

Chiral Solvent Discovery: Exploring Chiral Eutectic Mixtures and Deep Eutectic Solvents

Todd A. Hopkins, Liam VandenElzen, Brian P. Nelson, Vishnu Vaid, Jayme Brickley, Paola Ariza, Grace Whitacre, Inaya Patel, Olivia Gooch, Mandy Bechman, and Charlotte Jordan*

Department of Chemistry, Butler University, 4600 Sunset Avenue, Indianapolis, IN, 46208.

Corresponding author email: tahopkin@butler.edu

KEYWORDS. Deep eutectic solvents, chirality, chiral DES database, eutectic mixtures, tetrabutylammonium chloride, thymol

ABSTRACT.

Deep eutectic solvents (DES) are mixtures that have a melting point much lower than any of the components. Because the properties of a DES, such as chiral discrimination, can be controlled through choice of components, DES have potential as solvents in many chemical and industrial applications. However, the large number of potential components makes high throughput methods of DES discovery critical for their development. In this study, mixtures of small quantities of hydrogen bond acceptors (HBAs) and chiral hydrogen bond donors (HBDs) were mixed at 55 °C and cooled to 20 °C to screen for potential liquid formation. Variable molar ratios of 10 HBAs were mixed with 93 chiral HBDs to measure a total of 1250 mixtures, and 356 mixtures were liquid

at 20 °C. All of the results including mixtures that did not form liquids are provided in a publicly available database. Several of the mixtures were prepared in larger quantities to characterize their physical properties, including melting points, densities, and viscosities. The results of this study can be used to guide the discovery and development of new chiral solvents, such as DES and eutectic mixtures.

Introduction

A eutectic mixture is a mixture of components that has a melting point below that of the pure components, and a deep eutectic solvent (DES) is a type of eutectic mixture that has a particularly deep depression of the melting point from that of the pure components.¹⁻⁵ In a DES, the deep melting point depression is the result of strong interactions, such as hydrogen bonding and ionic interactions, between the components of the mixture. As liquids, DES have properties similar to ionic liquids, including low volatility, high thermal stability, and tunable physicochemical properties.^{1-3,6-83} Many DES are considered “green” solvents, because they are biodegradable, non-toxic, and inexpensive to synthesize.⁹⁻¹⁴ If the melting point is low enough, DES can be utilized as solvents for use in many chemical and industrial applications, including battery technologies, catalysis, separations, and waste processing.^{1,15-22}

The components of a DES are labeled as a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD), and are classified as type I-V based on the identity of the HBA and HBD. For example, type III DES have a quaternary ammonium salt as HBA, and the HBD is an organic molecule, type V DES have organic molecules as the HBA and HBD, and types I, II, and IV have metal chlorides.^{1,2} Many recent studies in the literature involve type III DES with choline chloride ((2-hydroxyethyl)-trimethylammonium chloride) or tetrabutylammonium chloride as the HBA,^{6,18,19,23-30} but there has also been an increase in the study of type V DES.^{14,31,32} Given the

number of potential HBA and HBDs available, the possible binary (and ternary) DES combinations is extremely large, but there are currently no models capable of predicting what combinations will result in DES.¹ This highlights the importance of exploring and characterizing new combinations of HBA and HBDs.

In principle, the properties of a DES depend upon the choice of HBA and HBD, which should make it possible to “tune” the properties of a DES. For example, incorporating a chiral HBA or HBD will result in a chiral DES solvent. Given the importance of chirality in chemistry and biochemistry, it could be useful to develop new chiral DES and/or eutectic mixtures for chiral applications. There are a number of recent studies of chiral DES used in asymmetric synthesis,^{33–37} chiral separations,^{24,38,39} and circularly polarized light emitting materials.^{40–42} Despite these reports, there are still a large number of possible chiral HBA and HBDs and lack of predictive capability make finding new chiral DES a time-consuming process of trial and error.

In this study, a process was utilized to screen a small number of achiral HBAs, both type III and type V DES components, with a large number of chiral HBDs for potential solvent (DES or eutectic mixture) formation. All of the HBA and HBDs in the database are commercially available. The HBA-HBDs were mixed and heated in varying molar ratios, and combinations that remain a liquid at room temperature are recorded as potential chiral DES candidates. The results of the screening are maintained in a publicly available database showing mixtures that form liquids, and more importantly showing mixtures that do not form liquids.⁴³ The mixtures in the database are compared for the impact of HBA and HBD on liquid formation. Several of the chiral solvent mixtures have been prepared in larger quantities to measure properties, such as water content, density, melting point, and viscosity. The melting point data is used to determine if the mixtures are DES or simple eutectic mixtures.^{1,31}

Experimental

Mixture preparation. All chemicals used in this study are shown in Table S1 in supporting information. They were purchased commercially from VWR, Sigma-Aldrich, Combi-Blocks, Chem-Impex and Tokyo Chemicals Inc. (TCI), and used without further purification. Chemicals were used within 1-2 days of receiving them or stored in a vacuum desiccator before use in mixture testing. Mixtures of HBA's and HBD's were added to wells in a 64-well plate in molar ratios (HBA:HBD) ranging from 1:6-12:1, although most mixtures were only evaluated a ratios from 1:2-3, with a total mass of 0.1 g. The well plate was placed in a Benchmark Incu-Shaker Mini incubator-shaker, shaken at 175 rpm and 55 °C for two hours. The samples in the well plate were observed to identify which mixtures were liquid, solid, or a combination. The well plate was allowed to cool to room temperature (20 °C), and once again observed within 30 minutes to identify which mixtures were liquid, solid or a combination. These observations were recorded into an accessible database.⁴³ Many of the eutectic mixtures that were liquids in the well plates were also prepared in larger quantities, ~ 1-2 g, for further study. These mixtures were prepared by adding the correct molar ratios of hydrogen bond acceptor and hydrogen bond donor to a sample vial, and stirring under heat at temperatures < 60 °C until a homogeneous liquid was formed (typically less than 1 hour). Water content of the mixtures was measured by volumetric Karl-Fischer titration (Metroohm 870 KF Titrino Plus).

Physical measurements. The melting points of mixtures were measured with a differential scanning calorimeter (DSC) (Instrument Specialists Incorporated DSC 550). Samples were prepared by adding 3-10 mg of the mixture to an aluminum pan and lid. The DSC was operated with a heating rate of 2 °C/min. under a constant flow of nitrogen gas. The water content of the

larger mass samples was measured immediately before measuring the density, or viscosity. Densities were obtained by determining the mass of DES in a 2.02 mL or a 0.500 mL glass pycnometer. The viscosity was measured with a Brookfield DV2T viscometer using a circulating water bath to control temperature. Viscosities were measured for mixtures between 283-323 K.

Results and Discussion

Table 1. An excerpt from the mixture screening database.

