparing betaine (A6) and choline chloride (A9) in Figure 5B as both HBAs have a very similar structure (trimethylethylammonium core) and are mainly different due to their ethanoate group versus the ethanol-chloride group. This is also consistent with the previous results since oxygen anions also have a smaller volume and higher electronegativity compared to Cl^- and Br^-. On the other hand, when comparing the central cationic cores of ammonium and phosphonium, it can be seen that the difference is minuscule. However, ammonium-based HBAs were slightly outperforming phosphonium-based HBAs [*e.g.*, TBACl (A17) > TBPCl (A18)]. Despite the fact that both HBAs have the same electric charge, the HBAs that contain a nitrogen core (smaller volume and higher polarity) tend to attract monosaccharides slightly better than a phosphorous core (larger with lower polarity).

Furthermore, the effect the alkyl chain length (n) of HBA on monosaccharide solubilities is shown in Figure 6A, where solubility increases as the alkyl chain length decreases [TM_1ACl (A3) > TE_2ACl (A7) > TP_3ACl (A11) > TB_4ACl (A17) > TP_5ACl (A20) > TH_6ACl (A25) > TH_7ACl (A29) > TO_8ACl (A35)]. This may be attributed to the rise in hydrophobicity of the molecule as a result of the increase in the chain length of the HBA, which causes a decrease in the solubility of the monosaccharides as they become highly different in nature (similarity−intermiscibility theory). Additionally, for further investigation, the γ_i^{∞} of $n = 0$ that corresponds to ammonium chloride [NH_4Cl (A1)] has also been determined, and it can be seen that the activity coefficients are extremely low at values of $\ln(\gamma_i^{\infty})$around−76. However, to our knowledge, no DESs have previously been reported using NH_4Cl as an HBA. Therefore, according to the

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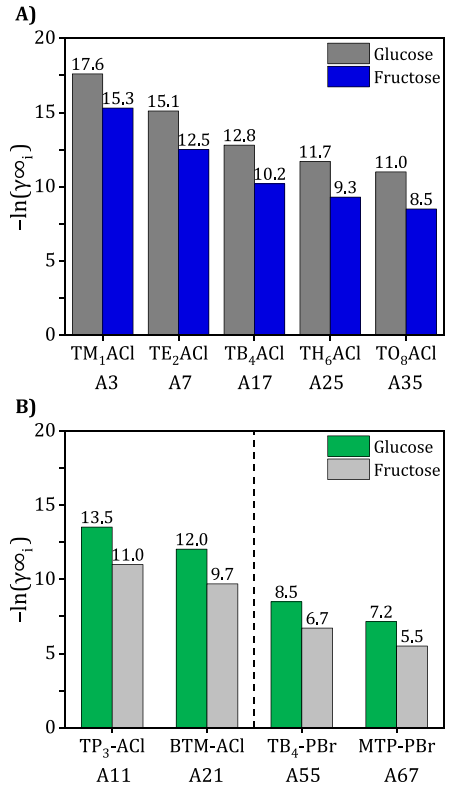

Figure 6. (A) Effect of cationic alkyl chain length (n) on the γ^{∞} of glucose and fructose [A3, A7, A17, A25, and A35]. (B) Comparison of the γ_i^{∞} of cations with linear chains and cations with rings [A11 & A21, A55 & A67].