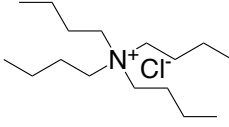
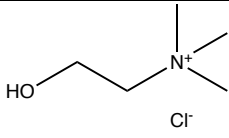
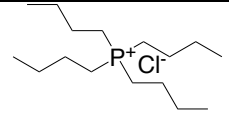
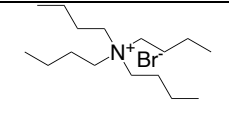
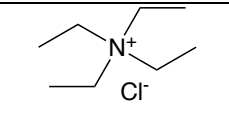
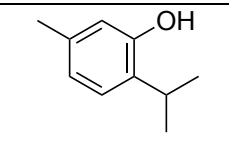
HBA mole ratio	HBD mole ratio	HBA	HBA (SMILES)	HBD	HBD (SMILES)	liquid at 55C	liquid at 20C
1	2	L-Menthol	<chem>C[C@@H]1CC[C@H]([C@@H](C1)O)C(C)C</chem>	L-glutamic acid	<chem>N[C@@H](CCC(O)=O)C(O)=O</chem>	n	n
1	1	L-Menthol	<chem>C[C@@H]1CC[C@H]([C@@H](C1)O)C(C)C</chem>	L-glutamic acid	<chem>N[C@@H](CCC(O)=O)C(O)=O</chem>	n	n
2	1	L-Menthol	<chem>C[C@@H]1CC[C@H]([C@@H](C1)O)C(C)C</chem>	L-glutamic acid	<chem>N[C@@H](CCC(O)=O)C(O)=O</chem>	n	n
3	1	L-Menthol	<chem>C[C@@H]1CC[C@H]([C@@H](C1)O)C(C)C</chem>	L-glutamic acid	<chem>N[C@@H](CCC(O)=O)C(O)=O</chem>	n	n
4	1	L-Menthol	<chem>C[C@@H]1CC[C@H]([C@@H](C1)O)C(C)C</chem>	L-glutamic acid	<chem>N[C@@H](CCC(O)=O)C(O)=O</chem>	n	n
5	1	L-Menthol	<chem>C[C@@H]1CC[C@H]([C@@H](C1)O)C(C)C</chem>	L-glutamic acid	<chem>N[C@@H](CCC(O)=O)C(O)=O</chem>	y	n
6	1	L-Menthol	<chem>C[C@@H]1CC[C@H]([C@@H](C1)O)C(C)C</chem>	L-glutamic acid	<chem>N[C@@H](CCC(O)=O)C(O)=O</chem>	y	n

Chiral mixture screening. Ten compounds were screened as HBAs, including L-menthol, thymol, choline chloride (ChCl), tetrabutylammonium chloride (TBACl), tetrabutylammonium bromide (TBAB), tetraethylammonium chloride (TEACl), tetrabutylphosphonium chloride (TBPCl), L-proline, citric acid, and (S)-2-acetoxypionic acid, with 93 individual (mostly) chiral HBDs to determine which mixtures form chiral solvents below 55 and 20 °C. HBA-HBD mixtures were screened in molar ratios between 1:6-12:1 HBA:HBD, but most mixtures were only screened at 1:2, 1:1, 2:1, and 3:1 HBA:HBD. At the time of writing this manuscript 1393 mixtures, including all molar ratios, have been prepared and measured for liquid formation. Of these

combinations, 576 mixtures were liquid at 55 °C and 392 of those were also liquid at 20 °C. All of the mixture screening data is contained in an accessible database.⁴³ A small excerpt of the database showing the screening of L-menthol as HBA and L glutamic acid as HBD is presented in Table 1. Columns include mole ratios of HBA and HBD, names of the HBA and HBD, SMILES structure representation of the HBA and HBD, and columns indicating if the mixture was observed as a complete liquid (y), complete solid (n), or partial liquid (p) at 55 and 20 °C. The database is organized by the identity of the HBA. For example, all of the mixtures of ChCl and chiral HBDs are grouped together in the database.

There are factors that need to be considered in the analysis of the chiral mixture screening database. First, since the mixtures were screened in ambient conditions, every sample has some amount of environmental water, but sample size (~0.1 g) precludes quantitative water determination.⁴⁴⁻⁴⁷ This means that many of the mixtures in the database should be considered a ternary mixture of HBA:HBD:water, and it is unclear what role water content plays in the formation of the liquid at 55 or 20 °C. Second, only a limited number of mole ratios have been explored for each of the mixtures, where different molar ratios may form liquids at 55 or 20 °C. Since the melting point information is gathered as two binary conditions, less than or greater than 55 and 20 °C, there is no way to use the results to determine the eutectic point of a mixture. However, the chiral mixture database does give qualitative information about what HBA and HBD mixtures could lead to new chiral solvents (eutectic mixtures or DES), and maybe more importantly, what mixtures would not. The results in the database are compared and discussed with respect to the impact of the HBA and HBD.

Table 2. Compounds used as HBAs.

Name	Structure	T _{fus} (°C) ^a
Tetrabutylammonium Chloride (TBACl)		37 ^a
Choline chloride (ChCl)		324 ^b
Tetrabutylphosphonium chloride (TBPCl)		62?
Tetrabutylammonium bromide (TBABr)		122 ^a
Tetraethylammonium chloride (TEACl)		64 ^c
Thymol		50

^a from ref 48 and 49, ^b estimated from ref 50. ^c measured by DSC (supporting information)

Impact of HBA component. The structures and melting points of six of the eleven compounds used as HBAs are shown in Table 2.⁴⁸⁻⁵⁰ The other five HBAs excluded from Table 2 were screened with fewer HBDs, and presented fewer successful liquids. Three of the HBAs shown in Table 2, TBACl, ChCl, and thymol, were screened with the largest number of chiral HBDs. The other three HBAs, TBPCl, TEACl, and TBABr, provide similarities with TBACl that allows for direct structural comparisons. Five of the HBAs in Table 2 are ionic compounds with only ChCl possessing a functional group traditionally associated as a hydrogen bond acceptor or donor. The sixth HBA in Table 2 is thymol, which is a non-ionic organic compound capable of

forming hydrogen bonding with the chiral HBDs. Only three of the eleven HBAs in the database are chiral, L-proline, L-menthol and (S)-acetoxypropionic acid, not shown in Table 2. The majority of the eutectic mixtures in the database have been developed by mixing an achiral HBA with a chiral HBD. Only TBACl and thymol have melting points below 55 °C, and therefore, will melt at the high temperature in the shaker/incubator. This improves the effectiveness of the mixing in the well plate, and may increase the likelihood of forming a liquid at the higher temperature (55 °C).