results obtained, further investigations using ammonium chloride as an HBA for the formation of DES (or diluted within a particular solvent system) could be a useful route to study for some specific applications. In addition to cations containing linear alkyl chains, the performance of HBAs containing benzyl and phenyl groups, such as alkyltriphenyl, benzyltrialkyl, and benzyltriphenyl cores, has been investigated. Notably, it can be observed that the ring-containing HBAs have lower ability to dissolve sugars than those of alkyl-containing HBAs. For example, when comparing HBAs with similar molecular weights (Figure 6B), it can be seen that TB_4-PBr (A55) outperforms MTP-PBr (A67). Similar results were found when comparing TP_3-ACl (A11) and BTM-ACl (A21). These results are noteworthy because it was initially hypothesized that ring-based HBAs would be better in extracting monosaccharides (as they are also ring-structured); however, the opposite was true. This is presumably due to the high steric effects that could hinder the interactions between the cations and the monosaccharide molecules. Furthermore, the results showed that the ethanol groups attached to the cations tend to perform well, which is the case in choline chloride (A9), dimethylethylethanolammonium chloride (A15), and diethylethanolammonium chloride (A16). This could be due to the hydrogen bonding between the monosaccharide molecules and the cationic species. Finally, according to the aforementioned results, it can be concluded that an HBA with a (1) small central cation, such as nitrogen, (2) short side chain lengths, (3) a chloride or a carboxylate anion, and (4) a hydroxy group are considered optimal for monosaccharide extraction.

3.2.2. Effect of Varying HBD. Compared to the benchmark solvents (ethanol and water), it was found that most HBAs had much better performance than the benchmarks, while for HBDs, their performance was variable: some HBDs showed similar performance, others better, and in some cases even lower than ethanol, as shown in Figure 4. Among all the HBDs, ethanol was ranked as #36 in Table 1, while water was ranked as #93. To find optimal HBDs, special interest was given to the common solvents used in biomass valorization, such as glycerol, ethylene glycol, levulinic acid, lactic acid, and glycolic acid, due to their availability and generally environmentally benign nature. These solvents demonstrated good performance; however, they were all ranked lower than the benchmark ethanol (D36) in the following order: D50, D40, D55, D54, and D60. Among the top 20 ranked HBDs, a few other promising natural candidates were also given special attention, such as oxalic acid (D5), ethanolamine (D7), citric acid (D13), triethylene glycol (D15), triethanolamine (D16), maleic acid (D18), and urea (D19). These constituents, coupled with a suitable HBA, could be utilized as a starting point to develop highly effective NADES to extract sugars.

By conducting additional analysis, it can be seen that the HBDs with the highest predicted performance are perfluorodecanoic acid (D1), trioctylphosphine oxide (D2), hexafluoroisopropanol (D3), and dodecyl-methyl sulfoxide (D4). From D1 and D3, it can be deduced that fluorinated HBDs have a tremendous ability to attract glucose and fructose. However, it should be noted that these fluorine-containing solvents tend to be corrosive and toxic and therefore would not be applicable in most food-based applications.[115] From D2 and D4, it can be seen that the functional groups of phosphine oxide (P=O) and sulfoxide (S=O) perform very well, especially when comparing D2 with trioctylphosphine (D74), which are very similar in structure, the only difference being the P=O group. Oxalic acid (D5), gallic acid (D11), and citric acid (D13) showed similar results, indicating that the carbonyl group (C=O) increases the affinity toward fructose and glucose. The acidic functional group −SOOOH group in 5-sulfosalicylic acid (D6) and *p*-toluenesulfonic acid (D10) showed similar results. One can conclude that these oxygen-based double bonds (X=O) have excellent capacity and affinity for monosaccharides, presumably due to their $\pi-\pi$ bonding and hydrogen bonding interactions. On the other hand, alkanolamines (D7 and D16), phenolic (D9, D12, D14, D17, and D20), and some glycols (D8 and D15) were also promising. At the other end of the spectrum, the least performing HBDs (D97−D123) are quite hydrophobic, which agrees with the fact that as the HBD chain length increases, the solubility decreases (hexanoic acid D85/hexanol D87 > heptanoic acid D90/heptanol D92 > octanoic acid D94/octanol D99). This is probably due to the large number of hydroxy groups on glucose and fructose, which makes it hard for these monosaccharides to dissolve in these non-polar HBDs. This result is also consistent with the results from HBAs, where the more hydrophobic HBAs with larger chain lengths tended to have lower affinities with the monosaccharides. Furthermore, similar to the results obtained for HBAs, the addition of aromatic rings led to a reduction in performance as can be observed when comparing acetic acid (D46) vs phenylacetic acid (D75) and glycolic acid (D60) vs mandelic acid (D65). As for mono-, di-, and tri-molecules such as ethanolamines, it can be observed that the trend is as follows: mono (D7) > tri (D16) > di (D28). This implies that

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HBDs with alkyl chains on the unexposed (inside) and functional groups surrounding the molecule (outside) are better for monosaccharide extraction.