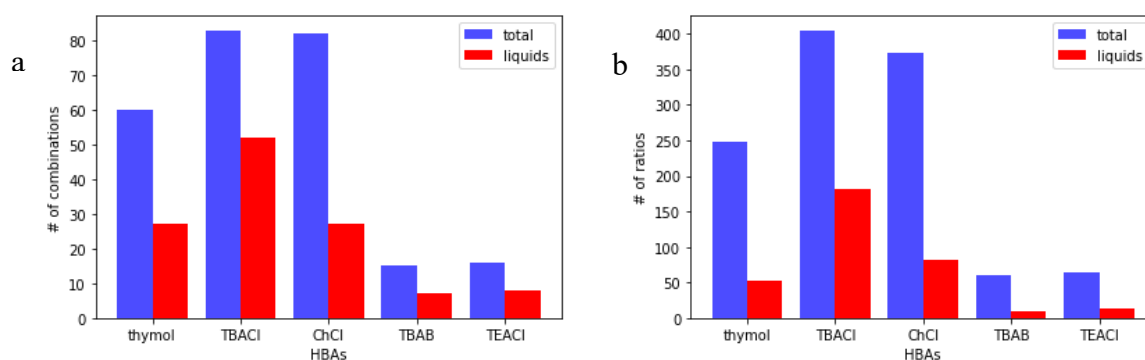


Figure 1. a) Comparison of total unique HBA-HBD combinations (blue) vs. HBA-HBD combinations that resulted in a liquid at 20 °C (red). The comparison is independent of the molar ratio, and is simply based on HBA-HBD combinations. b) Comparison of total binary HBA:HBD molar ratios (blue) vs. HBA-HBD molar ratios that resulted in a liquid at 20 °C (red).

Figure 1b shows a comparison of the HBA:HBD combinations attempted vs. combinations that resulted in liquid formation at room temperature (20 °C), and Figure 1a shows the comparison based on the identity of the HBA:HBD combination. The most effective HBA for forming liquids at room temperature was TBACl with ~45% of its molar ratios (Figure 1b) and ~60% of the HBA:HBD combinations successful at forming liquids.⁴³ As a comparison, both TBACl and ChCl were screened with the same number of HBDs, but only ~25% of the ChCl:HBD ratios were liquid at room temperature. Both TBACl and ChCl are hygroscopic salts, but the difference in successful

ratios indicates that the absorption of environmental water is not the only factor determining which combinations form liquids at room temperature. Direct comparison of the TBACl results with any of the other HBAs is complicated by the difference in the number of combinations studied. For example, TEACl and TBABr were introduced as HBAs to facilitate structural comparisons after it was evident that TBACl was the most successful HBA. This means that many of the unsuccessful TBACl:HBD combinations have not been attempted with TEACl and TBABr. This means that the comparison of successful TEACl:HBD and TBABr:HBD combinations (Figure 1a) overemphasize successful HBDs as compared to TBACl and ChCl. Figure 1 also shows that thymol is successful as an HBA with ~45% of thymol:HBD combinations (Figure 1a) as liquids at room temperature.⁴³

HBD components. As of this writing, the database has 93 unique HBDs that were combined with one or more of the 10 HBAs. All but two of the HBDs in the database are have at least one chiral carbon center. Among the 93 HBDs there is considerable structural diversity, but most include functional groups that can act as hydrogen bond donors, including acids, alcohols, amines, and amides. There are 32 combinations of HBA-HBDs that includes 24 unique HBDs that were liquid at room temperature for every ratio attempted. Table 3 lists the HBDs and HBAs that successfully formed liquids at all ratios. There is enough structural diversity among the 24 HBDs in Table 3 that makes it difficult to rationalize liquid formation of the mixtures based on the structure. However, the one common feature of the HBDs in Table 3 is that they have relatively low melting points, or are already liquids at room temperature. Ten of the 24 HBDs in Table 3 start as liquids at room temperature (shown in red in Table 4) before mixing, whereas the remaining 14 HBDs are solids, but only three have a melting point > 100 °C.⁵¹ For many of these HBDs, even modest depression of the melting point will result in liquids at room temperature, 20 °C. The

majority (21 out of 32) of the combinations in Table 3 include TBACl as the HBA, which is consistent with the data in Figure 1 that shows TBACl as the most effective HBA for liquid formation.

Table 3. Hydrogen bond donors that formed liquids at all molar ratios

HBD ^a	HBA (liquid in all ratios)	HBD ^a	HBA (liquid in all ratios)
(S)/(R)-2-acetoxypropionic acid	TBACl	L-tert-leucinol (30 °C)	TBACl
(R)-2-bromo-3-methylbutyric acid (39 °C)	TBACl, ChCl, thymol	L- α -hydroxyisovaleric acid	TBACl, ChCl
(R)-2-hydroxy-4-phenylbutyric acid (114 °C)	TBACl	L-proline methyl ester hydrochloride (73 °C)	TBACl, ChCl
Methyl-(S)-3-hydroxybutyrate	TBACl	Ethyl-(S)-3-hydroxybutyrate	TBACl
(S)-1-phenylethanol	TBACl	α -terpineol	TBACl
(R)-lactamide (73 °C)	ChCl	(-)-Terpinen-4-ol	TBACl
Methyl-(S)-lactate	TBACl, thymol	(2S,3S)-2-Amino-3-Methylpentan-1-ol (36 °C)	TBACl
(R)-2-octanol	TBACl	Dimethyl-D-malate (104 °C)	TBACl, ChCl
Methyl-(2R)-2-hydroxy-3-phenylpropanoate (43 °C)	TBACl, thymol	(R)-methyl mandelate (54 °C)	TBACl
(R)-ethyl mandelate (35 °C)	TBACl, thymol	(R)-citronellol	TBACl
L-lactic acid (53 °C)	ChCl	D-fructose (103 °C)	ChCl
(+)-diethyl L-tartrate	TBACl	(R)-(-)-1-Phenyl-1,2-ethanediol (64 °C)	TBACl

^a melting points of pure substance in parentheses as reported by suppliers. HBDs in red are liquid at room temperature

Mixture Physical Characterization. While the chiral mixture screening does provide insight into what mixtures result in liquids, it does very little to help explain why. For example, this screening cannot be used to distinguish between DES and simple eutectic mixtures, or even understand how environmental water may play a role in liquid formation.^{44,45} In order to better

understand the chiral liquids/solvents prepared by the screening process, it is important to measure the water content, thermal and physical properties. Since it is beyond the scope of this manuscript to document the properties of all of the successful liquid mixtures, a subset (< 100) were prepared in larger quantities to characterize their properties, and results from 20 of these mixtures are presented in this manuscript. A table of the measured water content along with the component mole fraction for these mixtures is included in the supporting information. Measured water content of most of the samples varied from 0.2-6.0 % (w/w), which corresponds to water mole fractions between 0.02-0.42. The samples with the highest water content have water as the largest component by moles in the mixture. However, none of these mixtures would be classified as an aqueous solution, and the mole fractions are within a range that has been characterized as “water in DES”.^{44,45} It is probably most accurate to characterize the chiral mixtures in this study as ternary eutectic mixtures, composed of HBA, HBD, and water.

Table 4. Melting points for several mixtures.