3.3. Multiselection Criteria of Potential DESs for Monosaccharide Extraction. To identify the best DESs as green solvents for the extraction of monosaccharides (fructose and glucose), certain properties that are important for food applications were evaluated, namely, toxicity, viscosity, density, and solubility.

3.3.1. Toxicity of DES Constituents. Toxicity data are vital information in the extraction application of bioactive compounds. However, unlike ionic liquids, DESs are poorly studied at the toxicological level due to their recent emergence. Given these challenges and limitations, a toxicity analysis was conducted using PubChem Database[116] for the 15 top-performing HBAs and HBDs. The complete list of all 30 constituents is available in Table S1 of the Supporting Information, whereas a summarized version of the least toxic constituents is shown in Table 2. Choline chloride and betaine

Table 2. Reported Toxicities and Typical Uses of the Selected HBAs and HBDs[b]

#	constituent	toxicity (LD_{50}: mg/kg)[a]	typical uses
A6	betaine	10,800	flavoring agents
A9	choline chloride	3900	flavoring agents and agrochemicals
D5	oxalic acid	2268	indirect food additive
D7	ethanolamine	700	agricultural chemicals, lubricants, surface-treating agents, solvents
D11	gallic acid	5000	flavoring agents, drugs
D13	citric acid	7280	flavoring agents, food additives, cosmetics, drugs
D15	triethyleneglycol	20,000	cleaning products, household care, microbicides

[a]50% of lethal dose. [b]Data were obtained from the PubChem Database.[116]

can be observed to be the least toxic HBAs, with LD_{50} values of 3900 and 10,800 mg/kg, respectively. These chosen HBAs have been commonly used in DES synthesis for various applications, including extraction, due to their environmentally benign nature. Both selected HBAs are approved by the US Food and Drug Administration (FDA) and are used as food additives at the industrial level.[17] For HBDs, ethanolamine, triethylene glycol, oxalic acid, gallic acid, and citric acid were selected because they are FDA-approved and used as a fruit-washing ingredient, nutrient supplement, and flavoring agent. To consider the synergistic effects of the DES constituents, the cytotoxicities of the ChCl-based DESs were studied by Radošević *et al.*,[117] and their results showed that the ChCl-DESs exhibited low cytotoxicity levels. On the other hand, the toxicity levels of the betaine-based DESs were not reported in the literature; hence, further research is needed in this area. Nonetheless, because DESs are mixtures, if the toxicity of the constituents is low, then the toxicity of the overall solvent can also generally be considered low in most cases. This behavior is different than that of ILs because ILs are synthesized using chemical reactions and thus their properties are not similar to the reactants.[118]

Based on the following selection of two HBAs and five HBDs, 10 binary combinations of DESs can be obtained. The eutectic molar ratios of the resulting combinations were surveyed in the literature and are shown in Table 3. Based on

Table 3. Reported Molar Ratios of Pre-screened DES Combinations in the Literature

#	HBA	HBD 1	molar ratios	ref
DES#01	betaine	ethanolamine		N.R.
DES#02	betaine	oxalic acid	2:1	17,119,120
DES#03	betaine	citric acid	1:1	13,17,121−123
DES#04	betaine	gallic acid		N.R.
DES#05	betaine	triethylene glycol	1:4	124,125
DES#06	choline chloride	ethanolamine	1:6	60,126,127
DES#07	choline chloride	oxalic acid	1:1	17,128,129
DES#08	choline chloride	citric acid	2:1	17,130−132
DES#09	choline chloride	gallic acid	2:1	110
DES#10	choline chloride	triethylene glycol	1:3	133

the literature survey, DES1 (betaine:ethanolamine) and DES4 (betaine:gallic acid) were not reported, and therefore, they were excluded from further investigation. The remaining eight DES combinations out of the 10 rationally chosen constituents are further considered for the thermophysical property prediction, namely, viscosity, density, and solubility.

3.3.2. Predicted Viscosities and Densities of the DESs. Viscosity is one of the primary features of desired solvents because it directly affects the mass transfer kinetics and ultimately the extraction efficiency. Among the selected DESs, acid-based DESs have been reported to have high viscosities, ≫1000 mPa·s, at room temperature due to the strong hydrogen bonding between their components.[130] The dilution of DES with water causes a significant reduction in its viscosity, leading to enhanced extraction efficiency. However, a rational DES to water ratio must be chosen to prevent reduction in DES's extraction capacity due to possible interference of water molecules and breakage of the hydrogen bond framework of DES.[21] In the literature, 20−40 wt % water addition was considered ideal to reduce the overall viscosities of the acid-based DESs to a level where it is close to a liquid viscosity of 100 mPa·s that is considered manageable at room temperature.[125,134] Particularly for the extraction of sugars, Gómez *et al.*[18] reported that the addition of 30 wt % of water (after DES synthesis) to acid-based DESs was found to be the best compromise between extraction efficiency and viscosity. Therefore, following the reported threshold value, the selected acid-DESs in this work (DESs 2, 3, 7, 8, and 9) were adjusted to include an additional 30 wt % of water. The predicted viscosities of the DESs at the chosen molar ratios and 298.2 K are presented in Table 4. It can be observed that the predicted viscosities for all selected DESs are all considered manageable, even for the acid-DESs. For example, the predicted viscosities for ChCl:CA (2:1) and ChCl:GA (2:1) before the addition of water were 10250.49 and 5760.78 mPa·s, respectively, and the addition of water led to a large reduction in viscosities, 6.45 and 6.13, respectively. These predictions are in agreement with the reported experimental trends in the literature, showing that the addition of 30 wt % of water to acid-DESs is necessary to reduce the viscosity.[18,22] Furthermore, the densities of the eight selected DESs were also predicted at 298.2 K (Table 4), and it can be observed that the predicted densities of all DESs were higher than those of water and ethanol.

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Table 4. Predicted Viscosities and Densities Using COSMO-RS for the Selected DESs and Ethanol at 298.2 K and 1.01 Bar

DES	μ_{pred} (mPa·s)	ρ_{pred} (g/mL)
DES#02: Bet:OxA (2:1 30 wt % H_2O)	2.65	1.1385
DES#03: Bet:CA (1:1 30 wt % H_2O)	3.83	1.1862
DES#05: Bet:TEG (1:4)	53.76	1.0969
DES#06: ChCl EA (1:6)	24.46	1.0267
DES#07: ChCl:OxA (1:1 30 wt % H_2O)	4.54	1.1997
DES#08: ChCl:CA (2:1 30 wt % H_2O)	6.45	1.1786
DES#09: ChCl:GA (2:1 30 wt % H_2O)	6.13	1.1916
DES#10: ChCl:TEG (1:3)	53.76	1.1152
ethanol	2.84	0.7769
water	0.89	0.9967