Mixture	T _{fus} (K) ^a	Mixture	T _{fus} (K) ^a
2:1 TBACl:D-glucose	269 ^b	2:1 TBACl:D-fructose	288 ^b
1:1 TBACl:dimethyl-D-malate	[T _g = 255]	1:1 ChCl:L-ascorbic acid	260 ^c
2:1 TBACl: Methyl-(2R)-2-hydroxy-3-phenylpropanoate	225	2:1 TBABr: Methyl-(2R)-2-hydroxy-3-phenylpropanoate	214
1:1 TBACl: (R)-(-)-1-Phenyl-1,2-ethanediol	241	2:1 TBACl:(S)-acetoxypionic acid	298 ^c
1:2 TBACl: (-)-terpinen-4-ol	236	1:1 [TBA]Cl:L-leucic acid	[T _g = 280] ^c
1:2 TBACl: (R)-ethyl-mandelate	213	1:2 TEACl: (R)-methyl-mandelate	284

^a uncertainty is ± 2 K, glass transitions in brackets

^b from reference 42

^c from reference 40

The only way to classify a mixture as a DES at the eutectic point is to measure a complete solid-liquid equilibrium curve,¹ which is impractical for the number of liquid mixtures in this study. However, a measure of the melting point depression upon mixing can provide a method to classify if the mixture is a simple eutectic or a DES.^{27,31} When the melting point depression is larger than what would be observed in an ideal mixture, the mixture can be classified as a DES. The thermodynamics of the solid liquid equilibrium for the mixtures can be described using the melting point depression expression shown in equation 1

$$\ln(\gamma_A x_A) = \frac{\Delta H_{fus}}{R} \left(\frac{1}{T_{fus}} - \frac{1}{T} \right) \quad (1)$$

where x_A and γ_A are the mole fraction and activity coefficients of component A of the mixture, R is the gas constant, T_{fus} and ΔH_{fus} are the melting point and enthalpy of fusion of the component A, and T is the melting point of the mixture. This equation is written assuming that the contribution from the change in heat capacity upon melting ($\Delta_{fus}C_p$) is negligible.⁴ If the liquid is the result of an ideal mixture, the activity coefficient determined from equation 1, $\gamma_A = 1$, and a liquid that is a DES would have $\gamma_A < 1$.

Among the many mixtures measured, only twelve exhibited transitions in the DSC. Table 4 shows the melting points and glass transitions measured for these mixtures. The main complication in applying equation 1 to the mixtures in Table 4 is the absence of literature values of the ΔH_{fus} for many of the individual components. However, there are literature values for the enthalpy of fusion and melting point of TBACl and lactic acid, which allows the use of equation 1 to calculate activity coefficients for at least one component of most mixtures in Table 4.^{48,49} Using the mole fractions from Table S2 (supporting information) that includes the water content, the melting point data from Table 4, and equation 1 shows that only 1:3 ChCl:L-lactic acid ($\gamma_{L-lacticacid}$

= 0.94) and 2:1 TBACl:(S)-acetoxypropionic acid ($\gamma_{\text{TBACl}} = 1.1$) have $\gamma \geq 1$.⁴⁰ The 1:1 TBACl:L-leucic acid and 1:1 TBACl: dimethyl-D-malate only show glass transitions, and the remaining mixtures in Table 4 have $\gamma_A < 1$ (equation 1) at the measured molar ratios indicating that the melting point depression is consistent with the classification as DES.

Table 5. Densities and viscosities of several mixtures at 293 K.

Mixture	ρ (g/mL) ^a	η (mPa-s) ^a	mol % water
1:2 TBACl: (S)-acetoxypropionic acid	1.03	1586	3
1:2 TBACl: (+)-terpinen-4-ol	0.942	1890	10
1:1 TBACl: L-leucic acid	0.992	1700	15
1:1 TEACl: (R)-(-)-1-Phenyl-1,2-ethanediol	1.07	1830	9
1:2 TBPCl: (R)-methyl mandelate	1.06	445	10
1:2 TBABr: (R)-methyl mandelate	1.12	1214	9
1:1 TBACl: (+)-diethyl-L-tartrate	1.03	1900	15
1:2 TBACl: (+)-diethyl-L-tartrate	1.08	1117	8
1:2 TBABr: (+)-diethyl-L-tartrate	1.18	3952	1
1:2 TEACl: (+)-diethyl-L-tartrate	1.15	2835	6
2:1 TBACl: N-Boc-L-Phenyl alaninol	0.976	33980	9
1:2 TBACl : α -terpineol	0.936	1290	13
1:2 TBACl: dimethyl-D-malate	1.07	157	10
1:2 TBABr: dimethyl-D-malate	1.13	473	3
1:2 TEACl: dimethyl-D-malate	1.15	203	8
2:1 TBACl: (+)-N,N'-Diallyl-L-tartardiamide	1.11	13840 (313 K)	7
3:1 TBACl: L-tert-leucine methylamide	0.962	28590	9
2:1 Thymol: α -terpineol	0.946	3155	2

1:2 Thymol: (2S,3S)-2-Amino-3-Methylpentan-1-ol	0.958	2836	8
2:1 Thymol: (S)-(+)-1-Cyclohexylethylamine	0.918	57	3

^a uncertainty in density is ± 0.001 g/mL, and the uncertainty in viscosity is ± 3 -5 mPa-s

The density and viscosity was measured for more mixtures, but Table 5 only shows the twenty mixtures with water content $< 1.5\%$ w/w (Table S2 in supporting information). The densities at 293 K range from 0.918-1.18 g/mL. Because of the variation in molar ratios and water content, it is difficult to compare densities across all of the mixtures. However, several mixtures have the same ratio, same HBD, and differing HBA, which may be useful to compare. For example, the density is higher for TBABr vs. TBACl mixtures (1:2 TBABr vs. TBACl: (+)-diethyl-L-tartrate and 1:2 TBABr vs. TBACl: dimethyl-D-malate), which could be the result of the lower water content in the TBABr mixtures.

The viscosities at 293 K (Table 5) range from 57-33980 mPa-s, but most of the mixtures have viscosities between 1000- 3000 mPa-s. To the authors knowledge, only three of the mixtures in Table 5 have been utilized in DES or eutectic mixtures prior to this study.^{40,52,53} Therefore, it is impossible to make direct comparisons with similar mixtures, but the viscosities in Table 5 are higher than those reported for ChCl based DES.^{1,6,54} Comparison of the viscosities for 1:2 TBACl vs. TBABr vs. TEACl: (+)-diethyl-L-tartrate and 1:2 TBACl vs. TBABr vs. TEACl: dimethyl-D-malate shows that higher water content corresponds to lower viscosity. The effect of water content on the viscosity of these liquids in Table 5 is much larger than on the density.⁵⁵ It is also interesting that the 1:2 TBACl, TBABr, and TEACl: dimethyl-D-malate have viscosities in the 100's mPa-s, which is an order of magnitude less viscous than the other ionic mixtures in Table 5. Comparison of 1:1 vs. 1:2 TBACl: (+)-diethyl-L-tartrate shows that the higher mole fraction of TBACl (1:1) corresponds to a higher viscosity, even though it has higher water content. The three high viscosity

mixtures (>13000 mPa-s) all have the highest ratio of TBACl, $\geq 2:1$ TBACl: HBD, which indicates that there is a correlation between TBACl and viscosity.

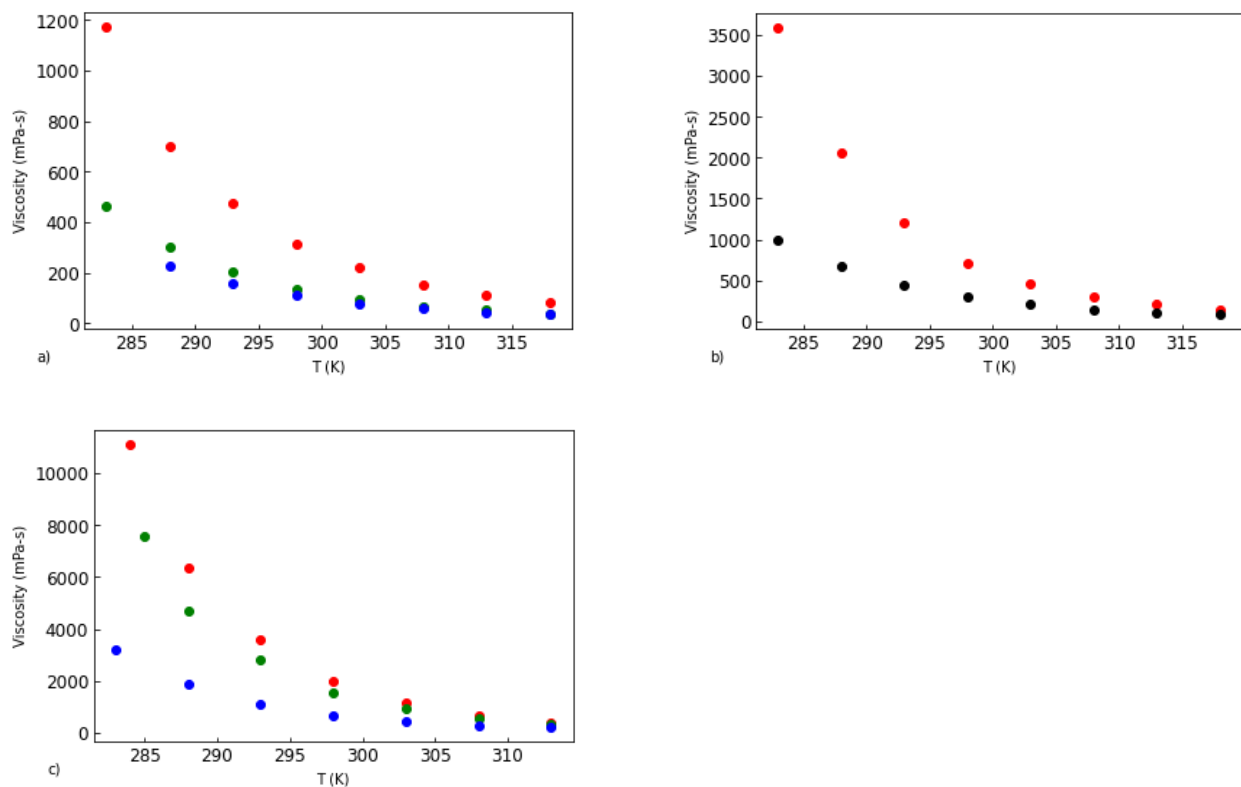


Figure 2. a) Viscosity vs. temperature (left upper panel) for 1:2 TBABr: dimethyl-D-malate (red circles), 1:2 TEACl: dimethyl-D-malate (green circles), and 1:2 TBACl: dimethyl-D-malate (blue circles). b) Viscosity vs. temperature (right upper panel) for 1:2 TBABr: (R)-methyl mandelate (red circles) vs. 1:2 TBPCl: (R)-methyl mandelate (black circles). c) Viscosity vs. temperature (lower left panel) for 1:2 TBABr: (+)-diethyl-L-tartrate (red circles), 1:2 TEACl: (+)-diethyl-L-tartrate (green circles), and 1:2 TBACl: (+)-diethyl-L-tartrate (blue circles).

The temperature dependent viscosities (283-318 K range) for eight of the mixtures from Table 5 are shown in Figure 2. Figure 2a-c show the temperature-dependent viscosities of mixtures of various HBAs with three HBDs, dimethyl-D-malate, (R)-methyl mandelate, and (+)-diethyl-L-tartrate. All of the mixtures in Figure 2 demonstrate Arrhenius-like temperature dependence to

their viscosities.⁵⁶ Figure 2a and 2c show the viscosities of 1:2 TBACl vs. TBABr vs. TEACl: dimethyl-D-malate and 1:2 TBACl vs. TBABr vs. TEACl: (+)-diethyl-L-tartrate, respectively. As shown in Table 5, 1:2 TBABr: HBD has the highest viscosities, but also has the lowest water content. Figure 2b shows a comparison of the viscosities of 1:2 TBABr vs. TBPCl: (R)-methyl mandelate, and the TBABr-based mixture has the higher viscosity. However, as shown in Table 5, the water content is very similar, 9 vs. 10 mole percent, for these two mixtures.

Conclusion

A method was used to screen for the formation of new chiral solvents based on eutectic mixtures and DES. Ten HBAs were combined with > 90 chiral HBDs to screen for the formation of low melting point mixtures. The screening included over 1000 mixtures of variable molar ratios, which resulted in > 300 mixtures as liquids at room temperature. Thirty-two HBA-HBD mixtures formed liquids at all of the molar ratios examined in the study. Successful liquid formation was most common for HBAs and chiral HBDs with the lowest individual component melting points. All of the screening data is recorded in a publicly available database.⁴³ Water content measurements show that all of the mixtures are ternary combinations of HBA:HBD:water. The thermal measurements of a small number of the mixtures showed that both DES and eutectic mixtures were formed. The densities and viscosities of a number of the mixtures were measured, and relative water content is important to the property.

Supporting Information. Supporting information includes a list of HBDs and purity information, water content of measured mixtures, DSC data, and temperature-dependent viscosities. The chiral DES database can be found at [10.6084/m9.figshare.19526092](https://doi.org/10.6084/m9.figshare.19526092).

ACKNOWLEDGMENT

This manuscript is based upon work supported by the National Science Foundation under CHE-1800269. The authors would also like to acknowledge William Mannelta for his contribution to the study.