3.3.3. Predicted Solubilities in DESs. The predicted glucose and fructose solubilities (g sugar/100 g solvent) in the eight chosen DESs compared to the benchmark solvent (ethanol) between 298 and 353 K are shown in Figure 7. The dashed lines indicate the betaine-based DESs, whereas the solid lines indicate the choline chloride-based DESs. First, it can be observed that the overall solubility increased considerably with increasing temperature for all DESs and the benchmark solvents, which is the general trend reported in the literature attributed to increased kinetic energy of the mixture that results in an enhanced solubilities.[135,136] It can also be observed that ChCl:EA (1:6) was predicted to have the highest solubility for both monosaccharides as compared to the rest of DESs and the benchmark. On the other hand, Bet:CA (1:1 30 wt % H_2O) showed the lowest solubility. Nonetheless, it can be observed that the predicted solubility in the majority of the selected DESs is higher than >50 g/100 g solvent at 303.2 K, which was chosen as an optimal operating condition to prevent Maillard reactions and browning effects on the extracted sugars that are reported to occur at elevated temperatures.[137]

4. CONCLUSIONS

Selecting an appropriate DES for a particular application is a very daunting task due to the designer nature of DESs and their theoretically infinite combinations of constituents and compositions. In this work, COSMO-RS screening of 212 DES constituents was conducted including 89 hydrogen bond acceptors (HBAs) and 123 hydrogen bond donors (HBDs) for predicting the solubility of glucose and fructose. The effects of HBA and HBD structures were carefully mapped to assess the impact of each functional group on the solubility of monosaccharides. The results showed that both DES constituents play a vital role due to their affinities toward glucose and fructose. It was concluded that the solubility can be specifically improved by an HBA with a small central cation (N^+), short side chains, and a small anionic volume with high electronegativity (Cl^- and O^-). As for HBDs, it was found that HBDs with alkyl chains on the inner side (unexposed) and with functional groups surrounding the molecule are more suitable for monosaccharide extraction. Thus, the predictions indicate that alkanolamines such as ethanolamine and di-/tri-carboxylic acids such as oxalic acid and citric acid are highly performing and are considered environmentally benign. In addition, the potential NADES combinations for the extraction of reducing sugars were selected based on criteria considering toxicity, viscosity, density, and solubility. It was found that eight of the shortlisted NADESs had high predicted solubilities, low predicted viscosities, and low toxicities. This work provides a better understanding of the roles of the DES constituents in the extraction of sugars. The results can be used as a molecular guide and database for the design of novel NADES that can be used in a variety of food applications, such as the valorization of sugars from fruit bio-wastes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c03326.

(Figure S1) Determined σ-profiles of ionic HBA constituents, (Figure S2) determined σ-profiles of neutral HBD constituents, and (Table S1) reported toxicities and typical uses of the top 15 HBAs and top 15 HBDs (PDF)

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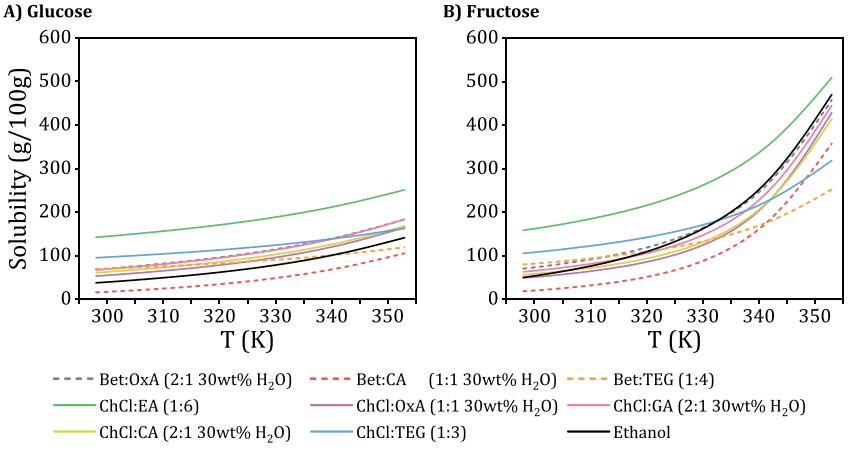

Figure 7. COSMO-RS predicted solubilities (g sugar/100 g solvent) for (A) glucose and (B) fructose.

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Notes

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