REFERENCES

- (1) Hansen, B. B.; Spittle, S.; Chen, B.; Poe, D.; Zhang, Y.; Klein, J. M.; Horton, A.; Adhikari, L.; Zelovich, T.; Doherty, B. W.; Gurkan, B.; Maginn, E. J.; Ragauskas, A.; Dadmun, M.; Zawodzinski, T. A.; Baker, G. A.; Tuckerman, M. E.; Savinell, R. F.; Sangoro, J. R. Deep Eutectic Solvents: A Review of Fundamentals and Applications. *Chem. Rev.* **2021**, *121* (3), 1232–1285. <https://doi.org/10.1021/acs.chemrev.0c00385>.
- (2) Smith, E. L.; Abbott, A. P.; Ryder, K. S. Deep Eutectic Solvents (DESs) and Their Applications. *Chem. Rev.* **2014**, *114* (21), 11060–11082. <https://doi.org/10.1021/cr300162p>.
- (3) Abbott, A. P.; Edler, K. J.; Page, A. J. Deep Eutectic Solvents—The Vital Link between Ionic Liquids and Ionic Solutions. *J. Chem. Phys.* **2021**, *155* (15), 150401. <https://doi.org/10.1063/5.0072268>.
- (4) Martins, M. A. R.; Pinho, S. P.; Coutinho, J. A. P. Insights into the Nature of Eutectic and Deep Eutectic Mixtures. *J. Solution Chem.* **2019**, *48* (7), 962–982. <https://doi.org/10.1007/s10953-018-0793-1>.
- (5) Gurkan, B.; Squire, H.; Pentzer, E. Metal-Free Deep Eutectic Solvents: Preparation, Physical Properties, and Significance. *J. Phys. Chem. Lett.* **2019**, *10* (24), 7956–7964. <https://doi.org/10.1021/acs.jpcclett.9b01980>.
- (6) Abbott, A. P.; Boothby, D.; Capper, G.; Davies, D. L.; Rasheed, R. K. Deep Eutectic Solvents Formed between Choline Chloride and Carboxylic Acids: Versatile Alternatives to Ionic Liquids. *J. Am. Chem. Soc.* **2004**, *126* (29), 9142–9147. <https://doi.org/10.1021/ja048266j>.
- (7) Francisco, M.; van den Bruinhorst, A.; Kroon, M. C. Low-Transition-Temperature Mixtures (LTTMs): A New Generation of Designer Solvents. *Angew. Chem. Int. Ed.* **2013**, *52* (11), 3074–3085. <https://doi.org/10.1002/anie.201207548>.
- (8) Kar, M.; Plechkova, N. V.; Seddon, K. R.; Pringle, J. M.; MacFarlane, D. R. Ionic Liquids – Further Progress on the Fundamental Issues. *Aust. J. Chem.* **2019**, *72* (2), 3–10. <https://doi.org/10.1071/CH18541>.
- (9) Dai, Y.; van Spronsen, J.; Witkamp, G.-J.; Verpoorte, R.; Choi, Y. H. Natural Deep Eutectic Solvents as New Potential Media for Green Technology. *Analytica Chimica Acta* **2013**, *766*, 61–68. <https://doi.org/10.1016/j.aca.2012.12.019>.
- (10) Zhao, B.-Y.; Xu, P.; Yang, F.-X.; Wu, H.; Zong, M.-H.; Lou, W.-Y. Biocompatible Deep Eutectic Solvents Based on Choline Chloride: Characterization and Application to the Extraction of Rutin from *Sophora Japonica*. *ACS Sustainable Chem. Eng.* **2015**, *3* (11), 2746–2755. <https://doi.org/10.1021/acssuschemeng.5b00619>.
- (11) Li, J.; Xiao, H.; Tang, X.; Zhou, M. Green Carboxylic Acid-Based Deep Eutectic Solvents as Solvents for Extractive Desulfurization. *Energy Fuels* **2016**, *30* (7), 5411–5418. <https://doi.org/10.1021/acs.energyfuels.6b00471>.

- (12) Qin, H.; Panzer, M. J. Chemically Cross-Linked Poly(2-Hydroxyethyl Methacrylate)-Supported Deep Eutectic Solvent Gel Electrolytes for Eco-Friendly Supercapacitors. *ChemElectroChem* **2017**, *4* (10), 2556–2562. <https://doi.org/10.1002/celec.201700586>.
- (13) Florindo, C.; Branco, L. C.; Marrucho, I. M. Quest for Green-Solvent Design: From Hydrophilic to Hydrophobic (Deep) Eutectic Solvents. *ChemSusChem* **2019**, *12* (8), 1549–1559. <https://doi.org/10.1002/cssc.201900147>.
- (14) van Osch, D.; Dietz, C. H. J. T.; van Spronsen, J.; Gallucci, F.; van Sint Annaland, M.; Tuinier, R.; Kroon, M. C. A Search for Hydrophobic Deep Eutectic Solvents Based on Natural Components. *ACS Sustainable Chem. Eng.* **2019**. <https://doi.org/10.1021/acssuschemeng.8b03520>.
- (15) Atilhan, M.; Aparicio, S. Review and Perspectives for Effective Solutions to Grand Challenges of Energy and Fuels Technologies via Novel Deep Eutectic Solvents. *Energy Fuels* **2021**, *35* (8), 6402–6419. <https://doi.org/10.1021/acs.energyfuels.1c00303>.
- (16) Cruz, H.; Jordao, N.; Pinto, A. L.; Dionisio, M.; Neves, L. A.; Branco, L. C. Alkaline Iodide-Based Deep Eutectic Solvents for Electrochemical Applications. *ACS Sustainable Chem. Eng.* **2020**, *8* (29), 10653–10663. <https://doi.org/10.1021/acssuschemeng.9b06733>.
- (17) Cruz, H.; Jordão, N.; Amorim, P.; Dionísio, M.; Branco, L. C. Deep Eutectic Solvents as Suitable Electrolytes for Electrochromic Devices. *ACS Sustainable Chem. Eng.* **2018**, *6* (2), 2240–2249. <https://doi.org/10.1021/acssuschemeng.7b03684>.
- (18) Chen, Y.; Lu, Y.; Liu, Z.; Zhou, L.; Li, Z.; Jiang, J.; Wei, L.; Ren, P.; Mu, T. Efficient Dissolution of Lithium-Ion Batteries Cathode LiCoO₂ by Polyethylene Glycol-Based Deep Eutectic Solvents at Mild Temperature. *ACS Sustainable Chem. Eng.* **2020**, *8* (31), 11713–11720. <https://doi.org/10.1021/acssuschemeng.0c03624>.
- (19) Liu, Y.; Zheng, J.; Xiao, J.; He, X.; Zhang, K.; Yuan, S.; Peng, Z.; Chen, Z.; Lin, X. Enhanced Enzymatic Hydrolysis and Lignin Extraction of Wheat Straw by Triethylbenzyl Ammonium Chloride/Lactic Acid-Based Deep Eutectic Solvent Pretreatment. *ACS Omega* **2019**, *4* (22), 19829–19839. <https://doi.org/10.1021/acsomega.9b02709>.
- (20) Lima, F.; Dave, M.; Silvestre, A. J. D.; Branco, L. C.; Marrucho, I. M. Concurrent Desulfurization and Denitrogenation of Fuels Using Deep Eutectic Solvents. *ACS Sustainable Chem. Eng.* **2019**, *7* (13), 11341–11349. <https://doi.org/10.1021/acssuschemeng.9b00877>.
- (21) Riaño, S.; Petranikova, M.; Onghena, B.; Hoogerstraete, T. V.; Banerjee, D.; Foreman, M. R. S.; Ekberg, C.; Binnemans, K. Separation of Rare Earths and Other Valuable Metals from Deep-Eutectic Solvents: A New Alternative for the Recycling of Used NdFeB Magnets. *RSC Adv.* **2017**, *7* (51), 32100–32113. <https://doi.org/10.1039/C7RA06540J>.
- (22) Ohashi, Y.; Asanuma, N.; Harada, M.; Tanaka, Y.; Ikeda, Y. Studies on Electrochemical Behavior of Uranium Species in Choline Chloride-Urea Eutectic for Developing Electrolytically Treating Method of Uranium-Bearing Wastes. *J Radioanal Nucl Chem* **2015**, *309* (2), 627–636. <https://doi.org/10.1007/s10967-015-4625-0>.
- (23) Muzio, S. D.; Russina, O.; Mastrippolito, D.; Benassi, P.; Rossi, L.; Paolone, A.; Ramondo, F. Mixtures of Choline Chloride and Tetrabutylammonium Bromide with Imidazole as Examples of Deep Eutectic Solvents: Their Structure by Theoretical and Experimental Investigation. *Journal of Molecular Liquids* **2022**, *352*, 118427. <https://doi.org/10.1016/j.molliq.2021.118427>.
- (24) Farooq, M. Q.; Odugbesi, G. A.; Abbasi, N. M.; Anderson, J. L. Elucidating the Role of Hydrogen Bond Donor and Acceptor on Solvation in Deep Eutectic Solvents Formed by

- Ammonium/Phosphonium Salts and Carboxylic Acids. *ACS Sustainable Chem. Eng.* **2020**, *8* (49), 18286–18296. <https://doi.org/10.1021/acssuschemeng.0c06926>.
- (25) Silva, L. P.; Araújo, C. F.; Abranches, D. O.; Melle-Franco, M.; Martins, M. A. R.; Nolasco, M. M.; Ribeiro-Claro, P. J. A.; Pinho, S. P.; Coutinho, J. A. P. What a Difference a Methyl Group Makes – Probing Choline–Urea Molecular Interactions through Urea Structure Modification. *Phys. Chem. Chem. Phys.* **2019**, *21* (33), 18278–18289. <https://doi.org/10.1039/C9CP03552D>.
- (26) Alcalde, R.; Gutiérrez, A.; Atilhan, M.; Aparicio, S. An Experimental and Theoretical Investigation of the Physicochemical Properties on Choline Chloride – Lactic Acid Based Natural Deep Eutectic Solvent (NADES). *Journal of Molecular Liquids* **2019**, *290*, 110916. <https://doi.org/10.1016/j.molliq.2019.110916>.
- (27) Crespo, E. A.; Silva, L. P.; Martins, M. A. R.; Fernandez, L.; Ortega, J.; Ferreira, O.; Sadowski, G.; Held, C.; Pinho, S. P.; Coutinho, J. A. P. Characterization and Modeling of the Liquid Phase of Deep Eutectic Solvents Based on Fatty Acids/Alcohols and Choline Chloride. *Ind. Eng. Chem. Res.* **2017**, *56* (42), 12192–12202. <https://doi.org/10.1021/acs.iecr.7b02382>.
- (28) Crespo, E. A.; Silva, L. P.; Martins, M. A. R.; Bülow, M.; Ferreira, O.; Sadowski, G.; Held, C.; Pinho, S. P.; Coutinho, J. A. P. The Role of Polyfunctionality in the Formation of [Ch]Cl–Carboxylic Acid-Based Deep Eutectic Solvents. *Ind. Eng. Chem. Res.* **2018**, *57* (32), 11195–11209. <https://doi.org/10.1021/acs.iecr.8b01249>.
- (29) Mjalli, F. S.; Naser, J.; Jibril, B.; Alizadeh, V.; Gano, Z. Tetrabutylammonium Chloride Based Ionic Liquid Analogues and Their Physical Properties. *J. Chem. Eng. Data* **2014**, *59* (7), 2242–2251. <https://doi.org/10.1021/je5002126>.
- (30) Hayyan, A.; Mjalli, F. S.; AlNashef, I. M.; Al-Wahaibi, Y. M.; Al-Wahaibi, T.; Hashim, M. A. Glucose-Based Deep Eutectic Solvents: Physical Properties. *Journal of Molecular Liquids* **2013**, *178*, 137–141. <https://doi.org/10.1016/j.molliq.2012.11.025>.
- (31) Schaeffer, N.; Abranches, D. O.; Silva, L. P.; Martins, M. A. R.; Carvalho, P. J.; Russina, O.; Triolo, A.; Paccou, L.; Guinet, Y.; Hedoux, A.; Coutinho, J. A. P. Non-Ideality in Thymol + Menthol Type V Deep Eutectic Solvents. *ACS Sustainable Chem. Eng.* **2021**. <https://doi.org/10.1021/acssuschemeng.0c07874>.
- (32) Cañada-Barcala, A.; Rodríguez-Llorente, D.; López, L.; Navarro, P.; Hernández, E.; Águeda, V. I.; Álvarez-Torrellas, S.; Parajó, J. C.; Rivas, S.; Larriba, M. Sustainable Production of Furfural in Biphasic Reactors Using Terpenoids and Hydrophobic Eutectic Solvents. *ACS Sustainable Chem. Eng.* **2021**, *9* (30), 10266–10275. <https://doi.org/10.1021/acssuschemeng.1c02798>.
- (33) Tiecco, M.; Alonso, D. A.; Níguez, D. R.; Ciancaleoni, G.; Guillena, G.; Ramón, D. J.; Bonillo, A. A.; Germani, R. Assessment of the Organocatalytic Activity of Chiral L-Proline-Based Deep Eutectic Solvents Based on Their Structural Features. *Journal of Molecular Liquids* **2020**, *313*, 113573. <https://doi.org/10.1016/j.molliq.2020.113573>.
- (34) Palomba, T.; Ciancaleoni, G.; Del Giacco, T.; Germani, R.; Ianni, F.; Tiecco, M. Deep Eutectic Solvents Formed by Chiral Components as Chiral Reaction Media and Studies of Their Structural Properties. *Journal of Molecular Liquids* **2018**, *262*, 285–294. <https://doi.org/10.1016/j.molliq.2018.04.096>.
- (35) Grecchi, S.; Arnaboldi, S.; Rizzo, S.; Mussini, P. R. Advanced Chiral Molecular Media for Enantioselective Electrochemistry and Electroanalysis. *Current Opinion in Electrochemistry* **2021**, *30*, 100810. <https://doi.org/10.1016/j.coelec.2021.100810>.

- (36) Arnaboldi, S.; Mezzetta, A.; Grecchi, S.; Longhi, M.; Emanuele, E.; Rizzo, S.; Arduini, F.; Micheli, L.; Guazzelli, L.; Mussini, P. R. Natural-Based Chiral Task-Specific Deep Eutectic Solvents: A Novel, Effective Tool for Enantiodiscrimination in Electroanalysis. *Electrochimica Acta* **2021**, *380*, 138189. <https://doi.org/10.1016/j.electacta.2021.138189>.
- (37) Alonso, D. A.; Burlingham, S.-J.; Chinchilla, R.; Guillena, G.; Ramón, D. J.; Tiecco, M. Asymmetric Organocatalysis in Deep Eutectic Solvents. *European Journal of Organic Chemistry* **2021**, *2021* (29), 4065–4071. <https://doi.org/10.1002/ejoc.202100385>.
- (38) Wang, R.; Sun, D.; Wang, C.; Liu, L.; Li, F.; Tan, Z. Biphasic Recognition Chiral Extraction of Threonine Enantiomers in a Two-Phase System Formed by Hydrophobic and Hydrophilic Deep-Eutectic Solvents. *Separation and Purification Technology* **2019**, *215*, 102–107. <https://doi.org/10.1016/j.seppur.2019.01.022>.
- (39) Roy, D.; Miller, L. Exploring the Utility of Natural Deep Eutectic Solvents as Additives in Super/Subcritical Fluid Chromatography- Insights into Chiral Recognition Mechanism. *Analytica Chimica Acta* **2022**, *1200*, 339584. <https://doi.org/10.1016/j.aca.2022.339584>.
- (40) Nelson, B.; VandenElzen, L.; Whitacre, G.; Hopkins, T. A. Chiral Eutectic Mixtures and Deep Eutectic Solvents for Induced Circularly Polarized Luminescence. *ChemPhotoChem* **2021**, *5* (12), 1071–1078. <https://doi.org/10.1002/cptc.202100139>.
- (41) VandenElzen, L.; Hopkins, T. A. Monosaccharide-Based Deep Eutectic Solvents for Developing Circularly Polarized Luminescent Materials. *ACS Sustainable Chem. Eng.* **2019**, *7* (19), 16690–16697. <https://doi.org/10.1021/acssuschemeng.9b04100>.
- (42) Wright, C. R.; VandenElzen, L.; Hopkins, T. A. Deep Eutectic Solvents for Induced Circularly Polarized Luminescence. *J. Phys. Chem. B* **2018**, *122* (37), 8730–8737. <https://doi.org/10.1021/acs.jpcc.8b06148>.
- (43) Chiral DES Database, 2022. <https://doi.org/10.6084/m9.figshare.19526092.v1>.
- (44) Kivelä, H.; Salomäki, M.; Vainikka, P.; Mäkilä, E.; Poletti, F.; Ruggeri, S.; Terzi, F.; Lukkari, J. Effect of Water on a Hydrophobic Deep Eutectic Solvent. *J. Phys. Chem. B* **2022**. <https://doi.org/10.1021/acs.jpcc.1c08170>.
- (45) López-Salas, N.; Vicent-Luna, J. M.; Imberti, S.; Posada, E.; Roldán, M. J.; Anta, J. A.; Balestra, S. R. G.; Madero Castro, R. M.; Calero, S.; Jiménez-Riobóo, R. J.; Gutiérrez, M. C.; Ferrer, M. L.; del Monte, F. Looking at the “Water-in-Deep-Eutectic-Solvent” System: A Dilution Range for High Performance Eutectics. *ACS Sustainable Chem. Eng.* **2019**, *7* (21), 17565–17573. <https://doi.org/10.1021/acssuschemeng.9b05096>.
- (46) Ma, C.; Laaksonen, A.; Liu, C.; Lu, X.; Ji, X. The Peculiar Effect of Water on Ionic Liquids and Deep Eutectic Solvents. *Chem. Soc. Rev.* **2018**, *47* (23), 8685–8720. <https://doi.org/10.1039/C8CS00325D>.
- (47) Chen, Y.; Yu, D.; Chen, W.; Fu, L.; Mu, T. Water Absorption by Deep Eutectic Solvents. *Phys. Chem. Chem. Phys.* **2019**, *21* (5), 2601–2610. <https://doi.org/10.1039/C8CP07383J>.
- (48) Coker, T. G.; Ambrose, J.; Janz, G. J. Fusion Properties of Some Ionic Quaternary Ammonium Compounds. *J. Am. Chem. Soc.* **1970**, *92* (18), 5293–5297. <https://doi.org/10.1021/ja00721a001>.
- (49) Domalski, E. S.; Hearing, E. D. Heat Capacities and Entropies of Organic Compounds in the Condensed Phase. Volume III. *Journal of Physical and Chemical Reference Data* **1996**, *25* (1), 1–525. <https://doi.org/10.1063/1.555985>.
- (50) Fernandez, L.; Silva, L. P.; Martins, M. A. R.; Ferreira, O.; Ortega, J.; Pinho, S. P.; Coutinho, J. A. P. Indirect Assessment of the Fusion Properties of Choline Chloride from

- Solid-Liquid Equilibria Data. *Fluid Phase Equilibria* **2017**, *448*, 9–14. <https://doi.org/10.1016/j.fluid.2017.03.015>.
- (51) Informatics, N. O. of D. and. *Welcome to the NIST WebBook*. <https://webbook.nist.gov/> (accessed 2022-04-06). <https://doi.org/10.18434/T4D303>.
- (52) Jouyban, A.; Ali Farajzadeh, M.; Afshar Mogaddam, M. R.; Khodadadeian, F.; Nemati, M.; Khoubnasabjafari, M. In-Situ Formation of a Hydrophobic Deep Eutectic Solvent Based on Alpha Terpineol and Its Application in Liquid-Liquid Microextraction of Three β -Blockers from Plasma Samples. *Microchemical Journal* **2021**, *170*, 106687. <https://doi.org/10.1016/j.microc.2021.106687>.
- (53) Hu, X.; Zhang, L.; Xia, H.; Peng, M.; Zhou, Y.; Xu, Z.; Peng, X. Dispersive Liquid-Liquid Microextraction Based on a New Hydrophobic Deep Eutectic Solvent for the Determination of Phenolic Compounds in Environmental Water Samples. *Journal of Separation Science* **2021**, *44* (7), 1510–1520. <https://doi.org/10.1002/jssc.202001055>.
- (54) Zhang, Y.; Poe, D.; Heroux, L.; Squire, H.; Doherty, B. W.; Long, Z.; Dadmun, M.; Gurkan, B.; Tuckerman, M. E.; Maginn, E. J. Liquid Structure and Transport Properties of the Deep Eutectic Solvent Ethaline. *J. Phys. Chem. B* **2020**, *124* (25), 5251–5264. <https://doi.org/10.1021/acs.jpcc.0c04058>.
- (55) Kivelä, H.; Salomäki, M.; Vainikka, P.; Mäkilä, E.; Poletti, F.; Ruggeri, S.; Terzi, F.; Lukkari, J. Effect of Water on a Hydrophobic Deep Eutectic Solvent. *J. Phys. Chem. B* **2022**, *126* (2), 513–527. <https://doi.org/10.1021/acs.jpcc.1c08170>.
- (56) Castro, V. I. B.; Mano, F.; Reis, R. L.; Paiva, A.; Duarte, A. R. C. Synthesis and Physical and Thermodynamic Properties of Lactic Acid and Malic Acid-Based Natural Deep Eutectic Solvents. *J. Chem. Eng. Data* **2018**, *63* (7), 2548–2556. <https://doi.org/10.1021/acs.jced.7b01037>.